

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
203752Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 203752

SUPPL #

HFD #

Trade Name Minivelle

Generic Name estradiol transdermal system

Applicant Name Noven Pharmaceuticals, Inc.

Approval Date, If Known October 29, 2012

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES NO

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

505(b)(1)

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

YES NO

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

The NDA was supported by a bioequivalence and a dose proportionality study (both bioavailability studies). Both studies measured the rate and extent to which the active ingredient/active moiety was absorbed.

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

d) Did the applicant request exclusivity?

YES NO

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

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

YES NO

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

No

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

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

YES NO

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES NO

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

NDA# See attached sheet

NDA#

NDA#

2. Combination product.

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

YES NO

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

NDA#

NDA#

NDA#

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

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If

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

YES NO

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

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

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

YES NO

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

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

YES NO

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

YES NO

If yes, explain:

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

YES NO

If yes, explain:

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

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

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

The Phase 3 trials (1003-A and 1003-B) conducted under Vivelle NDA 20323 and the Phase 4 trial (Protocol 036) submitted April 30, 1999 and approved on February 25, 2000 under Supplement 21 of Vivelle NDA 20323.

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

Investigation #1 YES NO

Investigation #2

YES NO

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

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

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

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

Investigation #1

YES NO

Explain:

Investigation #2

YES NO

Explain:

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

Investigation #1

YES
Explain:

NO
Explain:

Investigation #2

YES
Explain:

NO
Explain:

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

YES NO

If yes, explain:

=====

Name of person completing form: Samantha Bell
Title: Regulatory Health Project Manager

Name of Office/Division Director signing form: Hylton Joffe
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12
List of approved drug products containing the active moiety:

N021674 MENOSTAR
N020375 CLIMARA
N020538 VIVELLE-DOT

N020323 VIVELLE
N019081 ESTRADERM
N020655 ALORA
N021166 ESTROGEL
N021813 ELESTRIN
N022038 DIVIGEL
N020472 ESTRING
N022014 EVAMIST
N020908 VAGIFEM

There are also several approved products containing ETHINYL ESTRADIOL, ESTRADIOL ACETATE, ESTRADIOL CYPIONATE, ESTRADIOL HEMIHYDRATE, ESTRADIOL VALERATE.

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

/s/

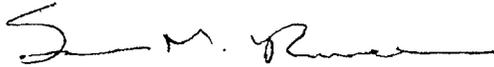
SAMANTHA S BELL
11/13/2012

HYLTON V JOFFE
11/13/2012

1.3. Administrative Information

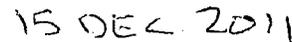
3. DEBARMENT CERTIFICATION

Noven Pharmaceuticals, Inc. 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.



Sean M. Russell

Associate Director, Regulatory Affairs



Date

Bell, Samantha

From: Greeley, George
Sent: Monday, October 15, 2012 11:58 AM
To: Bell, Samantha
Cc: Suggs, Courtney
Subject: RE: NDA 203752 Sept 19 PeRC meeting

Hi Samantha,

It was found during the review at PeRC on September 19th that NDA 23-752 Estradiol Transdermal System product did not trigger PREA.

No further action is necessary from the Division for this product as it relates to the PeRC and PREA.

Thank you.
George Greeley

George Greeley
Regulatory Health Project Manager
Pediatric and Maternal Health Staff
FDA/CDER/OND
10903 New Hampshire Avenue
Bldg. 22, Room 6467
Silver Spring, MD 20993-0002
Phone: 301.796.4025
Email: george.greeley@fda.hhs.gov
 Please consider the environment before printing this e-mail.

From: Bell, Samantha
Sent: Friday, October 12, 2012 11:48 AM
To: Suggs, Courtney; Greeley, George
Subject: NDA 203752 Sept 19 PeRC meeting

Hi Courtney and George,
I'm following up from the Sept 19 PeRC meeting when it was determined that NDA 203752 did not trigger PREA.

The Division would like to document the discussion at the meeting. Could you forward the minutes or respond to this email to confirm that no further action is necessary from the Division and as I understand the requirement is inapplicable for this application?

Thanks,
Samantha

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
WO22 - Room 5379
10903 New Hampshire Avenue

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹

| | | |
|---|--------------------------------------|--|
| NDA # 203752 BLA # | NDA Supplement # BLA Supplement # | If NDA, Efficacy Supplement Type: |
| Proprietary Name: Minivelle Established/Proper Name: estradiol transdermal system Dosage Form: film, extended release | | Applicant: Noven Pharmaceuticals, Inc. Agent for Applicant (if applicable): |
| RPM: Samantha Bell | | Division: Division of Reproductive and Urologic Products |

NDA and NDA Efficacy Supplements:

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

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

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

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

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

- This application does not rely upon a listed drug.
- This application relies on literature.
- This application relies on a final OTC monograph.
- This application relies on (explain)

For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

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

No changes Updated Date of check:

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

| | |
|--|---|
| <p>❖ Actions</p> <ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>October 29, 2012</u> Previous actions (<i>specify type and date for each action taken</i>) | <p><input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR</p> <p><input checked="" type="checkbox"/> None</p> |
|--|---|

The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

² For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

| | |
|--|--|
| <p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p> | <p><input type="checkbox"/> Received</p> |
| <p>❖ Application Characteristics³</p> <p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): 5</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <input type="checkbox"/> Restricted distribution (21 CFR 601.42)</p> <p>Subpart I Subpart H <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Communication Plan <input type="checkbox"/> Submitted in response to a Pediatric Written Request <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input checked="" type="checkbox"/> REMS not required</p> <p>Comments:</p> | |
| <p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p> | <p><input type="checkbox"/> Yes, dates</p> |
| <p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p> | <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> |
| <p>❖ Public communications (<i>approvals only</i>)</p> | |
| <ul style="list-style-type: none"> • Office of Executive Programs (OEP) liaison has been notified of action | <p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p> |
| <ul style="list-style-type: none"> • Press Office notified of action (by OEP) | <p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p> |
| <ul style="list-style-type: none"> • Indicate what types (if any) of information dissemination are anticipated | <p><input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other</p> |

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

| | |
|--|---|
| ❖ Exclusivity | |
| <ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes |
| <ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires: |
| <ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> | <input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires: |
| <ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> | <input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires: |
| <ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> | <input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires: |
| <ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10- year limitation expires: |
| ❖ Patent Information (NDAs only) | |
| <ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. | <input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic. |
| <ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. | 21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii) |
| <ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). | <input type="checkbox"/> No paragraph III certification Date patent will expire |
| <ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> | <input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified |

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

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

- (1) Have 45 days passed since the patent owner’s receipt of the applicant’s notice of certification?

Yes No

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

If “Yes,” skip to question (4) below. If “No,” continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant’s notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

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

If “No,” continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

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

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

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

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

If “No,” continue with question (5).

| | |
|---|--|
| <p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p> | <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> |
|---|--|

CONTENTS OF ACTION PACKAGE

| | |
|---|---|
| ❖ Copy of this Action Package Checklist ⁴ | Included |
| Officer/Employee List | |
| ❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>) | <input checked="" type="checkbox"/> Included |
| Documentation of consent/non-consent by officers/employees | <input checked="" type="checkbox"/> Included |
| Action Letters | |
| ❖ Copies of all action letters (<i>including approval letter with final labeling</i>) | Approved October 29, 2012 |
| Labeling | |
| ❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>) | |
| <ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. | <input checked="" type="checkbox"/> Included Final PI |
| <ul style="list-style-type: none"> • Original applicant-proposed labeling | 12-29-2011 <input checked="" type="checkbox"/> Included |
| <ul style="list-style-type: none"> • Example of class labeling, if applicable | |

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

| | |
|--|--|
| <ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) | <input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None |
| <ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. | Included Final PI |
| <ul style="list-style-type: none"> • Original applicant-proposed labeling | December 29, 2011 |
| <ul style="list-style-type: none"> • Example of class labeling, if applicable | |
| <ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) | |
| <ul style="list-style-type: none"> • Most-recent draft labeling | <input checked="" type="checkbox"/> Included Original and Final |
| <ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name. | Acceptable: Minivelle – August 7, 2012, August 8, 2012 Unacceptable: (b) (4) April 4, 2012, April 5, 2012 |
| <ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) | <input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEPA October 26, 2012 <input checked="" type="checkbox"/> DMPP/PLT (DRISK) October 1, 2012 <input checked="" type="checkbox"/> ODPD (DDMAC) October 9, 2012; October 23, 2012 <input checked="" type="checkbox"/> SEALD October 26, 2012; October 29, 2012 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews |
| Administrative / Regulatory Documents | |
| <ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) | <input checked="" type="checkbox"/> Included April 16, 2012 |
| <ul style="list-style-type: none"> ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte | <input checked="" type="checkbox"/> Not a (b)(2) |
| <ul style="list-style-type: none"> ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) | <input checked="" type="checkbox"/> Not a (b)(2) |
| <ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) | <input type="checkbox"/> Included |
| <ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm | |
| <ul style="list-style-type: none"> • Applicant is on the AIP | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |
| <ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action |

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

| | |
|--|---|
| ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC If PeRC review not necessary, explain: <u>Does not trigger PREA</u> • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) | <input type="checkbox"/> Included |
| ❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>) | <input checked="" type="checkbox"/> Verified, statement is acceptable |
| ❖ Outgoing communications (<i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i>) | <input checked="" type="checkbox"/> Included |
| ❖ Internal memoranda, telecons, etc. | February 17, 2012 OSI |
| ❖ Minutes of Meetings <ul style="list-style-type: none"> • Regulatory Briefing (<i>indicate date of mtg</i>) • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) • EOP2 meeting (<i>indicate date of mtg</i>) • Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) | <input checked="" type="checkbox"/> No mtg <input checked="" type="checkbox"/> N/A or no mtg <input checked="" type="checkbox"/> No mtg <input checked="" type="checkbox"/> No mtg |
| ❖ Advisory Committee Meeting(s) <ul style="list-style-type: none"> • Date(s) of Meeting(s) • 48-hour alert or minutes, if available (<i>do not include transcript</i>) | <input checked="" type="checkbox"/> No AC meeting |
| Decisional and Summary Memos | |
| ❖ Office Director Decisional Memo (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> None |
| Division Director Summary Review (<i>indicate date for each review</i>) | <input type="checkbox"/> None October 29, 2012 |
| Cross-Discipline Team Leader Review (<i>indicate date for each review</i>) | <input type="checkbox"/> None October 12, 2012; October 29, 2012 |
| PMR/PMC Development Templates (<i>indicate total number</i>) | <input checked="" type="checkbox"/> None |
| Clinical Information⁶ | |
| ❖ Clinical Reviews <ul style="list-style-type: none"> • Clinical Team Leader Review(s) (<i>indicate date for each review</i>) • Clinical review(s) (<i>indicate date for each review</i>) • Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) | See CDTL Review September 24, 2012 <input checked="" type="checkbox"/> None |
| ❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>) | <input checked="" type="checkbox"/> Included See clinical review September 24, 2012 |
| ❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) | <input checked="" type="checkbox"/> None |
| ❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>) | <input checked="" type="checkbox"/> Not applicable |

⁶ Filing reviews should be filed with the discipline reviews.

| | |
|---|--|
| ❖ Risk Management <ul style="list-style-type: none"> REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) | <input checked="" type="checkbox"/> None |
| ❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>) | <input checked="" type="checkbox"/> None requested |
| Clinical Microbiology <input checked="" type="checkbox"/> None | |
| ❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>) | <input type="checkbox"/> None |
| Clinical Microbiology Review(s) (<i>indicate date for each review</i>) | <input type="checkbox"/> None |
| Biostatistics <input type="checkbox"/> None | |
| ❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>) | <input type="checkbox"/> None |
| Statistical Team Leader Review(s) (<i>indicate date for each review</i>) | <input type="checkbox"/> None |
| Statistical Review(s) (<i>indicate date for each review</i>) | <input type="checkbox"/> None September 21, 2012 |
| Clinical Pharmacology <input type="checkbox"/> None | |
| ❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>) | <input type="checkbox"/> None |
| Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>) | <input type="checkbox"/> None |
| Clinical Pharmacology review(s) (<i>indicate date for each review</i>) | <input type="checkbox"/> None August 16, 2012 |
| ❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of DSI letters</i>) | <input type="checkbox"/> None |
| Nonclinical <input type="checkbox"/> None | |
| ❖ Pharmacology/Toxicology Discipline Reviews | |
| • ADP/T Review(s) (<i>indicate date for each review</i>) | <input type="checkbox"/> None |
| • Supervisory Review(s) (<i>indicate date for each review</i>) | <input type="checkbox"/> None |
| • Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>) | <input type="checkbox"/> None May 9, 2012 |
| ❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> None |
| ❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> No carc |
| ❖ ECAC/CAC report/memo of meeting | <input checked="" type="checkbox"/> None Included in P/T review, page |
| ❖ DSI Nonclinical Inspection Review Summary (<i>include copies of DSI letters</i>) | <input checked="" type="checkbox"/> None requested |

| Product Quality | <input type="checkbox"/> None |
|--|---|
| ❖ Product Quality Discipline Reviews | |
| • ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i> | <input type="checkbox"/> None |
| • Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i> | <input type="checkbox"/> None |
| • Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i> | <input type="checkbox"/> None CMC August 30, 2012 and September 28, 2012 Biopharmaceutics August 20, 2012 |
| ❖ Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i> | <input checked="" type="checkbox"/> Not needed |
| ❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i> | <input checked="" type="checkbox"/> None |
| ❖ Environmental Assessment (check one) (original and supplemental applications) | |
| <input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i> | <input checked="" type="checkbox"/> Included CMC Review August 30, 2012 |
| <input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i> | |
| <input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i> | |
| ❖ Facilities Review/Inspection | |
| <input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷)</i> | Date completed: August 15, 2012 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable |
| <input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i> | Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation |
| ❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i> | <input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review) |

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

Appendix to Action Package Checklist

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

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

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

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

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

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

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

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

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



NDA 203752

GENERAL ADVICE

Noven Pharmaceuticals, Inc.
Attention: Sean M. Russell
Associate Director, Regulatory Affairs
350 Fifth Avenue, 37th Floor
New York, NY 10118

Dear Mr. Russell:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for estradiol transdermal system.

We also refer to your April 27, 2012, submission, containing proposed labeling.

We have reviewed the referenced material and have the following comments:

1. Replace (b) (4) with an acceptable proprietary name.
2. Use different background colors on the carton and pouch labeling for each product strength to minimize the risk of product strength selection errors. It is also important to make sure the carton color matches the pouch color for each strength. As currently presented, the cartons and the pouches for each strength are very similar in color and can contribute to confusion that may lead to product strength selection errors as illustrated in the (b) (4) 0.0375 mg/day carton and pouch.

3. Select background colors for the carton and pouch labeling that will not overlap or appear similar to the carton and pouch labeling of the currently marketed Vivelle Dot®. These products will likely be stored in close proximity on pharmacy shelves and it is important to make them visually distinguishable to minimize the risk of product selection errors. As currently presented, the background color of the pouch labeling proposed for this product is very similar to the background color used for Vivelle Dot® as shown below.

4. Ensure that the established name is printed in letters that are at least half as large as the letters comprising the proprietary name and that the established name has the same prominence commensurate with the proprietary name taking into account typography, layout, contrast, and other printing features per 21 CFR 201.10(g)(2).
5. Increase the prominence of the strength statement following the proprietary and established name on the principal display panel.
6. Ensure that every presentation of the strength statement on the carton and pouch labeling includes the units of measure (mg/day) and is preceded by the proprietary and established names.
7. In the prescribing information (PI), the coextruded backing film is described as a (b) (4) film. The PI, pouch, and carton should consistently describe the backing membrane as part of the inactive ingredients.
8. Strength is expressed as both 0.1 and 0.10 mg/day. Information should be consistent throughout the labeling in terms of significant figures.

If you have any questions, call Samantha Bell, Regulatory Project Manager, at (301) 796-9687.

Sincerely,

{See appended electronic signature page}

Hylton V. Joffe, M.D., M.M.Sc.
Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

HYLTON V JOFFE
09/24/2012

McKnight, Rebecca

From: McKnight, Rebecca
Sent: Friday, August 24, 2012 9:22 AM
To: Strasinger, Caroline; Christner, Donna
Subject: FW: General Correspondence for NDA 203752
Attachments: Minivelle Response 27 Aug 12 Cover.pdf

[please see attached.](#)

From: Russell, Sean [mailto:SRussell@noven.com]
Sent: Friday, August 24, 2012 9:19 AM
To: McKnight, Rebecca
Subject: RE: General Correspondence for NDA 203752

Hi Becky,

Thanks for the clarification. Here is the response we intend to submit through the gateway on Monday. If this is sufficient please accept this as our official response. If you require any modifications please let me know and we will revise as needed.

Thanks again for all of your help through the review process.

Best,

Sean

From: McKnight, Rebecca [mailto:Rebecca.McKnight@fda.hhs.gov]
Sent: Thursday, August 23, 2012 3:10 PM
To: Russell, Sean
Subject: RE: General Correspondence for NDA 203752

[Sean,](#)

[Our purpose for these requests is to acknowledge your proposal made on July 31, 2012 and provide our concurrence that this is an acceptable path forward.](#)

[We seek confirmation of your commitment to these proposals in a formal letter to the NDA. The word "timely" was used to capture your plan of a concurrent stability study and that once sufficient data has been compiled to support the change of ink, a supplement should be submitted to the NDA. We do not seek a formal PMC at this time, but anticipate that the work will be initiated soon after product launch.](#)

[Thanks,
Becky](#)

From: Russell, Sean [mailto:SRussell@noven.com]
Sent: Thursday, August 23, 2012 1:51 PM
To: McKnight, Rebecca
Subject: RE: General Correspondence for NDA 203752

Hi Becky,

So qualifying a more distinguishable ink in a timely fashion sounds like a post approval commitment then. Is this correct?

Best,

Sean

From: McKnight, Rebecca [mailto:Rebecca.McKnight@fda.hhs.gov]
Sent: Thursday, August 23, 2012 1:45 PM
To: Russell, Sean
Subject: RE: General Correspondence for NDA 203752

Sean,

The commitment to qualify a more distinguishable ink is based on the IR response received on July 31, 2012. The Agency expects that you qualify a more distinguishable ink in a timely fashion and suggests qualifying multiple inks for potential use including (b) (4). Acceptability of the replacement ink, which will include an assessment of improved readability, will be a review issue at the time of the supplement submission.

Please add the above statement and your concurrence to your official confirmation letter requested in my August 21, 2012 email.

Thanks,
 Becky

From: Russell, Sean [mailto:SRussell@noven.com]
Sent: Thursday, August 23, 2012 1:17 PM
To: McKnight, Rebecca
Subject: Re: General Correspondence for NDA 203752

Hi Becky,

Will we hear back on my below email today? I was hoping we could commit to both (b) (4) in the response today. Please let me know.

Best,

Sean

On Aug 22, 2012, at 3:05 PM, "Russell, Sean" <SRussell@noven.com> wrote:

Hi Becky,

We are currently using (b) (4). We offered up (b) (4) based on the Agency's comments but it is a bit dark. We were hoping we could also use (b) (4). If we could have the option at approval of either (b) (4) that would be great. We could offer the same concurrent stability as is outlined below for the (b) (4).

Best,

Sean

On Aug 22, 2012, at 2:59 PM, "McKnight, Rebecca" <Rebecca.McKnight@fda.hhs.gov> wrote:

Hi Sean,

What color are you currently using?

Thanks,
Becky

From: Russell, Sean [mailto:SRussell@noven.com]
Sent: Wednesday, August 22, 2012 9:19 AM
To: McKnight, Rebecca
Subject: RE: General Correspondence for NDA 203752

Hi Becky,

I just wanted to confirm we have received this. Would it be possible to quickly discuss the backing color? Specifically, we would also like the opportunity to utilize "(b) (4)" for commercial production as well with the same commitment for "(b) (4)" below.

Best,
Sean

<!--[if !supportLists]--><!--[endif]--><!--[if !supportLists]--><!--[endif]--><!--[if !supportLists]--><!--[endif]--><!--[if !supportLists]--><!--[endif]-->

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

/s/

REBECCA A MCKNIGHT
08/31/2012

McKnight, Rebecca

From: McKnight, Rebecca
Sent: Tuesday, August 21, 2012 2:24 PM
To: 'Russell, Sean'
Subject: General Correspondence for NDA 203752

Hi Sean,

The Agency requests acknowledgement and concurrence with the following statements made in Information Request (IR) Responses received 2-JUL-2012 and 31-JUL-2012. Please confirm these commitments in a formal letter to the NDA.

- In the IR Response dated 2-JUL-2012 Noven proposed “to conduct the SEM-EDX analysis with the next GMP batch that is produced and to follow it through the end of stability. Noven will submit the data to FDA as available, postapproval.”
- In the IR Response dated 31-JUL-2012 Noven stated they “have started development of a method that will (b) (4) of the system for cold flow. Noven will submit that method when developed.”
- In the IR Response dated 31-JUL-2012 “A darker color of the current ink ((b) (4) can be utilized and Noven proposes to conduct a concurrent stability study to qualify this (b) (4)

Please respond no later than COB Thursday, August 23, 2012. In addition to the letter to the NDA, please also respond to me via email.

Thank you,

Rebecca McKnight
Regulatory Health Project Manager
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research
Food and Drug Administration
(301) 796-1765

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

/s/

REBECCA A MCKNIGHT
08/22/2012



NDA 203752

LABELING PMR/PMC DISCUSSION COMMENTS

Noven Pharmaceuticals, Inc.
Attention: Sean M. Russell
Associate Director, Regulatory Affairs
350 Fifth Avenue, 37th Floor
New York, NY 10118

Dear Mr. Russell:

Please refer to your December 29, 2011 New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for estradiol transdermal system.

We also refer to our March 9, 2012, letter in which we notified you of our target date of September 29, 2012 for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012."

On April 27, 2012, we received your proposed labeling submission to this application, and have proposed revisions that are included as an enclosure.

If you have any questions, call Samantha Bell, Regulatory Project Manager, at (301) 796-9687.

Sincerely,

{See appended electronic signature page}

Samantha Bell, B.S., B.A., R.A.C.
Regulatory Health Project Manager
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE: Content of Labeling

33 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

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

/s/

SAMANTHA S BELL
08/13/2012



NDA 203752

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Noven Pharmaceuticals, Inc.
350 Fifth Avenue, 37th Floor
New York, NY 10118

ATTENTION: Sean M. Russell
Associate Director, Regulatory Affairs

Dear Mr. Russell:

Please refer to your New Drug Application (NDA) dated December 29, 2011, received December 29, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for estradiol transdermal system, (b)(4) 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, 0.1 mg/day.

We also refer to your correspondence dated and received May 11, 2012, requesting review of your proposed proprietary name, Minivelle. We have completed our review of the proposed proprietary name, Minivelle and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your May 11, 2012, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. The proposed proprietary name Minivelle will be re-reviewed 90 days prior to approval of the application. The results of that re-review are subject to change.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Marcus Cato, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3903. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Samantha Bell at (301) 796-9687.

Sincerely,

{See appended electronic signature page}

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

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

/s/

CAROL A HOLQUIST
08/08/2012



NDA 203752

INFORMATION REQUEST

Noven Pharmaceuticals, Inc.
Attention: Sean M. Russell, Associate Director, Regulatory Affairs
Empire State Building
350 Fifth Avenue, 37th Floor
New York, NY 10118

Dear Mr. Russell:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the estradiol transdermal system.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request the following information to be provided to via email <rebecca.mcknight@fda.hhs.gov> and as an amendment to your application. Please provide your responses by Monday, July 30, 2012.

1) In reference to the IR Letter (22-MAY-2012) response received 2-JUL-2012 Question 9:

You reference section 3.2.P.2.3 to support a hold time (b) (4). Section 3.2.P.2.3 contains information regarding an investigation of a (b) (4) however, there is no reference to a hold time for an (b) (4). The proposed hold time appears to be different than (b) (4) discussed in section 3.2.P.2.3. Additionally, in your study it is noted that the (b) (4) is in use during the (b) (4) hold time.

- **Clarify the discrepancy in justification for hold time of the (b) (4) in the referenced section.**
- **Clarify if (b) (4) during the hold period.**
- **Acknowledge that you agree that expiry begins when (b) (4) and confirm that your provided stability data and proposed shelf-life include the hold-times discussed.**

2) Regarding your Cold Flow Method:

(b) (4)

(b) (4)

. Provide a method that also includes an assessment of the adhesive cold flow

(b) (4)

3) Regarding Stability:

Assure the stability protocol has been updated to reflect the current drug product specification.

4) Regarding the Identifying Label on the Transdermal System:

The Agency has the following suggestions to improve readability of the drug product before application and during wear:

- Use of a darker/more distinguishable ink color
- Decrease the number of rows printed per unit
- If a tradename is not to be used remove (b) (4) from (b) (4)

Submit color pictures of the intended printed commercial product.

If you have any questions, call Rebecca McKnight, Regulatory Project Manager, at (301) 796-1765.

Sincerely,

{See appended electronic signature page}

Terrance Ocheltree, Ph.D., R.Ph.
Director
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

/s/

TERRANCE W OCHELTRIE
07/19/2012



NDA 203752

INFORMATION REQUEST

Noven Pharmaceuticals, Inc.
Attention: Sean M. Russell, Associate Director, Regulatory Affairs
Empire State Building
350 Fifth Avenue, 37th Floor
New York, NY 10118

Dear Mr. Russell:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the estradiol transdermal system.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We acknowledge reviewing your response dated June 11, 2012 to our previous information request. We request the following information to be provided to via email <rebecca.mcknight@fda.hhs.gov> and as an amendment to your application to us by July 20, 2012 to expedite our review:

1. Based on release data/profiles submitted earlier, it appears that (b) (4) drug release for your proposed product in water can be achieved at 36 hours using your proposed method. Therefore, it is recommend that you establish sample points and acceptance ranges at 2, 6, 18 and 36 hours for your proposed patch which is to be worn for 84 hours.
2. Provide the currently approved release method and acceptance criteria for Vivelle (NDA 20-323) and Vivelle-DOT (NDA 20-538) including the dates of approval for these methods.

We also have the following observation you may want to consider.

It appears that you may be able to achieve higher release rate of the drug (b) (4) without loosing the discriminatory ability, which may reduce the total sampling period.

If you have any questions, call Rebecca McKnight, Regulatory Project Manager, at (301) 796-1765.

Sincerely,

{See appended electronic signature page}

Terrance Ocheltree, Ph.D., R.Ph.
Director
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

/s/

TERRANCE W OCHELTREE
07/13/2012



NDA 203752

**METHODS VALIDATION
MATERIALS RECEIVED**

Noven Pharmaceuticals, Inc.
Attention: Sean M. Russell
Associate Director, Regulatory Affairs
350 Fifth Avenue
37th floor
New York, NY 10118

Dear Sean Russell:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for (b) (4) (Estradiol Transdermal System); (b) (4) 0.0375, 0.05, 0.075, 01. mg/day and to our May 8, 2012, letter requesting sample materials for methods validation testing.

We acknowledge receipt on July 3, 2012, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy
MVP Coordinator
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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

/s/

MICHAEL L TREHY
07/05/2012



NDA 203752

INFORMATION REQUEST

Noven Pharmaceuticals, Inc.
Attention: Sean M. Russell, Associate Director, Regulatory Affairs
Empire State Building
350 Fifth Avenue, 37th Floor
New York, NY 10118

Dear Mr. Russell:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the estradiol transdermal system.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following information requests and comments.

For the following items (1-4), we request a prompt written response by June 1, 2012, in order to continue our evaluation of your NDA. Please provide your responses as a formal amendment to your application and via email to rebecca.mcknight@fda.hhs.gov.

Biopharmaceutics:

1. FDA recommends that the in vitro release profile covers at least (b) (4) of drug release, or if the percentage is lower, data demonstrating that a plateau has been reached should be provided. However, your proposed value for the last specification time point at 24 hours is only (b) (4). Please justify with data the selection of this specification-time point and value.
2. In your method development report, it is not clear whether different apparatus and testing conditions were evaluated (b) (4) along with different release media (including water) to generate profile data with higher/complete percent of drug released. Such modifications may yield the desired (b) (4) drug release as mentioned in the above bullet.
3. To support the approval of your proposed product, you conducted the pivotal BE study with the highest strength (1.65 mg estradiol/6.6 cm² (0.1 mg/day) and you are seeking approval of a biowaiver for the lower strengths (b) (4) 0.62 mg/2.48 cm² (0.375 mg/day); 0.83 mg/3.30 cm² (0.05 mg/day); 1.24 mg/4.95 cm (0.075 mg/day)]. However, note that your response dated April 10, 2012, did not include the complete information. Therefore, to support the biowaiver request for the lower strengths, you need to submit the in vitro drug release profile and similarity f2 data comparing each one of the lower strength vs. the highest strength tested in the BE study using the same testing conditions/methodology.

4. The similarity factor (f2) calculation should be based on the comparison of the overall profile (multipoint) data – not at each time point as reported in your response dated April 10, 2012. Please correct that and submit the f2 data.

For the following items (5-18), we request a prompt written response by June 22, 2012, in order to continue our evaluation of your NDA. Please provide your responses as a formal amendment to your application and via email to rebecca.mcknight@fda.hhs.gov.

General:

5. DMF (b) (4) is deficient. Contact the DMF holder for information. All DMFs must be adequate to support the NDA.
6. The (b) (4) penetrates the drug adhesive layer. Assess the impact of the (b) (4) on the finished product including the potential for microscopic crystal formation at the site of the cut, the impact on adhesion properties, and drug delivery. Provide information regarding process controls to assure the (b) (4) does not compromise the integrity of the ETS.

Manufacturing process/In-process controls:

7. Establish an in-process test for the (b) (4) to assure that the drug substance and excipients are fully dissolved and no solid particles/agglomerates are present. Alternatively, provide data demonstrating that agglomeration of the drug substance and excipients in the (b) (4) have been eliminated (b) (4).
8. Provide a sampling plan for in-process testing of the (b) (4) that assures blend uniformity (b) (4).
9. Provide hold times with appropriate justification for the following:
 - (b) (4)
 - (b) (4)
10. Establish a target, in addition to a range, for in-process controls for the potency acceptance criterion.
11. During product development, online samples were taken to check for coat weight and had a target coat weight of (b) (4) however an in-process control for such a test does not appear in the in-process control table provided. Update the in-process control table to include the test for coat weight or alternatively provide justification for its absence.

Impurities:

12. ICH Q3B(R2) does not apply to (b) (4) impurities. Test the (b) (4) impurities and provide acceptance criteria with justification for such impurities.

13. (b) (4) is present in the (b) (4) excipient and levels may rise above USP monograph acceptance criterion upon storage of the raw material. Clarify the maximum storage time of your (b) (4) excipient before it is used in the manufacturing process. Additionally, test the final laminate at release and on stability for (b) (4) as it may act as a permeation enhancer or adversely affect the transdermal system.

Drug Product Specification:

14. Establish a specification and acceptance criteria for the observation of crystals using microscopic methods.
15. Tighten the acceptance criterion to (b) (4) to update the specification as data becomes available.
16. Establish upper and lower limits for the acceptance criteria for release liner peel force and peel adhesion.

Stability:

17. Perform stress testing that includes exposure of the proposed transdermal system to 100% humidity and assess the systems adhesive properties, cold flow and crystal formation (using microscopic methods). The Agency acknowledges the stress test of 100% humidity performed during product development however, it is unclear if the test was performed on the final formulation and if the (b) (4) was included on the ETS in the product development stress test. If these were evaluated during development, provide that data.

Container Closure:

18. Clarify that *Table I:* (b) (4)

If you have any questions, call Rebecca McKnight, Regulatory Project Manager, at (301) 796-1765.

Sincerely,

{See appended electronic signature page}

Terrance Ocheltree, Ph.D., R.Ph.
Division Director
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

/s/

REBECCA A MCKNIGHT
05/22/2012

TERRANCE W OCHELTRIE
05/22/2012



NDA 203-752

**REQUEST FOR METHODS
VALIDATION MATERIALS**

Noven Pharmaceuticals, Inc.
Attention: Sean M. Russell
350 Fifth Avenue, 37th floor, New York, NY 10118

Dear Mr. Russell:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for (b) (4) (Estradiol Transdermal System); (b) (4) 0.0375, 0.05, 0.075, 0.1 mg/day.

We will be performing methods validation studies on (b) (4) (Estradiol Transdermal System); (b) (4), 0.0375, 0.05, 0.075, 0.1 mg/day, as described in NDA 203-752.

In order to perform the necessary testing, we request the following sample materials and equipments:

Method, current version full method

Analytical Procedures [Estradiol, transdermal systems from release liners]

1. Determination of the Force to Remove Transdermal Systems from Release Liners
2. Shear Adhesion of Transdermal Systems with Small Area
3. Peel Adhesion Test for Transdermal Systems
 - a. Were strips cut to a specific size?
4. Probe Tack Test for Transdermal Systems
 - a. Instrument parameters ((b) (4))
5. Cold Flow

Samples and Reference Standards

| | |
|-----|-----------------------|
| 200 | (b) (4) |
| 200 | 0.0375 mg/day patches |
| 200 | 0.05 mg/day patches |
| 200 | 0.075 mg/day patches |
| 200 | 0.1 mg/day patches |

Equipment

6 (b) (4)

Please include the MSDSs and the Certificates of Analysis for the samples.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: Michael L. Trehy
1114 Market Street, Room 1002
St. Louis, MO 63101

Please notify me upon receipt of this letter. If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy
MVP coordinator
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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

/s/

MICHAEL L TREHY
05/08/2012



NDA 203752

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Noven Pharmaceuticals, Inc.
Empire State Building
350 Fifth Avenue, 37th Floor
New York, New York 10118

ATTENTION: Sean M. Russell
Associate Director, Regulatory Affairs

Dear Mr. Russell:

Please refer to your New Drug Application (NDA) dated December 29, 2011, received December 29, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Estradiol Transdermal System (b) (4) 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day.

We also refer to your January 6, 2012, correspondence, received January 6, 2012, requesting review of your proposed proprietary name, (b) (4). We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons:

(b) (4)

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Maria Wasilik, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0567.

For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Samantha Bell at 301-796-9687.

Sincerely,

{See appended electronic signature page}

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

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

/s/

CAROL A HOLQUIST
04/05/2012



NDA 203752

FILING COMMUNICATION

Noven Pharmaceuticals Inc.
Attention: Sean M. Russell
Associate Director, Regulatory Affairs
11960 Southwest 144th St.
Miami, FL 33186

Dear Mr. Russell:

Please refer to your New Drug Application (NDA) dated and received December 29, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for (b) (4) (estradiol transdermal system) (b) (4), 0.0375, 0.05, 0.075, and 0.1 mg/day.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is October 29, 2012.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by September 29, 2012.

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

Highlights (HL)

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

Adverse Reactions

Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).

Patient Counseling Information Statement

Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”).**”

Contents: Table of Contents (TOC)

The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.

There should be no zeros or periods behind the whole numbers in the TOC.

Full Prescribing Information (FPI)

Adverse Reactions

Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.

We request that you resubmit labeling that addresses these issues by March 23, 2012. The resubmitted labeling will be used for further labeling discussions.

For more information regarding labeling, please see

<http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

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

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

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

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

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call George Lyght, R.Ph., Sr. Regulatory Project Manager, at (301) 796-0948.

Sincerely,

{See appended electronic signature page}

Audrey Gassman, M.D.
Acting Deputy Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

AUDREY L GASSMAN
03/09/2012



NDA 203752

INFORMATION REQUEST

Noven Pharmaceuticals, Inc.
Attention: Sean M. Russell, Associate Director, Regulatory Affairs
Empire State Building
350 Fifth Avenue, 37th Floor
New York, NY 10118

Dear Mr. Russell:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the estradiol transdermal system.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following information requests and comments. We request a prompt written response by April 27, 2012, in order to continue our evaluation of your NDA. Please also submit your responses via email to rebecca.mcknight@fda.hhs.gov.

1. Provide a copy of your proposed Master Batch Record to the application.
2. Describe the sampling plan for in process testing of the (b) (4) and how it assures consistency throughout the (b) (4) from a quality perspective. Samples should be taken (b) (4)
3. Regarding the Drug Product Release Specification and Stability Testing:
 - a. Provide the methods for all adhesion tests for all sizes of the transdermal system.
 - b. Establish acceptance criteria for all release and stability tests, including a target (in addition to a range) for potency.
 - c. Include in Appearance acceptance criterion an observation for the absence of crystals and/or visible particulates.
 - d. USP <905> does not specify for transdermal systems. Provide a sampling plan for Content Uniformity testing that assures consistency throughout (b) (4)
 - e. Establish tests and acceptance criteria for the following, to be used at release and on stability. Include upper and lower limits where appropriate for all sizes of the transdermal system.

- i. cold flow,
 - ii. adhesion to steel (or other substrate),
 - iii. tack,
 - iv. shear adhesion,
 - v. release liner peel force.
 - f. Establish package integrity or burst test and acceptance criteria.
4. Perform stability challenging studies such as temperature excursions, freeze/thaw, and/or crystal seeding studies to assess the potential for drug substance crystallization.
 5. Acknowledge that you agree that expiry begins [REDACTED] (b) (4)
 6. Provide additional stability data no later than month 4 from the original NDA submission date.
 7. Provide scientific justification to support the amount of residual drug in the proposed TDDS. This may be included in the 3.2.P.2 section of the common technical document (CTD) format discussion of the product and process development and justification for the final formulation and system design. The level of information in the submission should be sufficient enough to demonstrate product and process understanding and assure that a science and risk based approach has been taken to minimize the amount of residual drug in a system after use. The justification for the percent of residual drug and the overall amount of remaining drug will be assessed during review. Refer to the Guidance for Industry – Residual Drug in Transdermal and Related Drug Delivery Systems for additional information.
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM220796.pdf>.
 8. Provide extractable and leachable information for the container closure system.
 9. Delete the phrase [REDACTED] (b) (4) from the DESCRIPTION section of the label.
 10. Provide the *in vitro* drug release method development and validation report supporting the selection of the proposed test. The report should include the following information:
 - a. Detailed description of the *in vitro* drug release method proposed for your product and the developmental parameters (*i.e.*, selection of the equipment/apparatus, *in vitro* drug release media, agitation/rotation speed, pH, assay, sink conditions, etc.) used to select/identify the proposed drug release method as the most appropriate. The testing conditions used for each test should be clearly specified,
 - b. The complete drug release profile data (*individual, mean, SD, profiles*) for your product. The drug release data should be reported as the cumulative percentage of drug being released with time (*the percentage is based on the product's label claim*), and

- c. Include the testing conducted to demonstrate the discriminating capability of the selected drug release test as well as the validation data for the drug release method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.).
11. We could not locate the comparative *in vitro* drug release profiles for the proposed product vs. the reference Vivelle 29.0 cm² patch, except for the proposed 6.6 cm² size product. Provide the comparative drug release profiles for the other size systems along with the raw data and f2 values associated with these calculations.

General Comments:

1. Update the NDC numbers on all carton/containers and the PI.
2. To aid in review of the NDA, provide 3 samples of all sizes of the proposed transdermal system and include the batch numbers associated with the provided drug products. The transdermal systems may be sent to the Attention of:

FDA – White Oak
Rebecca McKnight - CDER/OPS/ONDQA
Bldg. 21, Rm 2667
10903 New Hampshire Avenue
Silver Spring, MD 20993
3. It is recommended to qualify adhesives both prior to and post drug formulation. This insures both optimum product quality attributes in transdermal and topical formulations, and a seamless post-approval change process, in case the raw materials, manufacturing process, or manufacturer of the adhesive(s) is changed. The following tests are not required for release of the drug product but rather to qualify the adhesive component. Proper qualification of the adhesives used to formulate the drug product may include the following when applicable:
 - a. Readily available polymer - molecular weight distribution, polydispersity, spectroscopic analysis (IR), thermal analysis, intrinsic viscosity, and measurement of residual monomers, dimers, solvents, heavy metals, catalysts and initiators.
 - b. Adhesive as a Lamina (without drug substance or other adhesive matrix excipients) - residual solvents, extractable and leachables, and an evaluation for peel, tack, shear, and adhesion.
 - c. Adhesive in the final Drug Product - residual monomers, dimers and solvents, viscosity, IR identification, loss on drying, impurities, and content uniformity. Functionality parameters to be assessed include but are not limited to peel, shear, adhesion, tack, *in vitro* drug release, and *in vitro* drug permeation.
4. As migration of the drug substances and excipients within the individual drug product throughout shelf life is of potential concern, a complete understanding of the (b) (4), specifically where the active drug substances are within the (b) (4) and what changes

the ^{(b) (4)} may undergo from the time of manufacture to product expiry is suggested. Useful tools to support your explanation for the above may include SEM imaging and Elemental Mapping (via SEM-EDX) of the cross section and surface of the Transdermal Drug Delivery System (TDDS) at release and through the end of stability. Information should be included in the 3.2.P.2 section of the common technical document (CTD) format discussion of the product and process development.

If you have any questions, call Rebecca McKnight, Regulatory Project Manager, at (301) 796-1765.

Sincerely,

{See appended electronic signature page}

Terrance Ocheltree, Ph.D., R.Ph.
Division Director
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

/s/

TERRANCE W OCHELTREE
03/08/2012



NDA 203752

NDA ACKNOWLEDGMENT

Noven Pharmaceuticals Inc.
Attention: Sean M. Russell
Associate Director, Regulatory Affairs
11960 Southwest 144th St.
Miami, FL 33186

Dear Mr. Russell:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: (b) (4) (estradiol transdermal system)

Date of Application: December 29, 2011

Date of Receipt: December 29, 2011

Our Reference Number: NDA 203752

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 27, 2012, in accordance with 21 CFR 314.101(a).

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have any questions, call me, at (301) 796-0948.

Sincerely,

{See appended electronic signature page}

George Lyght, RPh.
Sr. Regulatory Health Project Manager
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

GEORGE A LYGHT
01/17/2012