CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-538/S-015

ADMINISTRATIVE DOCUMENTS

EXCLUSIVITY SUMMARY for NDA # 20-538 SUPPL # 015

Trade Name Vivelle-Dot™ Generic Name estradiol transdermal system 0.0275, 0.0375, 0.05, 0.075 and 0.1 mg/day

Applicant Name Novartis Pharmaceuticals Corporation HFD-580

Approval Date November 19, 2001

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain 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 an original NDA? YES/___/ NO /_X__/

   b) Is it an effectiveness supplement? YES /_X__/ NO /___/

      If yes, what type(SE1, SE2, etc.)? SE-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 /_X__/

      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.

      Bioequivalence data was submitted to demonstrate that the new lower dose of Vivelle-Dot was bioequivalent to the lowest dose of Vivelle (NDA 20-323). Clinical data for Vivelle was referenced in support of the osteoporosis prevention indication.

      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 /_X__/

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 /_X__/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /_X__/ NO /___/

If yes, NDA #20-323 _____ Drug Name Vivelle®

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES /___/ NO /___/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (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 #

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

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 #

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 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

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 9.

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(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 9:**

(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:

Investigation #1, Study #

Investigation #2, Study #

Investigation #3, Study #

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 /___/
Investigation #3	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:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(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 /___/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(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"):

Investigation #__, Study #

Investigation #__, Study #

Investigation #__, Study #

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

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

Investigation #1

IND # _____ YES /___/ NO /___/ Explain:

Investigation #2

IND # _____ YES /___/ NO /___/ Explain:

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

Investigation #1

YES /___/ 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: _____

_____

_____

{See appended electronic signature page}

_____

Signature of Preparer Date

Title: Regulatory Project Manager

{See appended electronic signature page}

Signature of Office or Division Director Date

cc:
Archival NDA 20-538/S-015
HFD-580/Division File
HFD-580/D.Moore
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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

/s/

Diane V. Moore
11/14/01 01:10:55 PM
CSO

Daniel A. Shames
11/16/01 03:06:27 PM
MEDICAL OFFICER

Patent Submission

Time Sensitive Patent Information

pursuant to 21 C.F.R. 314.53

for VIVELLE-DOT™

NDA # 20-538

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

- Trade Name: VIVELLE-DOT™
- Active Ingredient(s): ESTRADIOL
- Strength(s): 0.025 mg/24hrs; 0.0375 mg/24hrs; 0.05 mg/24hrs; 0.075mg/24hrs; 0.1mg/24hrs
- Dosage Form: Film, Extended Release, Transdermal
- Approval Date:

A. This section should be completed for each individual patent

U.S. Patent Number: 5,474,783
Expiration Date: December 12, 2012
Type of Patent--Indicate all that apply:

1.	Drug substance (Active Ingredient)		Y	N
2.	Drug Product (Composition/Formulation		√Y	N
3.	Method of Use	Y N		

a. If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by patent

Name of Patent Owner: Noven Pharmaceuticals, Inc.

U.S. Agent (if patent owner or applicant does not reside or have place of business in the US):

(for purposes of this document only)

A. This section should be completed for each individual patent

U.S. Patent Number: 5,656,286
Expiration Date: August 12, 2014
Type of Patent--Indicate all that apply:

4.	Drug substance (Active Ingredient)		Y	N
5.	Drug Product (Composition/Formulation		√Y	N
6.	Method of Use	Y N		

a. If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by patent:

Name of Patent Owner: Noven Pharmaceuticals, Inc.

U.S. Agent (if patent owner or applicant does not reside or have place of business in the US):

(for purposes of this document only)

A. This section should be completed for each individual patent

U.S. Patent Number: 5,958,446
Expiration Date: December 12, 2012
Type of Patent--Indicate all that apply:

		Y	N
1.	Drug substance (Active Ingredient)		
2.	Drug Product (Composition/Formulation	√Y	N
3.	Method of Use	Y	N

a. If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by patent

---

Name of Patent Owner: Noven Pharmaceuticals, Inc.

U.S. Agent (if patent owner or applicant does not reside or have place of business in the US):

(for purposes of this document only)

A. This section should be completed for each individual patent

U.S. Patent Number: 6,024,976
Expiration Date: January 7, 2014
Type of Patent--Indicate all that apply:

		Y	N
4.	Drug substance (Active Ingredient)		
5.	Drug Product (Composition/Formulation	√Y	N
6.	Method of Use	Y	N

a. If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by patent:

Name of Patent Owner: Noven Pharmaceuticals, Inc.

U.S. Agent (if patent owner or applicant does not reside or have place of business in the US):

(for purposes of this document only)

B. The following declaration statement is required if any of the above listed patents have Composition/Formulation or Method of Use claims.

The undersigned declares that the above stated United States Patent Number 5,474,783 covers the composition, formulation and/or method of use of Vivelle-Dot™ (name of drug product). This product is:

- _____ currently approved under section 505 of the Federal Food, Drug, _____ and Cosmetic Act)

or

- ___√___ the subject of this application for which approval is being sought.)

B. The following declaration statement is required if any of the above listed patents have Composition/Formulation or Method of Use claims.

The undersigned declares that the above stated United States Patent Number 5,656,286 covers the composition, formulation and/or method of use of Vivelle-Dot™ (name of drug product). This product is:

- _____ currently approved under section 505 of the Federal Food, Drug, _____ and Cosmetic Act)

or

- ___√___ the subject of this application for which approval is being sought.)

B. The following declaration statement is required if any of the above listed patents have Composition/Formulation or Method of Use claims.

The undersigned declares that the above stated United States Patent Number 5,958,446 covers the composition, formulation and/or method of use of Vivelle-Dot™ (name of drug product). This product is:

- _____ currently approved under section 505 of the Federal Food, Drug, _____ and Cosmetic Act)

or

- ___√___ the subject of this application for which approval is being sought.)

B. The following declaration statement is required if any of the above listed patents have Composition/Formulation or Method of Use claims.

The undersigned declares that the above stated United States Patent Number 6,024,976 covers the composition, formulation and/or method of use of Vivelle-Dot™ (name of drug product). This product is:

- _____ currently approved under section 505 of the Federal Food, Drug, _____ and Cosmetic Act)

or

- ___√___ the subject of this application for which approval is being sought.)

Signed: Carol G. Loeschorn

Carol A. Loeschorn

Title: Senior Patent Attorney

Date: November 17, 2000

Telephone Number: (908)522-6932

A copy of the above information should be submitted to the NDA with the original application or as correspondence to an existing NDA. For patents issued after the NDA is filed or approved, the applicant is required to submit the information within 30 days of the date of issuance of the patent.

To expedite publication in the ***The Orange Book,**** a deskcopy should be submitted to:

Mailing address: (US Mail)

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Data Management and Services
Information Services Team
HFD-93
5600 Fishers Lane
Rockville, MD 20857

OF

Location address: (for FedX deliveries)

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Data Management and Services
Information Services Team
Building A
HFD-93 Room #235
Nicholson Lane Research Center
5516 Nicholson Lane
Kensington, MD 20895

OR faxed to: (301)-594-6463

* - Please note that patents for unapproved compositions, formulations, or uses will NOT be published in the ***The Orange Book***.

NOVARTIS

Novartis Pharmaceuticals Corporati
East Hanover, New Jersey

sNDA No. 20-538

Vivelle-DOT™
(estradiol transdermal system)
Supplemental New Drug Application

NOVARTIS CERTIFICATION
IN COMPLIANCE WITH THE
GENERIC DRUG ENFORCEMENT ACT OF 1992

NOVARTIS PHARMACEUTICALS CORPORATION certifies that it did not and will not use in any capacity the services of any person debarred under section 306(a) or 306(b) of the Federal Food, Drug and Cosmetic Act in connection with this application.

1/22/01
Date

Lynn Mellor
Lynn Mellor
Associate Director
Drug Regulatory Affairs

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 20-538 /SE-1 - 015

Drug Vivelle-Dot (transdermal system) 0.0275 mg Applicant Novartis Pharmaceuticals

RPM D. Moore Phone (301) 827-4260

X505(b)(1)
☐505(b)(2) Reference listed drug

☐Fast Track ☐Rolling Review Review priority: XS ☐P

Pivotal IND(s) IND 40,773 also NDA 20-323

Application classifications:
Chem Class 3
Other (e.g., orphan, OTC)

PDUFA Goal Dates:
Primary November 23, 2001
Secondary January 23, 2002

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

GENERAL INFORMATION:

- User Fee Information: ☐ User Fee Paid
  ☐ User Fee Waiver (attach waiver notification letter)
  X User Fee Exemption

- Action Letter..... XAP ☐ AE ☐NA

- Labeling & Labels
  - FDA revised labeling and reviews..... X
  - Original proposed labeling (package insert, patient package insert) X
  - Other labeling in class (most recent 3) or class labeling..... class labeling
  - Has DDMAC reviewed the labeling? .....(see September 24, 2001 meeting minutes) ..... X Yes (include review) ☐ No
  - Immediate container and carton labels X
  - Nomenclature review ..... N/A; OPDRA Label Review

- Application Integrity Policy (AIP) ☐ Applicant is on the AIP. This application ☐ is X is not on the AIP.
  - Exception for review (Center Director's memo)..... N/A
  - OC Clearance for approval..... N/A

- Status of advertising (if AP action) ☐ Reviewed (for Subpart H – attach review) — X Materials requested in AP letter

- Post-marketing Commitments — N/A
  - Agency request for Phase 4 Commitments..... N/A
  - Copy of Applicant's commitments ..... N/A

- Was Press Office notified of action (for approval action only)?..... ☐ Yes ☐ No
  - Copy of Press Release or Talk Paper.....

- Patent
  - Information [505(b)(1)] X
  - Patent Certification [505(b)(2)]..... X
  - Copy of notification to patent holder [21 CFR 314.50 (i)(4)]..... N/A

- Exclusivity Summary X

- Debarment Statement X

- Financial Disclosure
  - No disclosable information ..... N/A
  - Disclosable information – indicate where review is located ..... X (separate review)

- Correspondence/Memoranda/Faxes X

- Minutes of Meetings X
  - Date of EOP2 Meeting no meeting held
  - Date of pre NDA Meeting no meeting held
  - Date of pre-AP Safety Conference N/A for efficacy supplement

- Advisory Committee Meeting ..... N/A
  - Date of Meeting ..... N/A
  - Questions considered by the committee ..... N/A
  - Minutes or 48-hour alert or pertinent section of transcript ..... N/A

- Federal Register Notices, DESI documents ..... N/A

CLINICAL INFORMATION: **Indicate N/A (not applicable), X (completed), or add a comment.**

- Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo) X

- Clinical review(s) and memoranda X

- ♦ Safety Update review(s) X

- ♦ Pediatric Information
  X Waiver/partial waiver (Indicate location of rationale for waiver) ☐ Deferred
  Pediatric Page..... February 12, 2001 amendment
  ☐ Pediatric Exclusivity requested? ☐ Denied ☐ Granted X Not Applicable

- ♦ Statistical review(s) and memoranda ..... N/A

- ♦ Biopharmaceutical review(s) and memoranda..... X

- ♦ Abuse Liability review(s) ..... N/A
  Recommendation for scheduling ..... N/A

- ♦ Microbiology (efficacy) review(s) and memoranda ..... N/A

- ♦ DSI Audits ..... N/A
  ☐Clinical studies ☐ bioequivalence studies ..... N/A

CMC INFORMATION: **Indicate N/A (not applicable), X (completed), or add a comment.**

- ♦ CMC review(s) and memoranda X

- ♦ Statistics review(s) and memoranda regarding dissolution and/or stability ..... N/A ~~see CMC review~~

- ♦ DMF review(s) ..... N/A

- ♦ Environmental Assessment review/FONSI/Categorical exemption X

- ♦ Micro (validation of sterilization) review(s) and memoranda ..... N/A

- ♦ Facilities Inspection (include EES report)
  Date completed April 30, 2001 ..... X Acceptable ☐ Not Acceptable

- ♦ Methods Validation ..... ☐ Completed ☒ Not Completed

PRECLINICAL PHARM/TOX INFORMATION: **Indicate N/A (not applicable), X (completed), or add a comment.**

- ♦ Pharm/Tox review(s) and memoranda ..... N/A

- Safety Update review(s) X

- Pediatric Information
  X Waiver/partial waiver (Indicate location of rationale for waiver) ☐ Deferred
  Pediatric Page..... February 12, 2001 amendment

  ☐ Pediatric Exclusivity requested? ☐ Denied ☐ Granted X Not Applicable

- Statistical review(s) and memoranda ..... N/A

- Biopharmaceutical review(s) and memoranda..... X

- Abuse Liability review(s) ..... N/A
  Recommendation for scheduling ..... N/A

- Microbiology (efficacy) review(s) and memoranda ..... N/A

- DSI Audits ..... N/A
  ☐Clinical studies ☐ bioequivalence studies ..... N/A

CMC INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- CMC review(s) and memoranda X

- Statistics review(s) and memoranda regarding dissolution and/or stability ..... see CMC review

- DMF review(s) ..... N/A

- Environmental Assessment review/FONSI/Categorical exemption X

- Micro (validation of sterilization) review(s) and memoranda ..... N/A

- Facilities Inspection (include EES report)
  Date completed April 30, 2001 ..... X Acceptable ☐ Not Acceptable

- Methods Validation ..... ☐ Completed X Not Completed

PRECLINICAL PHARM/TOX INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- Pharm/Tox review(s) and memoranda ..... N/A

- Memo from DSI regarding GLP inspection (if any) ..... N/A
- Statistical review(s) of carcinogenicity studies ..... N/A
- CAC/ECAC report ..... N/A

USER FEE VALIDATION SHEET

NDA # 20-538 Supp. Type & # SE 8-015 UFID # N/A
(e.g., N000, SLR001, SE1001, etc.)

1. YES (NO) User Fee Cover Sheet Validated? MIS_Elements Screen Change(s):

2. YES (NO) APPLICATION CONTAINS CLINICAL DATA?
(Circle YES if NDA contains study or literature reports of what are explicitly or implicitly represented by the application to be adequate and well-controlled trials. Clinical data do not include data used to modify the labeling to add a restriction that would improve the safe use of the drug (e.g., to add an adverse reaction, contraindication or warning to the labeling).

(REF) IF NO CLINICAL DATA IN SUBMISSION, INDICATE IF CLINICAL DATA ARE CROSS REFERENCED IN ANOTHER SUBMISSION. NDA 20-323

3. YES (NO) SMALL BUSINESS EXEMPTION

4. YES (NO) WAIVER GRANTED

5. YES (NO) NDA BEING SPLIT FOR ADMINISTRATIVE CONVENIENCE (other then bundling).
If YES, list all NDA #s, review division(s) and those for which an application fee applies.

NDA #	Division		
N_____	HFD-_____	Fee	No Fee
N_____	HFD-_____	Fee	No Fee

6. (YES) NO BUNDLING POLICY APPLIED CORRECTLY? No Data Entry Required
(Circle YES if application is properly designated as one application or is properly submitted as a supplement instead of an original application. Circle NO if application should be split into more than one application or be submitted as an original instead of a supplement. If NO, list resulting NDA #s and review division(s).

NDA #	Division	NDA #	Division
N_____	HFD-_____	N_____	HFD-_____

7. P (S) PRIORITY or STANDARD APPLICATION?

Diane Marx
PM Signature / Date

Terri G. Rumble 1/30/01
CPMS Concurrence Signature / Date

2/14/00

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center For Drug Evaluation and Research

DATE: October 18, 2001

FROM: The Division of Metabolic and Endocrine Drug Products

TO: The Division of Reproductive and Urologic Drug Products

SUBJECT: Consultation on Vivelle-Dot labeling

The Division of Reproductive and Urologic Drug Products (DRUDP) plans to approve the Vivelle-Dot transdermal estrogen system based on its bioequivalency to the currently approved Vivelle transdermal estrogen system. The following doses of Vivelle are approved for the prevention of postmenopausal osteoporosis: 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day.

In their consult request, DRUDP asks that we review the proposed labeling for the Vivelle-Dot system, paying particular attention to the language for the osteoporosis indication.

Comments

Given that the Vivelle-Dot system is to be approved based on bioequivalency with the original Vivelle system, I can think of no reason why, save mention of the bioequivalency data in the Vivelle-Dot label, that the label for the Vivelle-Dot system should differ from that of the original Vivelle label. That being said, there are some notable differences between the approved labeling for the Vivelle system and the proposed labeling for the Vivelle-Dot system. These include:

1. Indications and Usage
   The language for the Prevention of postmenopausal osteoporosis indication for the Vivelle-Dot system should be identical to the wording from the Vivelle system, and they are not.

2. Contraindications:
   Under point one, the Vivelle label has (**see Precautions**), while the Vivelle-Dot has (see Boxed Warning).

3. Pediatric Use:
   The Vivelle system has "The safety and effectiveness in pediatric patients have not been established", whereas, the Vivelle-Dot label proposed additional language about pubertal delay, acceleration of episphyseal closure, etc.

4. Adverse Reactions:
   The entire section of the proposed label differs from that of the Vivelle label.

It is noted that the proposed "Information for the Patient" leaflet for Vivelle-Dot is also different from the Vivelle patient information leaflet. Specifically, the sections describing the effects of estrogen on bone differ between the two products. As mentioned above, the information provided in the patient leaflet for the Vivelle-Dot system should be the same as that for the original Vivelle system.

Eric Colman, MD

cc: consult file

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/s/

Eric Colman
10/22/01 03:39:29 PM
MEDICAL OFFICER

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: 5/18/01	DUE DATE: 10/12/01	OPDRA CONSULT: 01-0120

TO:

Susan Allen, M.D.
Director, Division of Reproduction and Urologic Drug Products
HFD-580

THROUGH:

Diane Moore
Project Manager, Division of Reproduction and Urologic Drug Products
HFD-580

PRODUCT NAME:	**MANUFACTURER:** Noven Pharmaceuticals, Inc.
Vivelle-Dot (estradiol transdermal system) 0.025 mg/day **NDA #:** 20-538/S-015	**DISTRIBUTOR:** Novartis Pharmaceuticals Corporation

SAFETY EVALUATOR: Jennifer Fan, Pharm.D.

SUMMARY: In response to a consult from the Division of Reproduction and Urologic Drug Products (HFD-580), OPDRA conducted a review of the proposed packaging for a lower strength of the drug product "Vivelle-Dot".

OPDRA RECOMMENDATION: Please see review for OPDRA recommendations.

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: 301-827-3246
Fax: 301-443-5161

Martin Himmel, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

HFD-400; Rm. 15B32
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: October 1, 2001

NDA NUMBER: 20-538/S-015

NAME OF DRUG: Vivelle-Dot (estradiol transdermal system), 0.025 mg/day

NDA HOLDER: Novartis

I. INTRODUCTION:

This consult was written in response to a request from the Division of Reproduction and Urologic Drug Products (HFD-580) for assessment of the labeling and packaging of the new lower strength (0.025 mg/day) of the drug product, *Vivelle-Dot.*

PRODUCT INFORMATION

Vivelle-Dot is an estradiol transdermal system that is designed to release 17β-estradiol continuously upon application of intact skin. *Vivelle-Dot*, which is a smaller patch version of *Vivelle*, has been on the market since January 8, 1999. Currently, *Vivelle-Dot* is available as a 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day patch. The sponsor is now submitting a lower strength for *Vivelle-Dot*, 0.025 mg/day. The initial dose of *Vivelle-Dot* is 0.05 mg/day patch twice a week. The indications for this new lower strength are the same as the previously approved higher strengths. Those indications include the treatment of moderate-to-severe vasomotor symptoms associated with menopause, the treatment of vulval and vaginal atrophy, and the treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure.

II. RISK ASSESSMENT:

A search was conducted through the FDA Adverse Event Reporting System *(AERS)* database for all post-marketing safety reports of medication errors reported for terms "viv%", using the Meddra Preferred Term, DRUG MALADMINISTRATION. The search yielded no medication error reports with *Vivelle-Dot.* However, one medication error report (Case# 5431140) was submitted on the confusion between *Vivelle* and *Estraderm.*

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

A. GENERAL COMMENTS

1. The black print on a purple background (back panel of the physician sample carton) is difficult to read.

B. CONTAINER LABEL (0.025 mg/day)

1. The label is identical in design and color to the other strengths. The strengths should be highlighted to the corresponding strength color on the carton labeling.

C. CARTON LABELING (0.025 mg/day; Physician Sample-2 system package, Physician Sample Box-5 of the 2 system package, 8 system package, Box-3 of the 8 system package)

1. We recommend that the statement "Dosage and Administration: See package insert" be revised to state "Usual Dosage: Apply patch twice a week. See package insert."

2. On the Physician Sample Box, which contains 5 of the 2 system package, the "Rx Only" statement should appear on the main panel.

3. The box that contains 3 of the 8 system package resembles in design and color to the box that contains the patient calendar packs of Estraderm. The boxes should be differentiated by using different colors in the lettering or by using a different design on the box.

IV. RECOMMENDATIONS:

OPDRA recommends the above labeling revisions to encourage the safest possible use of the product.

OPDRA would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, R.Ph. at 301-827-3231.

Jennifer Fan, Pharm.D.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

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/s/

Jennifer Fan
10/12/01 03:47:52 PM
PHARMACIST

Jerry Phillips
10/12/01 03:52:45 PM
DIRECTOR

Martin Himmel
10/15/01 10:49:16 AM
MEDICAL OFFICER

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: 5/18/01	DUE DATE: 10/12/01	OPDRA CONSULT: 01-0120

TO:

Susan Allen, M.D.
Director, Division of Reproduction and Urologic Drug Products
HFD-580

THROUGH:

Diane Moore
Project Manager, Division of Reproduction and Urologic Drug Products
HFD-580

PRODUCT NAME:	**MANUFACTURER:** Noven Pharmaceuticals, Inc.
Vivelle-Dot (estradiol transdermal system) 0.025 mg/day **NDA #:** 20-538/S-015	**DISTRIBUTOR:** Novartis Pharmaceuticals Corporation

SAFETY EVALUATOR: Jennifer Fan, Pharm.D.

SUMMARY: In response to a consult from the Division of Reproduction and Urologic Drug Products (HFD-580), OPDRA conducted a review of the proposed packaging for a lower strength of the drug product "Vivelle-Dot".

OPDRA RECOMMENDATION: Please see review for OPDRA recommendations.

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: 301-827-3246
Fax: 301-443-5161

Martin Himmel, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: June 5, 2001

From: Jeanine Best, M.S.N., R.N.
Regulatory Project Manager
Division of Reproductive and Urologic Drug Products (HFD-580)

Subject: Review of Financial Disclosure documents

To: NDA 20-258/S-015

I have reviewed the financial disclosure information submitted by Novartis Pharmaceuticals Corporation in support of their sNDA 20-538/S-015 for Vivelle-Dot™ (estradiol transdermal system).

Approval of Vivelle-Dot™ was based on demonstrating equivalence to Vivelle®. The purpose of this Efficacy Supplement (SE8) is to update the Vivelle-Dot™ label to make it consistent with the Vivelle® label changes approved on August 16, 2000. This supplemental application seeks approval for Vivelle-Dot™ 0.025 mg/day to 0.1 mg/day in the indication "prevention of postmenopausal osteoporosis" based on bioequivalence between Vivelle-Dot™ and Vivelle® and dose proportionality between Vivelle-Dot™ 0.025 mg/day, Vivelle-Dot™ 0.0375 mg/dl, Vivelle-dot 0.05 mg/dl and Vivelle-Dot™— mg/dl. Study 1012 (basis of approval of Vivelle-Dot™) demonstrated bioequivalence of Vivelle-Dot™ 0.1 mg/day and Vivelle™ 0.1 mg/day and dose proportionality between Vivelle-Dot™ 0.05 mg/day and Vivelle-Dot™ 0.1 mg/day. Three additional bioavailability clinical/pharmacology studies were performed with Vivele-Dot™ to demonstrate safety and local tolerability, and adhesion. The study numbers and the results of the review of financial disclosure documents are summarized below:

Study Number/Title	Study Status	Financial Disclosure Review
Study 1012/ A bioequivalence/local skin tolerance study in 12 postmenopausal women (basis of approval for NDA 20-538, Vivelle-Dot™)	Study completed prior to 2/2/99	Appropriate documentation received, no financial disclosure submitted.
Study N09-005 / An open label, single dose, randomized. Four treatment (Vivelle-Dot™ 0.025, 0.0375, 0.05, and 0.1 mg/day) four-period, crossover, bioavailability study in 32 postmenopausal women.	Study completed prior to 2/2/99	Appropriate documentation received, no financial disclosure submitted.
Study N09-004 / An open label, multiple (4) dose, randomized, two-treatment (Vivelle-Dot™ 0.05 mg/day and Vivelle® 0.05 mg/day), two-period, crossover, steady state in 32 postmenopausal women.	Study completed prior to 2/2/99	Appropriate documentation received, no financial disclosure submitted.

Study N09-008 / A two-phase study: Phase 1: An open label, randomized, two-treatment, parallel, comparative study (Vivelle-Dot™ 0.05 mg twice weekly and Climara® 0.05 mg once a week) in 100 postmenopausal women. Phase2: An open label, randomized, two-treatment (Vivelle-Dot™ 0.05 mg and Climara® 0.05 mg), two-way, crossover, bioavailability study in 12 postmenopausal women.	Study completed prior to 2/2/99	Appropriate documentation received, no financial disclosure submitted.

Documents Reviewed:

- Financial Certification Information submitted January 22, 2001
- request for additional Financial Disclosure information submitted May 18, 2001 (a table listing study number, site, number of patients, and investigators)

Study 1012
There were 3 principal and subinvestigators (investigators) at 1 site in this trial.

Study N09-004
There were 3 principal and subinvestigators (investigators) at 1 site in this trial.

Study N09-005
There were 4 principal and subinvestigators (investigators) at 2 sites in this trial.

Study N09-008
There were 3 principal and subinvestigators (investigators) at 1 site in this trial.

All of the aforementioned studies were completed prior to February 2, 1999, therefore, due diligence to obtain financial information from the individual investigators is not required per the financial disclosure regulations. The sponsor has submitted certification (Form FDA 3454) "as the applicant submitting studies that were sponsored by another firm or party other than the applicant" (NDA ownership was transferred from another sponsor), for the requirements under 21 CFR 54.2, that none of the investigators participating in the studies had compensation affecting the outcome of clinical studies or proprietary interests in the product.

Conclusion:
Adequate documentation was submitted to comply with 21 CFR 54. There was no disclosure of financial interests that could bias the outcome of the trials.

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/s/

Jeanine Best
6/5/01 03:35:19 PM
CSO

15-OCT-2001

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 20538/015
Stamp: 23-JAN-2001 Regulatory Due: 23-NOV-2001
Applicant: NOVARTIS PHARMS
59 RT 10
EAST HANOVER, NJ 079361080

Priority: 5S Org Code: 580
Action Goal: District Goal:
Brand Name: VIVELLE-DOT
Established Name:
Generic Name: ESTRADIOL
Dosage Form: TDP (TRANSDERMAL PATCH)
Strength: 0.025,0.0375,ETC MG/DAY

FDA Contacts: A. MITRA (HFD-580) 301-827-4238 , Review Chemist

Overall Recommendation:

ACCEPTABLE on 30-APR-2001 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: 1058171
NOVEN PHARMACEUTICALS INC
11960 SOUTHWEST 144TH ST
MIAMI, FL 33186

DMF No:
AADA No:

Profile: TDP OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 30-APR-2001
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: FINISHED DOSAGE MANUFACTURER

15-OCT-2001

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 20538/015
Stamp: 23-JAN-2001
Regulatory Due: 23-NOV-2001
Applicant: NOVARTIS PHARMS
59 RT 10
EAST HANOVER, NJ 079361080
Priority: 5S
Org Code: 580

Action Goal:
District Goal:
Brand Name: VIVELLE-DOT
Estab. Name:
Generic Name: ESTRADIOL

Dosage Form: (TRANSDERMAL PATCH)
Strength: 0.025,0.0375,ETC MG/DAY

Application Comment: THIS IS AN EFFICACY SUPPLEMENT TO INCLUDE 0.025 MG STRENGTH FOR OSTEOPORESIS (on 31-JAN-2001 by A. MITRA (HFD-580) 301-827-4238)

FDA Contacts: A. MITRA (HFD-580) 301-827-4238 , Review Chemist

Overall Recommendation: ACCEPTABLE on 30-APR-2001 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: 1058171
NOVEN PHARMACEUTICALS INC
11960 SOUTHWEST 144TH ST
MIAMI, FL 33186

DMF No:
AADA:
Responsibilities: FINISHED DOSAGE MANUFACTURER
Profile: TDP
OAI Status: NONE
Estab. Comment: NOVEN MANUFACTURES AND RELEASES THE DRUG PRODUCT (on 31-JAN-2001 by A. MITRA (HFD-580) 301-827-4238)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	31-JAN-2001				MITRAA
SUBMITTED TO DO	01-FEB-2001	GMP			FERGUSONS
DO RECOMMENDATION	27-APR-2001			ACCEPTABLE BASED ON FILE REVIEW	PFIGAROL
OC RECOMMENDATION	30-APR-2001			ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ

NDA 20-538/S-015
Vivelle-Dot™ (estradiol transdermal system) 0.0025 mg/day
Novartis Pharmaceuticals Corporation

User Fee Information

This Supplemental Application references clinical data previously reviewed in another application. This Supplemental Application is exempt from User Fees.

Diane Moore
11/19/01

NDA 20-538/S-015
Vivelle-Dot™ (estradiol transdermal system) 0.0025 mg/day
Novartis Pharmaceuticals Corporation

Memo from DSI regarding GLP inspection (if any)

No GLP inspection was needed from DSI for this drug product.

Diane Moore
11/19/01

NDA 20-538/S-015
Vivelle-Dot™ (estradiol transdermal system) 0.0025 mg/day
Novartis Pharmaceuticals Corporation

Statistical Review(s) of Carcinogenicity Studies

No carcinogenicity studies were performed with this product.

Diane Moore
11/19/01

NDA 20-538/S-015
Vivelle-Dot™ (estradiol transdermal system) 0.0025 mg/day
Novartis Pharmaceuticals Corporation

CAC/ECAC Report

No CAC/ECAC report was needed for this product.

Diane Moore
6/19/01

NDA 20-538/S-015
Vivelle-Dot™ (estradiol transdermal system) 0.0025 mg/day
Novartis Pharmaceuticals Corporation

Methods Validation

Methods validation are pending.

Diane Moore
11/19/01

NDA 20-538/S-015
Vivelle-Dot™ (estradiol transdermal system) 0.0025 mg/day
Novartis Pharmaceuticals Corporation

Advertising Material

No advertising material has been submitted.

Diane Moore
11/19/01

NDA 20-538/S-015
Vivelle-Dot™ (estradiol transdermal system) 0.0025 mg/day
Novartis Pharmaceuticals Corporation

Post-marketing Commitments

There were no post-marketing commitments made for this drug product.

Renee Moore
11/19/01

NDA 20-538/S-015
Vivelle-Dot™ (estradiol transdermal system) 0.0025 mg/day
Novartis Pharmaceuticals Corporation

DDMAC Review

DDMAC review comments were included in the labeling meeting held on September 24, 2001 (see meeting minutes of that meeting).

Diane Moore
11/19/01

NDA 20-538/S-015
Vivelle-Dot™ (estradiol transdermal system) 0.0025 mg/day
Novartis Pharmaceuticals Corporation

Statistics review(s) and memoranda regarding dissolution and/or stability

A statistical review of drug stability is not applicable. No statistical data was submitted. All stability data was reviewed in the Chemistry review (see Chemistry reviews #1 page 7. dated October 18, 2001).

Diane Mony
11/19/01

NDA 20-538/S-015
Vivelle-Dot™ (estradiol transdermal system) 0.0025 mg/day
Novartis Pharmaceuticals Corporation

DMF Review(s)

No Drug Master Files were referenced for this NDA. Therefore, no DMF reviews were needed.

Diane Moore
11/19/01

NDA 20-538/S-015
Vivelle-Dot™ (estradiol transdermal system) 0.0025 mg/day
Novartis Pharmaceuticals Corporation

Environmental Assessment

A categorical exclusion is claimed for this NDA supplement in accordance with 21 CFR part 25.31 (b), as amended in the 29-Jul-1997 Federal Register. The sponsor submitted the expected introductory concentration (EIC) calculation for Vivelle-Dot on October 16, 2001. This was found to be satisfactory (see Chemistry Review #1 dated October 18, 2001, page 8).

Diane Moore
11/19/01

NDA 20-538/S-015
Vivelle-Dot™ (estradiol transdermal system) 0.0025 mg/day
Novartis Pharmaceuticals Corporation

Micro (validation of sterilization) Review(s) and Memoranda

This is not a sterile product. No microbiology review is required.

Dione Moody
11/19/01

NDA 20-538/S-015
Vivelle-Dot™ (estradiol transdermal system) 0.0025 mg/day
Novartis Pharmaceuticals Corporation

Microbiology Review

This Supplemental Application references the approved product, Vivelle. This Supplemental Application does not require a subsequent microbiology review.

Diane Moore
11/19/01

NDA 20-538/S-015
Vivelle-Dot™ (estradiol transdermal system) 0.0025 mg/day
Novartis Pharmaceuticals Corporation

DSI Audit of Clinical Studies

The clinical study referenced in this application was reviewed under NDA 20-323/S-023. No additional clinical audits from the Division of Scientific Investigation regarding this study are required.

Diane Moore
11/19/01

NDA 20-538/S-015
Vivelle-Dot™ (estradiol transdermal system) 0.0025 mg/day
Novartis Pharmaceuticals Corporation

Division Director's Memo

The application will be signed off at the Division level. No memo is necessary.

Diane Moog
11/19/01

NDA 20-538/S-015
Vivelle-Dot™ (estradiol transdermal system) 0.0025 mg/day
Novartis Pharmaceuticals Corporation

Division Deputy Director's Memo

The Division Deputy Director is acting as Division Director. The application will be signed off at the Division level The Medical Team Leader Memo summarizes the application. No Division Deputy Director memo is necessary.

Diane Moore
11/19/01

NDA 20-538/S-015
Vivelle-Dot™ (estradiol transdermal system) 0.0025 mg/day
Novartis Pharmaceuticals Corporation

Pediatric Page

This supplemental application is not being approved during this cycle. No Pediatric Page is needed.

Diane Moore
11/19/01

NDA 20-538/S-015
Vivelle-Dot™ (estradiol transdermal system) 0.0025 mg/day
Novartis Pharmaceuticals Corporation

Abuse Liability review(s)

This product does not require an abuse liability review.

Diane Moore
11/19/01

NDA 20-538/S-015
Vivelle-Dot™ (estradiol transdermal system) 0.0025 mg/day
Novartis Pharmaceuticals Corporation

Advisory Committee Meeting Minutes

This application was not the subject of an Advisory Committee Meeting.

Diane Moore
11/19/04

NDA 20-538/S-015
Vivelle-Dot™ (estradiol transdermal system) 0.0025 mg/day
Novartis Pharmaceuticals Corporation

Federal Register Notices

This application was not the subject of any Federal Register Notices.

Diane Moody
11/19/01

Memorandum for the Record

Date: November 15, 2001

From: M. Welch (HFD-715)

To: D. Moore (HFD-580)

Re: NDA 20-538 (S-014/S-015)
Vivelle Dot™ (estradiol transdermal system)

As NDA 20-538 Supplements 014 and 015 do not involve new clinical efficacy trials, written statistical reviews are not necessary.

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/s/

Mike Welch
11/20/01 12:20:08 PM
BIOMETRICS

Team Leader Memorandum

NDA:	**20-538/Supplement 14 (S-014), Supplement 15 (S-015)**
Drug:	Vivelle-Dot™
Indications:	1. Treatment of moderate-to-severe vasomotor symptoms associated with the menopause 2. Treatment of vulvar and vaginal atrophy 3. Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure 4. Prevention of postmenopausal osteoporosis (**S-015** only)
Dosage/Form/Route:	0.0375 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day transdermal system (**S-014**) 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day transdermal system (**S-015**))
Applicant:	Novartis Pharmaceutical Corporation
Original Submission Date:	January 18, 2001 (**S-014**) January 22, 2001 (**S-015**)
Primary Review Completed:	November 6, 2001
Date of Memorandum:	November 9, 2001

Background and Issues:

Vivelle-Dot™ in doses of 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day was approved under NDA 20-538 on January 8, 1999. The approval of Vivelle-Dot™ was based on its bioequivalence to Vivelle® (NDA 20-323).

Vivelle® (0.0375 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day) was approved on October 28, 1994. The originally approved labeling for Vivelle contained restrictive language for the 0.0375 mg/day dose, "Some women taking the 0.0375 mg/day dosage may experience a delayed onset of efficacy". This statement had been included in the label because there was a discrepancy between the two trials in the original NDA with respect to the efficacy of the 0.0375 mg/day dose. In NDA 20-323, S-021, the Sponsor submitted data from a 3rd randomized, double-blind, parallel group, placebo-controlled trial which demonstrated that the 0.0375 mg/day dose was effective in the treatment of vasomotor symptoms with the effectiveness demonstrated by week 4 and maintained through week 12. On February 25, 2000, NDA 20-323, S-021 was approved with a change to the label, which removed the restrictive language on the 0.0375 mg dose. The Vivelle® label includes a figure that presents the efficacy of the 0.0375 mg/day dose for the treatment of vasomotor symptoms at 4, 8, and 12 weeks. While four doses (0.0375, 0.05, 0.075 and 0.1 mg/day) of Vivelle® are approved for the treatment of vasomotor symptoms, the label recommends initiation of the therapy at the 0.0375 mg/day dose. On August 16, 2000, NDA 21-167 and NDA 20-323, S-023 for Vivelle® 0.025 mg/day were approved for the indication of prevention of postmenopausal osteoporosis.

In NDA 20-538, **S-014**, the Sponsor is seeking to remove (based on Vivelle-Dot™ bioequivalence to Vivelle®) the restrictive language concerning the efficacy of the 0.0375 mg/day dose of Vivelle-Dot™ and to incorporate in to the Vivelle-Dot™ label, the labeling changes that were approved on February 25, 2000 for Vivelle®.

In NDA 20-538, **S-015**, the Sponsor is seeking to gain the indication of prevention of postmenopausal osteoporosis for the 0.025-mg dose of Vivelle-Dot™ based on the bioequivalence of Vivelle-Dot™ to Vivelle®.

There were no Preclinical Pharmacology issues, as Vivelle-Dot™ is an approved drug and the Sponsor is seeking approval (**S-015**) of a lower dose than those already approved. Updated stability information for the 0.025 mg/day dosage strength was submitted in an amendment, dated October1, 2001 to **S-015**. In that same amendment, the Sponsor incorporated the acceptance criteria for ———— The sponsor provided the EIC calculation in support of the categorical exclusion claim for Environmental Assessment in an amendment, dated 10-16-01. These amendments were both acceptable. From the Chemistry, Manufacturing and Control view, both supplements can be approved.

There is no new clinical efficacy data presented in either **S-014** or **S-015**. In **S-015**, the Sponsor requests a biowaiver for the 0.025mg/day strength based on the following clinical pharmacology data:

Vivelle-Dot™was shown to be bioequivalent to Vivelle® at the highest strength of 0.1 mg/day in the original NDA 20-538 (January 8, 1999).

Vivelle-Dot™ is bioequivalent to Vivelle® at 0.05 mg/day following multiple dose administration at steady state. This is the result of a multiple dose steady state bioequivalence study (submitted in **S-015**) which was conducted in 32 healthy postmenopausal women. Each woman received a 5 cm^2 (0.05 mg/day) Vivelle-Dot™ system every 84 hours for 4 dosing intervals, followed by a 1 week washout period and then a 14.5 cm^2 Vivelle® system every 84 hours for 4 dosing intervals.

Different doses of Vivelle-Dot™ are compositionally proportional as they are cut from the same laminate.

In vitro dissolution profiles of all strengths of Vivelle-Dot™ are comparable (F2>50).

The pharmacokinetics of Vivelle-Dot™ are dose proportional over the dose range of 0.025 to 1 mg/day. This was result of data presented in **S-015** of an open-label, single dose randomized, 4-treatment, 4-period crossover study in 32 healthy postmenopausal women who were treated with each of four doses of Vivelle-Dot (0.025, 0.0375, 0.05 and 0.1 mg/day).

Adhesion data for Vivelle-Dot™ was collected in two bioavailability studies (N09-004, N09-005) and one adhesion study (N09-008) submitted in **S-015**. Based on the combined adhesion data (see Clinical Pharmacology review), about 85% of Vivelle-Dot™ transdermal systems adhered completely over a 3.5 day wear period, while 12 % had edges lift off and 4% were "half off". About 3% of the transdermal systems detached completely during the 3.5 day wear period and were reapplied or replaced. Eighty percent (80%) of the systems evaluated in the three studies were the 0.05 mg/day strength of Vivelle-Dot™.

From a Clinical Pharmacology view both **S-014** and **S-015** are acceptable. Based on the Clinical Pharmacology, the Clinical reviewer recommends approval of both supplements. In addition to the removal of the restrictive language for the 0.0375mg/day dose and the addition of the 0.025 mg/day dose for the treatment of osteoporosis, the Division has recommended that the Vivelle-Dot label conform to the 1995 Draft Labeling Guidance for Estrogen and Estrogen/Progestin Products. I concur that **S-014** and **S-015** should be approved pending submission and receipt of the recommended changes to the label (see Clinical review). The recommended revised labels are included in this action package.

. Shelley R. Slaughter, MD. Ph.D.

Addendum to the Medical Officer Team Leader Review

On November 6, 2001, November8, 2001, November 13, 2001, November 15, 2001 and November 16, 2001, Novartis submitted revised labeling to the Agency. The Sponsor's submissions largely retained the language in the original submission of January 22, 2001 and failed to incorporate most of the Agency's substantial number of recommended labeling revisions as sent in the October 24, 2001information request letter. The Sponsor was asked to provide a single "Adverse Events" table summarizing the most frequently reported adverse experiences/medical events (≥2%) by body system for the adequately controlled trials of Vivelle®. None of the Sponsor's submissions have included this requested table. The Sponsor has indicated that a different company conducted two of the adequate and well-controlled trials during a different time period and different dictionaries to define adverse events terms were utilized. In a teleconference of November 13, 01, the Sponsor indicated to the Agency that because of the need to involve another company and the discrepancy in dictionary terms, it would take several months to compile and submit the requested adverse events table. Therefore, my recommendation is that **S-014** and **S-015** receive approvable actions for this review cycle.

Shelley R. Slaughter, M.D., Ph.D.
November 16, 2001

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/s/

Shelley Slaughter
11/19/01 03:27:26 PM
MEDICAL OFFICER

Combined review S-014 and S-015

Daniel A. Shames
11/19/01 05:44:06 PM
MEDICAL OFFICER

Division of Reproductive and Urologic Drug Products

ADMINISTRATIVE REVIEW OF APPLICATION

Application Number: 20-538

Name of Drug: Vivelle-Dot™

Sponsor: Novartis Pharmaceuticals Corporation

Material Reviewed: Supplement-015

Submission Date: January 22, 2001

Receipt Date: January 23, 2001

Filing Date: March 24, 2001

User-Fee Goal Date(s): November 23, 2001; January 23, 2002

Proposed Indication: Prevention of postmenopausal osteoporosis

Other Background Information: NDA 21-167; NDA 20-323/S-023

Review

PART I: OVERALL FORMATTING[a]

Y=Yes (Present), N=No (Absent)

	Y	N	COMMENTS (list volume & page numbers)
1. Cover Letter (original signature)	X		Volume 1
2. Form FDA 356h (original signature)	X		Volume 1
a. Reference to DMF(s) & Other Applications	X		In cover letter
3. Patent information & certification	X		Volume 1, page 13-1
4. Debarment certification (note: must have a definitive statement)	X		Volume 1, page 16-1
5. Financial Disclosure	X		Volume 1, page 19-1
6. Comprehensive Index	X		Volume 1, page 1-1 through 1-5

7. Pagination	X		Entire submission
8. Summary Volume	X		Volume 1, pages 3-1 through 3-102
9. Review Volumes	X		Volumes 3 through Volume 19
10. Labeling (PI, container, & carton labels)	X		Volumes 1 and 2
a. unannotated PI	X		Volume 2, page 2-2 through 2-22
b. annotated PI	X		Volume 1, page 3-2 through 3-23
c. immediate container		X	Volume 1, page 2-25 through 2-26
d. carton		X	Volume 1, page 2-27 through 2-33
e. foreign labeling (English translation)		X	Vivelle-Dot is not currently marketed in foreign countries
11. Foreign Marketing History	X		Volume 1, page 3-25 Vivelle-Dot has been submitted in ———and ———————for marketing authorization
12. Case Report Tabulations (CRT) (paper or electronic) (by individual patient data listing or demographic)		X	Referenced to NDA 21-167
13. Case Report Forms (paper or electronic) (for death & dropouts due to adverse events)		X	Referenced to NDA 21-167

Y=Yes (Present), N=No (Absent)

PART II: SUMMARY[b]

Y=Yes (Present), N=No (Absent)

	Y	N	COMMENTS (list volume & page numbers)
1. Pharmacologic Class, Scientific Rationale, Intended Use, & Potential Clinical Benefits		X	Referenced to NDA 21-167 and NDA 20-323/S-023 Volume 1, page 3-22 (dated 10/19/99)
2. Summary of Each Technical Section			
a. Chemistry, Manufacturing, & Controls (CMC)	X		Referenced to NDA 20-323/S-021
b. Nonclinical Pharmacology/Toxicology		X	Not applicable as this drug product is already approved at higher dosage strengths
c. Human Pharmacokinetic & Bioavailability	X		Volume 1, page 3-61
d. Microbiology		X	Not applicable; this dosage strength is already approved in NDA 21-167
e. Clinical Data & Results of Statistical Analysis	X		Volume 1, page 3-68
3. Discussion of Benefit/Risk Relationship & Proposed Postmarketing Studies	X		Referenced to NDA 21-167 and NDA 20-323/S-023 (Volume 1, page 3-86 dated 10/19/00)
4. Summary of Safety	X		Referenced to NDA 20-323/S-021
5. Summary of Efficacy	X		Referenced to NDA 20-323/S-021

Y=Yes (Present), N=No (Absent)

PART III: CLINICAL/STATISTICAL SECTIONS[c]

Y=Yes (Present), N=No (Absent)

	Y	N	COMMENTS (list volume & page numbers)
1. List of Investigators	X		Volume 10, page 8-3
2. Controlled Clinical Studies			
a. Table of all studies	X		Volume 10, page 8-95
b. Synopsis, protocol, related publications, list of investigators, & integrated clinical & statistical report for each study (including completed, ongoing, & incomplete studies)	X		Volume 10, 8-1 through 8-43
c. Optional overall summary & evaluation of data from controlled clinical studies	X		Volume 10, 8-1 through 8-8
3. Integrated Summary of Efficacy (ISE)		X	Referenced to NDA 21-167 and NDA 20-323/S-023 (volume 53, page 8-1 that refers to Vol. 5, page 8-108, dated 10/19/99)
4. Integrated Summary of Safety (ISS)		X	Referenced to NDA 21-167 and NDA 20-323/S-023 (volume 56, page 8-2, dated 10/19/99)
5. Drug Abuse & Overdosage Information		X	Referenced to NDA 21-167 and NDA 20-323/S-023 (volume 56, page 8-1, dated 10/19/99)
6. Integrated Summary of Benefits & Risks of the Drug	X		Referenced to NDA 21-167 and NDA 20-323/S-023 (volume 56, page 8-2, dated 10/19/99)
7. Gender/Race/Age Safety & Efficacy Analysis Studies		X	

Y=Yes (Present), N=No (Absent)

PART IV: MISCELLANEOUS

Y=Yes (Present), N=No (Absent)

	Y	N	COMMENTS (list volume & page numbers)
1. Written Documentation Regarding Drug Use in the Pediatric Population	X		Requested a waiver for pediatric population; Volume 1, page 20-1
2. Diskettes			
a. Proposed unannotated labeling in MS WORD 8.0	X		Volume 1
b. Stability data in SAS data set format		X	
c. Efficacy data in SAS data set format		X	
d. Biopharmacological information & study summaries in MS WORD 8.0		X	
e. Animal tumorigenicity study data in SAS data set format		X	
3. User-fee payment receipt		X	This supplement does not require User fees as it is based on bioequivalence data

Y=Yes (Present), N=No (Absent)

[a] "GUIDELINE ON FORMATTING, ASSEMBLING, AND SUBMITTING NEW DRUG AND ANTIBIOTIC APPLICATIONS" (FEBRUARY 1987).

[b] "GUIDELINE FOR THE FORMAT AND CONTENT OF THE SUMMARY FOR NEW DRUG AND ANTIBIOTIC APPLICATIONS" (FEBRUARY 1987).

[c] "GUIDELINE FOR THE FORMAT AND CONTENT OF THE CLINICAL AND STATISTICAL SECTIONS OF NEW DRUG APPLICATIONS" (JULY 1988).

Additional Comments:

Conclusions: This efficacy supplement references data from previously approved NDA supplements and bioequivalence studies. The supplement can be filed from a regulatory perspective.

_____

Regulatory Health Project Manager

_____

Concurrence

cc:

Original NDA
HFD-580/Div. Files
HFD-580/PM/D.Moore
HFD-580/S.Allen/D.Shames
HFD-580/S.Slaughter/P.Price/M.Rhee/A.Mitra/A.Jordan/K.Raheja/A.Parekh/V.Jarugula
draft: May 14, 2001
final: May 15, 2001

ADMINISTRATIVE REVIEW

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

/s/

Diane V. Moore
5/15/01 05:32:48 PM
CSO

Terri F. Rumble
5/16/01 11:57:30 AM
CSO

Minutes of Teleconference

Date: November 13, 2001 **Time:** 11:00 AM - 11:30 PM **Place:** Parklawn; Ms. Moore's Office

NDA: 20-538/S-014 and S-015 **Drug Name:** Vivelle-Dot (estradiol transdermal system)

Indication: Estrogen Replacement Therapy (ERT)

External Constituent: Novartis Pharmaceuticals, Inc.

Type of Meeting: Labeling Discussion

FDA Lead: Ms. Diane Moore **Sponsor Lead:** Ms. Lynn Mellor

Meeting Recorder: Ms. Diane Moore

FDA Participants:
Diane Moore – Regulatory Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

External Participant:
Lynn Mellor – Associate Director, Drug Regulatory Affairs, Novartis

Meeting Objective: To discuss the sponsor's response to the Division's proposed labeling revisions in the October 24, 2001, Agency letter.

Background: The Division sent the sponsor a letter on October 24, 2001, with proposed labeling revisions for the Vivelle-Dot supplemental applications S-014 and S-015.

Discussion Items:

- the sponsor informed the Division that they were having difficulty in pooling the safety data from the two efficacy trials referenced in the supplemental NDA submissions (S-014 and S-015)
  - the data from the 3-month vasomotor symptom (VMS) trial for Vivelle® was generated by Noven Pharmaceuticals; the data from the 1-year clinical study for the prevention of osteoporosis indication was generated by Novartis Pharmaceuticals; the sponsor is working with Noven Pharmaceuticals to obtain the necessary information
  - a different data base was used in the VMS study from the data base used in the clinical trial for the prevention of osteoporosis indication; the two data bases are not compatible
  - the data dictionaries used in the two studies differ for the adverse events
  - in order to pool the two data-bases, the sponsor must use a special software program and then manually validate the data generated; the sponsor estimates that the time that will be required to accomplish this is 6 to 8 weeks
- the sponsor proposed to have two adverse event tables, one for each study
- the sponsor requested that the Agency consider a [redacted] cut-off instead of the 2% cut-off because the list of 2% adverse events is considerably longer and more cumbersome than a table with [redacted] adverse events

Decisions:

- the Project Manager will inform the reviewers of the above proposals

- **Action Items:**

• **Item:**	**Responsible Party:**	**Due Date:**
• send minutes to sponsor	Ms. Moore	one month

{See appended electronic signature page}

Post Meeting Addendum:

On November 16, 2001, Diane Moore, Regulatory Project Manager contacted Ms. Lynn Mellor and informed her that the Division prefers that only one (pooled) adverse event table be included in the labeling and that the Division prefers that a 2% cut-off be used for adverse events; other estrogen labels will be revised to include 2% adverse event tables.

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/s/

Diane V. Moore
11/19/01 05:19:21 PM

Meeting Minutes

Date: October 29, 2001 **Time:** 3:00 - 3:30 PM **Place:** Parklawn; Rm. 17B43

NDA: 20-538/S-014 and S-015 **Drug Name:** Vivelle-Dot (estradiol transdermal system)

Indication: Estrogen Replacement Therapy (ERT)

Sponsor: Novartis Pharmaceuticals, Inc.

Type of Meeting: Labeling Status Meeting

FDA Lead: Dr. Shelley Slaughter

Meeting Recorder: Ms. Diane Moore

FDA Participants:
Shelley Slaughter, M.D., Ph.D. –Medical Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Phill Price, M.D. - Medical Officer, DRUDP (HFD-580)
Diane Moore – Regulatory Project Manager, DRUDP (HFD-580)
Amit Mitra, Ph.D. - Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)

Meeting Objective: To discuss the labeling response from sponsor.

Background: The information request letter with proposed labeling revisions was sent to the sponsor on October 24, 2001.

On October 26, 2001, Lynn Mellor, from Novartis called with feedback regarding the labeling sent to them in the October 24, 2001, letter. The comments follow:

Discussion Items:

1. **Black Box Warning**
   - the sponsor suggested that we include wording to let women who have a uterus know that they should be taking a progesterone with estrogen (for long term use) in both Physician and Patient Information inserts

2. CMC issue: on page 3, second paragraph, the chemists request that the "17β" be deleted from the term "17β estradiol." The sponsor was told that the first time it is used (as a USP associated name) the "17 β" could be kept. The "17 β" has been deleted in the rest of the text.

3. **INDICATIONS AND USAGE** section (page 10)
   - Item 4. Prevention of postmenopausal osteoporosis — Second sentence that reads, " — The sponsor wants to keep the term in so that it reads —

4. **WARNINGS** section, page 11 under Endometrial cancer subsection,
   - [redacted]

5. In the **Thromboembolic disorders, Venous thromboembolism** subsection, the sentence that reads, "Several epidemiologic studies have found an increased risk of [redacted] thromboembolism (VTE) in users of estrogen replacement therapy . . ." The sponsor wants to include a clause that mentions the studies used orally administered estrogen products. Do we have additional references that include other types of estrogen administration in addition to oral administration?

6. **Gallbladder disease** subsection: In the sentence that reads, "A 2-to 4-fold increase in the risk of gallbladder disease requiring surgery in women receiving postmenopausal estrogens has been reported." The word "oral" has been deleted. Is there new data available to warrant the removal of the word "oral"?

7. Under **PRECAUTIONS** section, item 3, **Elevated blood pressure**, the following two [redacted]

8. Under item [redacted] **Familial hyperlipoproteinemia**, the wording was revised. The sponsor wants to keep the present wording. that reads, "Estrogen therapy may be associated with massive elevations of plasma triglycerides leading to pancreatitis and other complications in patients with familial defects of lipoprotein metabolism." The sponsor has it in their overseas labeling. They have references to support the wording.

9. **Pregnancy Category X** The wording was shortened. The sponsor recalls that some wording from the black box warning was moved here. Is it somewhere else or deleted, or is this an oversight?

10. **Adverse Reactions:**
    - The sponsor says that they cannot pool the data from the VMS and PMO trials. It may be something to do with databases that are inconsistent. Anyway, They do not have data from Vivelle-Dot trials. I told them to use data from Vivelle (since that is the trial data that is being relied upon for approval). [redacted] They want to keep the [redacted] AEs for liability purposes. I told them we were revising all the labels in the class the same.

11. **Patient Information** Insert in the section entitled, "Vivelle-Dot Is Approved For use In the Following Ways:"

- In the first section, last sentence, the labeling reads, "The majority of women do not need estrogen replacement for longer than six months for these symptoms." In order to keep the labeling balanced, the sponsor suggests to add wording to the osteoporosis indication to let patients know that the drug needs to be taken longer than six month period of time such as " a period of time determined by the healthcare provider. The Vivelle label says that when estrogen therapy is discontinued, bone mass . . . ."

12. **WHO SHOULD NOT USE VIVELLE DOT** section, fifth bullet, After childbirth or when breastfeeding a baby subsection,

13. **WHAT ARE THE POSSIBLE RISKS AND SIDE EFFECTS** section, the sponsor is ok with the common side effects, except that they want to add

14. **WHAT CAN I DO TO LOWER MY CHANCES OF GETTING A SERIOUS SIDE EFFECT WITH VIVELLE DOT** section

-

It was suggested to the sponsor that they need to look at their integrated summary of safety and the Vivelle trial AEs for their table so that they can work on it . The Division would be discussing these comments the following week. The sponsor will be sending us a hard copy of their comments. The sponsor sent a formal submission on November 6, 2001.

Decisions:

- 1. **Black Box Warning**
  - this drug product is an estrogen product, not a combination estrogen/progestin product; the indications VMS and VVA are short-term indications that have been granted to estrogen only products; the addition of a progestin when a woman has not had a hysterectomy should be addressed in the **PRECAUTIONS** section where it is addressed
  - the physician should be able to make the determination to add a progestin to a patient's short-term regimen based on knowledge of that individual
- 2.
  - all estrogen labeling is uniformly being revised to remove the "17β" from the term "17 β estradiol" in accordance to proper USAN designation
- 3. **INDICATIONS AND USAGE**
  -
- 4. **WARNINGS**
  -

- In the first section, last sentence, the labeling reads, "The majority of women do not need estrogen replacement for longer than six months for these symptoms." In order to keep the labeling balanced, the sponsor suggests to add wording to the osteoporosis indication to let patients know that the drug needs to be taken longer than six month period of time such as " a period of time determined by the healthcare provider. The Vivelle label says that when estrogen therapy is discontinued, bone mass . . . ."
- **FDA response:**
  - the Agency may consider additional wording regarding the long term use in osteoporosis prevention

12. **WHO SHOULD NOT USE VIVELLE DOT** section, fifth bullet, After childbirth or when breastfeeding a baby subsection,

13. **WHAT ARE THE POSSIBLE RISKS AND SIDE EFFECTS** section, the sponsor is ok

14. **WHAT CAN I DO TO LOWER MY CHANCES OF GETTING A SERIOUS SIDE EFFECT WITH VIVELLE DOT** section

- Carton and immediate container labels
- On the Physician sample Box, which contains five of the 2-system packages, the "Rx Only" statement should appear on the main panel.

Decisions:

- The sponsor will respond to the Agency letter the week of November 5, 2001

- **Action Items:**

Item:	**Responsible Party:**	**Due Date:**
send minutes to sponsor	Ms. Moore	one month/

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/s/

Diane V. Moore
11/19/01 04:46:12 PM

Minutes of Teleconference

Date: October 30, 2001 **Time:** 11:00 AM - 12:00 PM **Place:** Parklawn; Ms. Moore's Office

NDA: 20-538/S-014 and S-015 **Drug Name:** Vivelle-Dot (estradiol transdermal system)

Indication: Estrogen Replacement Therapy (ERT)

External Constituent: Novartis Pharmaceuticals, Inc.

Type of Meeting: Labeling Discussion

FDA Lead: Ms. Diane Moore **Sponsor Lead:** Ms. K. Basmadjian

Meeting Recorder: Ms. Diane Moore

FDA Participants:
Diane Moore – Regulatory Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

External Participant: Kathleen Basmadjian, Associate Director, Drug Regulatory Affairs, Novartis

Meeting Objective: To convey the Division's comments regarding the sponsor's comments to the Division's October 24, 2001, letter.

Background: The Division sent the sponsor a letter on October 24, 2001, with proposed labeling revisions for the Vivelle-Dot supplemental applications S-014 and S-015.
On October 26, 2001, Lynn Mellor, from Novartis, conveyed comments regarding the October 24, 2001 Agency letter to Diane Moore, Project Manager, DRUDP.

Discussion Items:

1. **Black Box Warning**

- the sponsor suggested that the labeling include wording to let women who have a uterus know that they should be taking a progesterone with estrogen (for long term use) in both Physician and Patient Information inserts
- **FDA response:**
  - this drug product is an estrogen product, not a combination estrogen/progestin product; the indications VMS and VVA are short-term indications
  - the addition of a progestin when a woman has not had a hysterectomy is addressed in the **PRECAUTIONS** section of the labeling
  - the physician can make the determination to add a progestin to a patient's regimen on an individual basis

2. **CMC issue:** on page 3, second paragraph, the "17β" from the "17β estradiol" was deleted. The sponsor was told that the first time it is used (as a USP associated name) the "17 β" could be retained. The "17 β" has been deleted in the rest of the text.

- **FDA response:**
  - all estrogen labeling is uniformly being revised to remove the "17β" from the term "17 β estradiol" in the Package Insert in accordance to proper USAN designation

3. **INDICATIONS AND USAGE** section (page 10)

- Item 4. Prevention of postmenopausal osteoporosis ——— Second sentence that reads, '
  The sponsor wants to keep the term in so that it reads '
- **FDA response:**
  -

4. **WARNINGS** section, page 11 under Endometrial cancer subsection,

-

- **FDA response:**
  - the sentence marked for deletion should not be kept in the labeling

5. In the **Thromboembolic disorders, Venous thromboembolism** subsection, the sentence that reads, "Several epidemiologic studies have found an increased risk of thromboembolism (VTE) in users of estrogen replacement therapy . . ." to include a clause that mentions the studies used orally administered estrogen products. Do we have additional references that include other types of estrogen administration in addition to oral administration?

- **FDA response:**
  - the sentence is being revised in all estrogen labeling; the information is also pertinent to transdermal forms of administration
  - the sponsor can submit data for review to justify inclusion of information in the labeling

6. **Gallbladder disease** subsection: In the sentence that reads, "A 2-to 4-fold increase in the risk of gallbladder disease requiring surgery in women receiving postmenopausal estrogens has been reported." The word "oral" has been deleted. Is there new data available to warrant the removal of the word "oral"?

- **FDA response:**
  - the sentence is being revised in all estrogen labeling
  - if the sponsor would like to propose that this language be applied exclusively to products given by an oral route of administration and not to transdermal products, the sponsor can submit supportive data or literature references for review

7. Under **PRECAUTIONS** section, item 3, **Elevated blood pressure** [redacted]

- **FDA response:** [redacted]

8. Under item [redacted] **Familial hyperlipoproteinemia**, the wording was revised. The sponsor wants to keep the present wording. that reads, "Estrogen therapy may be associated with massive elevations of plasma triglycerides leading to pancreatitis and other complications in patients with familial defects of lipoprotein metabolism." The sponsor has it in their overseas labeling. They have references to support the wording.
- **FDA response:**
  - the labeling revision is consistent with recent labeling revisions to other estrogen drug products; if the sponsor has data to support their claim that estrogen therapy may be associated with "massive" elevations of plasma triglycerides leading to pancreatitis and other complications in patients with familial defects of lioprotein metabolism, they can submit it for review

9. **Pregnancy Category X** The wording was shortened. The sponsor recalls that some wording from the black box warning was moved here. Is it somewhere else or deleted, or is this an oversight?
- **FDA response**:
  - the language is the same in all other current estrogen labels

10. **Adverse Reactions:**
- The sponsor says that they cannot pool the data from the VMS and PMO trials. It may be something to do with databases that are inconsistent. Anyway, They do not have data from Vivelle-Dot trials. I told them to use data from Vivelle (since that is the trial data that is being relied upon for approval). [redacted] They want to keep the [redacted] AEs for liability purposes. I told them we were revising all the labels in the class the same.
- **FDA response:**
  - the sponsor should put the data from the two trials in one table using a 2% cutoff
  - the 2% level for adverse events will include any adverse events seen in the adequate clinical trials at this level and provides more information than a cut-off of [redacted]; serious adverse reactions and potential safety hazards are covered in the rest of the label

11. **Patient Information** Insert in the section entitled, **"Vivelle-Dot Is Approved For use In the Following Ways:"**

- 5. Thromboembolic disorders
  - the sentence is being revised in all estrogen labeling; the information is pertinent to transdermal forms of administration
- 6. Gallbladder disease
  - the sentence is being revised in all estrogen labeling
  - if the sponsor has literature that would support applying this language exclusively to products given by an oral route of administration and not a transdermal route of administration, this should be provided to the Agency for review
- 7. **PRECAUTIONS** section
  - the two sentences that were removed do not add any pertinent information to the section; they should not be retained
- 8. **Familial hyperlipoproteinemia**
  - the labeling revision is consistent with recent labeling revisions to other estrogen drug products; the language recommended by the Agency addresses elevation of triglycerides and resultant pancreatitis associated with estrogen use in patients with this familial defect; if the sponsor has data to support the addition of the word "massive" to the language, the sponsor can submit it for review
- 9. **Pregnancy Category X**
  - the language is the same in all other current estrogen labels
- 10. **Adverse Reactions**
  - the sponsor should put the data from the two trials in one table using a 2% cutoff
  - the 2% level for adverse events will include any adverse events seen in the adequate clinical trials at this level and provides more information than a cut-off of –5; serious adverse reactions and potential safety hazards are covered in other safety portions of the label
- 11. Patient Information, '
  - the Agency may consider the addition of language that prevention of osteoporosis involves a long-term use
- 12. **WHO SHOULD NOT USE VIVELLE DOT**
  -
- 13. **WHAT ARE THE POSSIBLE RISKS AND SIDE EFFECTS**
  -

Comments from OPDRA consult dated October 1, 2001, were also discussed

- 1. General comments
  - "The black print on a purple background (back panel of the physician sample carton) is difficult to read"
    - the Division felt that the black print was sufficiently different in color from the purple background to enable reasonable readability
    - the black writing on the purple background is an approved combination for higher strengths
    - the Division can pursue this at a later date if deemed necessary
- CONTAINER LABEL (0.025 mg/day)

- The label is identical in design and color to the other strengths. The strengths should be highlighted to the corresponding strength color on the carton labeling
  - the strengths are highlighted by a box of different colors for each strength with the strength inside in bold black lettering; the 0.1 square is beige, the 0.075 mg square is white, the 0.05 mg square is dark purple, the 0.0375 mg square is light blue and the 0.025 mg square is light green
  - the highlighted squares delineate the different doses clearly; the colors of the entire boxes do not appear to need to be changed
- CARTON LABELING (0.025 mg/day Physician Sample-2 system package, Physician Sample Box-5 of the 2 system package, 8 system package, Box-3 of the 8 system package)
  - 1. OPDRA recommends that the statement "Dosage and Administration: See package insert" be revised to state "Usual Dosage: Apply patch twice a week. See package insert."
    - the Division does not use the term "Usual Dosage" for these products; the directions to apply twice a week are included in the package insert and do not need to be repeated here
  - 2. On the Physician sample Box, which contains five of the 2-system package, the "Rx Only" statement should appear on the main panel.
    - the Division agrees with this suggestion
  - 3. The box that contains 3 of the 8 system package resembles in design and color to the box that contains the patient calendar packs of Estraderm. The boxes should be differentiated by using different colors in the lettering or by using a different design on the box.
    - the Estraderm product is also manufactured by Novartis Pharmaceuticals; the company uses the same trade packer boxes for all their products to delineate the manufacturer; the Division does not feel the similarity of the trade packer boxes is a safety issue and will not pursue revising this at this time

- **Action Items:**

Item:	**Responsible Party:**	**Due Date:**
convey Division comments to sponsor	Ms. Moore	1-2 days

{See appended electronic signature page} *{See appended electronic signature page}*

Concurrence:

S.Slaughter 11.15.01/P.Price 11.13.01
Response not received from A.Mitra

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/s/

Diane V. Moore
11/19/01 03:49:29 PM

Shelley Slaughter
11/19/01 04:04:19 PM

Meeting Minutes

Date: October 11, 2001 **Time**: 2:30 - 3:30 PM **Place**: Parklawn; Rm. 17B43

NDA: 20-538/S-014 and S-015 **Drug Name**: Vivelle-Dot (estradiol transdermal system)

Indication: Estrogen Replacement Therapy (ERT)

Sponsor: Novartis Pharmaceuticals, Inc.

Type of Meeting: 9-month Status Meeting

FDA Lead: Dr. Shelley Slaughter

Meeting Recorder: Ms. Diane Moore

FDA Participants:
Shelley Slaughter, M.D., Ph.D. –Medical Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Phill Price, M.D. - Medical Officer, DRUDP (HFD-580)
Diane Moore – Regulatory Project Manager, DRUDP (HFD-580)
Amit Mitra, Ph.D. - Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Venkateswar R. Jarugula, Ph.D. - Pharmacokinetic Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)

Meeting Objective: To discuss the status of reviews for both efficacy supplements.

Background: Labeling comments have been placed on the N drive. A consult to HFD-510 has been sent to review the osteoporosis section of the labeling.

Decisions Reached:
- Chemistry, Manufacturing and Quality Control
  - review pending; target for week of October 15, 2001
- Clinical Pharmacology and Biopharmaceutics
  - review pending: target for week of October 22, 2001
- Clinical
  - review pending; target for week of October 22, 2001
- Statistics
  - no formal review is needed because the clinical study was reviewed in NDA 20-323/S-023
- Pharmacology
  - no formal review is needed; a memo will be written for labeling
- Regulatory
  - all reviews are due to Dr. Slaughter by November 5, 2001; Dr. Shames will require one week to review the action package
- Labeling
  - in the Physician insert, under **PRECAUTIONS**, C. Laboratory Tests, the section was revised to read, "Estrogen administration should be guided by clinical response at the lowest dose for the

treatment of vasomotor symptoms and vulvar and vaginal atrophy. [redacted]

- in the **ADVERSE REACTIONS** section, the second paragraph was revised to read, " See **WARNINGS** regarding induction of malignant neoplasma, thromboembolic disorders, gallbladder disease and hypercalcemia: see **PRECAUTIONS** regarding cardiovascular risk and elevated blood pressure."

- **Action Items:**

• **Item:**	**Responsible Party:**	**Due Date:**
• send letter to sponsor	Ms. Moore	week of October 22, 2001

{See appended electronic signature page} *{See appended electronic signature page}*

drafted: dm/10.19.01/N20538SM101101.doc
Concurrence:
S.Slaughter 10.25.01/ P.Price, V.Jarugula 11.6.01
No response received from A.Mitra,

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/s/

Diane V. Moore
11/19/01 07:00:32 PM

Shelley Slaughter
11/20/01 09:24:17 AM

Meeting Minutes

Date: September 24, 2001 **Time:** 3:30 - 4:30 PM **Place:** Parklawn; Rm. 17B43

NDA: 20-538/S-014 and S-015 **Drug Name:** Vivelle-Dot (estradiol transdermal system)

Indication: Estrogen Replacement Therapy (ERT)

Sponsor: Novartis Pharmaceuticals, Inc.

Type of Meeting: 8-month Status Meeting

FDA Lead: Dr. Shelley Slaughter

Meeting Recorder: Ms. Diane Moore

FDA Participants:
Shelley Slaughter, M.D., Ph.D. –Medical Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Phill Price, M.D. - Medical Officer, DRUDP (HFD-580)
Diane Moore – Regulatory Project Manager, DRUDP (HFD-580)
Amit Mitra, Ph.D. - Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Venkateswar R. Jarugula, Ph.D. - Pharmacokinetic Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)

Meeting Objective: To discuss the labeling for both efficacy supplements.

Background: The ten-month goal date for Supplement 014 is November 19, 2001. The ten-month goal date for Supplement 015 is November 23, 2001.

Decisions Reached:

- Chemistry, Manufacturing and Quality Control
  - the **DESCRIPTION** and **HOW SUPPLIED** sections of the labeling are acceptable; the backing labeling appears to be acceptable; the carton labeling is under review
  - the sponsor has not responded to the request made on September 6, 2001, for a new specification sheet for the drug product and the certificate of analysis (COA) with ———— ————; the sponsor was also asked to update the stability data for the drug product, including data from the third lot that was to be placed on stability
- Clinical Pharmacology and Biopharmaceutics
  - the labeling does not include steady-state PK levels
  - the new 0.025 mg dose does not need to be included in the graph with the other approved doses; the doses are dose proportional and the addition of the new strength would make the graph unnecessarily complex
  - adhesion section of the labeling needs to be revised to quantitate the percentage of systems that lifted and that did not lift; the wording in the Climara label can be used as a format guide (see attached revised label)
- Clinical
  - the prevention of osteoporosis indication should be revised

  - the **Adverse Reactions** section should be revised to include tables
- Statistics
  - no issues
- Pharmacology
  - no issues
- Regulatory
  - all reviews are due to Dr. Slaughter by November 5, 2001; Dr. Shames will require one week to review the action package
- DDMAC
  - DDMAC has proposed revisions to the Patient Information section of the package insert (see attached)

- **Action Items:**

Item:	**Responsible Party:**	**Due Date:**
revise Clinical Pharmacology section	Dr. Jarugula	1 week
update label on community drive	Dr. Price	1 week
send sponsor regulatory letter with proposed revisions	Ms. Moore	when labeling is updated

{See appended electronic signature page} *{See appended electronic signature page}*

Post Meeting Addendum: See attached revised labeling.

drafted: dm/9.30.01/N20538SM92401.doc
cc:
Concurrence:
J.Best, L.Stockbridge, A.Mitra 10.1.01/M.Rhee 10.2.01/P.Price 10.4.01/S.Slaughter 10.18.01

29 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

__X__ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/

Diane V. Moore
10/23/01 05:38:06 PM

Shelley Slaughter
10/25/01 09:26:46 AM

Meeting Minutes

Date: August 22, 2001 **Time:** 11:00 - 11:35 AM **Place:** Parklawn; Rm. 17B43

NDA: 20-538/S-014 and S-015 **Drug Name:** Vivelle-Dot (estradiol transdermal system)

Indication: Estrogen Replacement Therapy (ERT)

Sponsor: Novartis Pharmaceuticals, Inc.

Type of Meeting: 7-month Status Meeting

FDA Lead: Dr. Shelley Slaughter

Meeting Recorder: Ms. Diane Moore

FDA Participants:
Daniel Shames, M.D. – Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Shelley Slaughter, M.D., Ph.D. –Medical Team Leader, DRUDP (HFD-580)
Phill Price, M.D. -Medical Officer, DRUDP (HFD-580)
Diane Moore – Regulatory Project Manager, DRUDP (HFD-580)
Amit Mitra, Ph.D. - Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Venkateswar R. Jarugula, Ph.D. - Pharmacokinetic Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)

Meeting Objective: To discuss the status and time-line for both efficacy supplements.

Background: The ten-month goal date for Supplement 014 is November 19, 2001. The ten-month goal date for Supplement 015 is November 23, 2001.

Decisions Reached:
- Clinical
  - no issues
- Statistics
  - no issues
- Pharmacology
  - no issues
- Clinical Pharmacology and Biopharmaceutics
  - review pending
- Regulatory
  - the approval of both supplements hinge on the Clinical Pharmacology and Biopharmaceutics review of the submitted studies; labeling for both supplements could be approved in a combined action letter providing both supplements are approved
  - all reviews are due to Dr. Slaughter by November 5, 2001; Dr. Shames will require one week to review the action package

- it may be necessary to include representatives from the Division of Metabolic and Endocrine Drug Products (DMEDP) at the labeling discussions for S-015 because the supplement adds wording for the prevention of osteoporosis indication

- Chemistry, Manufacturing and Quality Control
  - when the sponsor submitted Supplements S-014 and S-015, the certificate of analysis (COA) for the [redacted] was omitted; [redacted], therefore, this [redacted] specification must be maintained in the specification sheet; a new specification sheet for the drug product should be submitted that includes the [redacted] specifications
  - updated stability data for the drug product, including data from the third lot that was to be placed on stability, should be submitted

- **Action Items:**

• **Item:**	**Responsible Party:**	**Due Date:**
• request COA for [redacted] from sponsor	Ms. Moore	1-2 weeks
• request updated stability data from sponsor	Ms.Moore	1-2 weeks

{See appended electronic signature page} *{See appended electronic signature page}*

Post Meeting Addendum: On September 6, 2001, Diane Moore, regulatory project manager, contacted Ms. Lynn Mellor and requested a new specification sheet for the drug product to include the [redacted] specifications. Updated stability data, including data from the third lot placed on stability, was also requested.

drafted: dm/8.30.01/N20538SM82201.doc
cc:
Concurrence:
T.Rumble 9.6.01/D.Shames 9.7.01/S.Slaughter 9.13.01/A.Mitra, P.Price, V.Jarugula 9.18.01

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/s/

Diane V. Moore
9/18/01 03:22:34 PM

Daniel A. Shames
9/21/01 02:25:29 PM

Meeting Minutes

Date: March 7, 2001 **Time**: 1:00 - 1:30 PM **Place**: Parklawn; Rm. 17B43

NDA: 20-538/-014 and 015 **Drug Name**: Vivelle-Dot (estradiol transdermal system)

Indication: Estrogen Replacement Therapy (ERT)

External Constituent: Novartis Pharmaceuticals Corporation

Type of Meeting: Filing

FDA Lead: Dr. Susan Allen

Meeting Recorder: Ms. Diane Moore

FDA Participants:
Susan Allen, M.D., M.P.H. - Director, Division of Reproductive and Urologic Drug Product (DRUDP; HFD-580)
Daniel Shames, M.D. – Deputy Director, DRUDP (HFD-580)
Shelley Slaughter, M.D., Ph.D. –Medical Team Leader, DRUDP (HFD-580)
Phill Price, M.D. - Medical Officer, DRUDP (HFD-580)
Terri Rumble – Chief, Project Management Staff, DRUDP (HFD-580)
Diane Moore – Regulatory Project Manager, DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Amit Mitra, Ph.D. - Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Venkateswar R. Jarugula, Ph.D. - Pharmacokinetic Reviewer, OCPB @ DRUDP (HFD-580)
Mike Welch – Biometrics Team Leader Division of Biometrics II (DBII; HFD-715)
Lisa Stockbridge, Ph.D. - Regulatory Reviewer, Division of Drug Marketing and Communication (DDMAC; HFD-42)

Meeting Objective: To discuss the Fileability of Supplements-014 and 015.

Background: Supplement-014 was submitted on January 18, 2001, received January 19, 2001. The 10-month goal date is November 19, 2001. The 12-month goal date is January 19, 2002. This supplement proposes to revise the labeling to remove the restrictive language regarding vasomotor symptoms associated with the menopause for the 0.0375 mg strength (delayed onset of efficacy).
Supplement-015 was submitted on January 22, 2001, received January 23, 2001. The 10-month goal date is November 23, 2001 and the 12-month goal date is January 23, 2002. This supplement incorporates labeling revisions for a new prevention of postmenopausal osteoporosis indication.

Discussion Items:
- the sponsor has studies that investigate the effect of swimming on the systems; this is reflected in the current labeling

NDA 20-538/S-014/S-016
Meeting Minutes – March 7, 2001

Decisions Reached:

- Regulatory
  - Supplement–014 is fileable; Supplement–015 is fileable
  - the reference in the cover letter should clarify more clearly which studies are being referenced
  - the sponsor has requested a waiver for pediatric studies
- Clinical Pharmacology and Biopharmaceutics
  - Supplement–014 is fileable; Supplement–015 is fileable
  - both supplements reference the bioequivalence study that supported the approval of the Vivelle-Dot NDA (NDA 20-538); this study demonstrated bioequivalence between the Vivelle transdermal system (NDA 20-323) and the Vivelle-Dot transdermal system (NDA 20-538)
  - a dose proportionality study and a multiple-dose bioequivalence study using the 0.05 mg dose of Vivelle and Vivelle-Dot were also submitted to Supplement 15 for the new lower dose
- Chemistry and Manufacturing and Quality Control
  - Supplement–014 is fileable; Supplement–015 is fileable
  - the test methods reference NDA 20-323
  - a request for a categorical exclusion is needed
  - there is limited stability data for the product; the sponsor has requested a 24-month expiration date
- Clinical
  - Supplement–014 is fileable; Supplement–015 is fileable
  - the same clinical study data that was submitted to NDA 21-167 (NDA 20-323/S-023) to support the prevention of postmenopausal osteoporosis indication is referenced in support of Supplement 015 for the same indication
  - Novartis is the sponsor for both the Vivelle and Vivelle-Dot NDAs; they performed or sponsored the referenced studies
- Statistics
  - Supplement–014 is fileable; Supplement–015 is fileable; because the clinical efficacy data referenced to support the two supplements has been reviewed previously, no formal statistical reviews are needed; any statistical comments regarding the clinical studies or labeling should be requested by the Project Manager or Medical Officer during the review cycle, and these can be included in the clinical reviews
- Pharmacology
  - Supplement–014 is fileable; Supplement–015 is fileable
  - this product is approved for higher doses; there are no pharmacology/toxicology issues to be reviewed—per Pharmacology reviewer
- Labeling
  - the labeling for Supplement 015 should be consulted to the Division of Metabolic and Endocrine Drug Products (DMEDP) for the osteoporosis labeling section

NDA 20-538/S-014/S-016
Meeting Minutes – March 7, 2001

• **Action Items:**		
• **Item:**	**Responsible Party:**	**Due Date:**
• request revised reference letter	Ms. Moore	1-week
• remind the sponsor that they need to request a categorical exclusion	Ms. Moore	1-week

Signature, recorder

Concurrence, Chair

Post Meeting Addendum: On March 7, 2001, the sponsor submitted a revised cover letter to more clearly describe the clinical studies to be referenced for Supplement 014.

drafted: dm/3.17.01/N20538FM3701.doc
cc:
Concurrence:
T.Rumble 3.19.01/L.Stockbridge 3.20.01/M.Welch 3.21.01/D.Shames, A.Mitra 3.23.01
S.Slaughter 3.27.01/A.Parekh, V.Jarugula 3.28.01/M.Rhee, P.Price 3.29.01/S.Allen 6.8.01

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/s/

Diane V. Moore
7/2/01 03:20:13 PM

Susan Allen
7/6/01 04:07:25 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-538/S-015

CORRESPONDENCE

FOOD AND DRUG ADMINISTRATION
DIVISION OF REPRODUCTIVE AND
UROLOGIC DRUG PRODUCTS, HFD-580
DOCUMENT CONTROL ROOM 17B-20
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857

DATE: 9/3/02

TO:

Name: ANN Shey

Fax No: 973-781-3966

Phone No: 973-781-3665

Location:

FROM:

Name: Dornette Spell-LeSane

Fax No: (301) 827-4267

Phone No: (301) 827-4260

Location: FDA, Division of Reproductive and Urologic Drug Products

Comments:

Approval Letter & Labeling

concurrence:

Novartis Pharmaceuticals Corporation

Fax

To: Diane Moore **From:** Lynn Mellor

Fax: 301 827-4267 **Pages:**

Phone: 301 827-4236 **Date:** 11/16/01

Re: Vivelle-Dot NDA 20-538/S-012, S-014, S-015 **CC:**

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Dear Ms. Moore,

Reference to Vivelle-Dot supplements S-012, S-014, and S-015. Attached for your information is the draft Physician and Patient Information labeling.

If you have any questions please contact me at (973) 781-3665.

Sincerely,

Lynn Mellor

Lynn Mellor
Drug Regulatory Affairs

T2000-57
T2000-56/T2000-57
89001003
CL100922-1

REV: November 2001 Printed in U.S.A.

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Miami, FL 33186

Distributed by
Novartis Pharmaceuticals Corporation
East Hanover, NJ 07936

31 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

3/4/02

NOVARTIS

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

Lynn Mellor
Tel: 973-781-3665
Fax: 973-781-3966
email address: lynn.mellor@pharma.novartis.com

March 1, 2002

Susan Allen, MD
Project Manager
Division of Reproductive and Urological
Drug Products/HFD-580
Office of Drug Evaluation II
Attn: Center for Drug Evaluation and Research
Food and Drug Adminstration
Document and Records Section
12229 Wilkins Avenue
Rockville, Maryland 20852

NDA No. 20-538/S-012, S-014,S-015

Vivelle-Dot® (estradiol transdermal system)

Amendment to a Pending Application: Draft Labeling

Dear Dr. Allen:

Reference is made to your approvable letter dated November 19, 2001 for our supplemental new drug applications dated November 12, 2000 (S-012), January 18, 2001 (S-014) and January 22, 2001 (S-015) for Vivelle-Dot® (estradiol transdermal system) 0.025, 0.0375, 0.05, 0.075 and 0.1 mg/day.

At this time we wish to file an amendment to the applications to address the issues raised by the Agency.

Attached is draft labeling that incorporates the revisions in the Package insert and Patient Information insert identified in your letter dated November 19, 2001 and in a subsequent telephone conversation with Ms. Diane Moore on November 21, 2001 (Attachment 1). Also provided is a draft annotated (marked up) package insert and Patient Information insert (Attachment 2). In addition, attached are revised labeling components. The "Rx Only" statement has been moved to the main panel of the box for the Packer Sample, IFC Sample, Packer Trade, and IFC trade (Attachment 3).

The draft label contains pooled adverse event data from Vivelle® (estradiol transdermal system) studies [Protocol 035 a 2 year study in the prevention of postmenopausal osteoporosis, and Protocol 1003A and 1003B both 3 month studies in the treatment of postmenopausal symptoms]. The Agency had requested a cutoff of ≥2%, however presented in the draft label is an adverse event table with a cut off of ≥ —. A summary report is included that provides the justification for the — table (Attachment 4).

As requested we are updating the NDA with all safety information available to date. No new clinical studies have been conduced with Vivelle or Vivelle-Dot (the last update was the 120 Day Safety Update submitted November 6, 2001). Attached for your information is a copy of the most recent periodic safety reports for Vivelle and Vivelle-Dot (Attachment 5). In summary, the data derived from the post-marketing experience do not exhibit any new or unknown aspects that lead to a changing of the safety profile for Vivelle-Dot.

Included is an updated estimate of use for the drug marketed in other countries (Attachment 6). Also provided is a copy of current approved foreign labeling not previously provided (Attachment 7).

If you have any questions or comments concerning this submission, please contact me at (973) 781-3665.

Sincerely yours,

Lynn Mellor

Lynn Mellor
Associate Director
Drug Regulatory Affairs

LM/alj
Attachments: Form 356h
Submitted in Duplicate
20020302.doc

31 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICATION INFORMATION

NAME OF APPLICANT
NOVARTIS PHARMACEUTICALS CORPORATION

DATE OF SUBMISSION
March 1, 2002

TELEPHONE NO. (*Include Area Code*)
(973) 781-3665

FACSIMILE (FAX) Number (*Include Area Code*)
(973) 781-3590

APPLICANT ADDRESS (*Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*

One Health Plaza
East Hanover, New Jersey 07936-1080

AUTHORIZED U.S. AGENT NAME & ADDRESS (*Number, Street, City, State, ZIP Code, telephone & FAX number*) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (*If previously issued*) **20-538/S-012, 014, 015**

ESTABLISHED NAME (*e.g., Proper name, USP/USAN name*)
estradiol

PROPRIETARY NAME (*trade name*) IF ANY
Vivelle Dot®

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (*If any*)

CODE NAME (*If any*)

DOSAGE FORM:
Transdermal delivery system

STRENGTHS:

ROUTE OF ADMINISTRATION:

(PROPOSED) INDICATION(S) FOR USE:

APPLICATION INFORMATION

APPLICATION TYPE
(check one)

☐ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Amendment To A Pending Application: Draft Labeling

PROPOSED MARKETING STATUS *(check one)* ☐ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1

THIS APPLICATION IS ☐ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: (*Check all that apply*)	
	1. Index
X	2. Labeling *(check one)* ☒ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50 (d)(1); 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g., 21 CFR 314.50 (e)(2)(i); 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50 (d)(2); 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50 (d)(3); 21 CFR 601.2)
	7. Clinical Microbiology (e.g., 21 CFR 314.50 (d)(4))
	8. Clinical data section (e.g., 21 CFR 314.50 (d)(5); 21 CFR 601.2)
	9. Safety update report (e.g., 21 CFR 314.50 (d)(5)(vi)(b); 21 CFR 601.2)
	10. Statistical section (e.g., 21 CFR 314.50 (d)(6); 21 CFR 601.2)
	11. Case report tabulations (e.g., 21 CFR 314.50 (f)(1); 21 CFR 601.2)
	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b)(2) or (j)(2)(A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k)(3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. Financial Information (21 CFR Part 54)
	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowlegde are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Lynn Mellor	Lynn Mellor, Associate Director Drug Regulatory Affairs	02-MAR-02

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
One Health Plaza East Hanover, New Jersey 07936-1080	(973) 781-3665

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

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FORM FDA 356h (4/00)

Novartis Pharmaceuticals Corporation

Fax

To:	Diane Moore	**From:**	Lynn Mellor
Fax:	301 827-4267	**Pages:**	
Phone:	301 827-4236	**Date:**	11/16/01
Re:	Vivelle-Dot NDA 20-538/S-012, S-014, S-015	**CC:**	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Dear Ms. Moore,

Reference to Vivelle-Dot supplements S-012, S-014, and S-015. Attached for your information is the draft Physician and Patient Information labeling.

If you have any questions please contact me at (973) 781-3665.

Sincerely,

Lynn Mellor

Lynn Mellor
Drug Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

November 19, 2001

Susan Allen, MD
Project Manager
Division of Reproductive and Urological
Drug Products/HFD-580
Office of Drug Evaluation II
Attn: Document Control Room 17B-20
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 20-538/S-012, S-014,S-015

Vivelle-Dot™ (estradiol transdermal system)

Response to Request for Information - DRAFT LABELING

Dear Dr. Allen:

Reference is made to our submissions on November 6, 8, and 15 2001 which provided draft labeling for the efficacy supplements for Vivelle-Dot™ (estradiol transdermal system), S-014 submitted on January 18, 2001 and S-015 submitted on January 22, 2001. Also included are the changes in S-012 dated November 13, 2000.

Reference is made to a request from Ms. Diane Moore on November 16, 2001 to provide the updated draft labeling on a CD-ROM. The draft labeling has been updated in response to the Division's request for changes. However, we cannot provide a pooled adverse event table from the 3 month vasomotor symptom trials and the 2 year postmenopausal osteoporosis trial at this time as the databases reside in two different companies and different adverse event coding dictionaries were used.

Enclosed is a CD-ROM that contains the draft physician and patient information labeling for Vivelle-Dot (as a WORD document and in a PDF). In addition, a paper copy of the draft labeling and the draft annotated labeling is provided.

If you have any questions or comments concerning this submission, please contact me at (973) 781-3665.

Sincerely yours,

Lynn Mellor
Associate Director
Drug Regulatory Affairs

Novartis Pharmaceuticals Corporation

Fax

To:	Diane Moore	**From:**	Lynn Mellor
Fax:	301 827-4267	**Pages:**	13
Phone:	301 827-4236	**Date:**	11/16/01
Re:	Vivelle-Dot NDA 20-538/S-012, S-014, S-015	**CC:**	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Dear Ms. Moore,

Reference to Vivelle-Dot supplements S-012, S-014, and S-015. Attached for your information is the AE table at the ≥ 2% cutoff for P035 (2 year PMO trial).

If you have any questions please contact me at (973) 781-3665.

Sincerely,

Lynn Mellor

Lynn Mellor
Drug Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

Novartis Pharmaceuticals Corporation

Fax

To:	Diane Moore	**From:**	Lynn Mellor
Fax:	301 827-4267	**Pages:**	
Phone:	301 827-4236	**Date:**	11/16/01
Re:	Vivelle-Dot NDA 20-538/S-012, S-014, S-015	**CC:**	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Dear Ms. Moore,

Reference to Vivelle-Dot supplements S-012, S-014, and S-015. Attached for your information is the draft Physician and Patient Information labeling.

If you have any questions please contact me at (973) 781-3665.

Sincerely,

Lynn Mellor

Lynn Mellor
Drug Regulatory Affairs

Novartis Pharmaceuticals Corporation

Fax

To:	Diane Moore	**From:**	Lynn Mellor
Fax:	301 827-4267	**Pages:**	4
Phone:	301 827-4236	**Date:**	11/13/01
Re:	Vivelle-Dot NDA 20-538/S-012, S-014, S-015	**CC:**	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Dear Ms. Moore,

Reference to Vivelle-Dot supplements S-012, S-014, and S-015. As requested attached for your information is the draft Adverse Event tables. There are two tables; the first from the 3 month vasomotor symptoms trials and the second from the 2 year osteoporosis trial. Also, please note that we are working on identifying additional adverse events that we wish to include as text after the second table. We will provide as soon as possible.

If you have any questions please contact me at (973) 781-3665.

Sincerely,

Lynn Mellor
Drug Regulatory Affairs

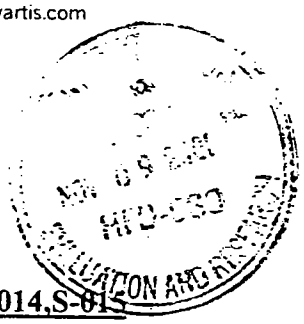
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

Lynn Mellor
Tel: 973-781-3665
Fax: 973-781-3966
email address: lynn.mellor@pharma.novartis.com

NOVARTIS

ORIGINAL

November 8, 2001



Susan Allen, MD
Project Manager
Division of Reproductive and Urological
Drug Products/HFD-580
Office of Drug Evaluation II
Attn: Document Control Room 17B-20
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 20-538/S-012, S-014,S-015

Vivelle-Dot™ (estradiol transdermal system)

[redacted] AMEND SLR01
SE8014
SE101

Request for Information

Dear Dr. Allen:

Reference is made to our submission on November 6, 2001, which provided draft labeling for the efficacy supplements for Vivelle-Dot™ (estradiol transdermal system), S-014 submitted on January 18, 2001 and S-015 submitted on January 22, 2001. Also included are the changes in S-012 dated November 13, 2000.

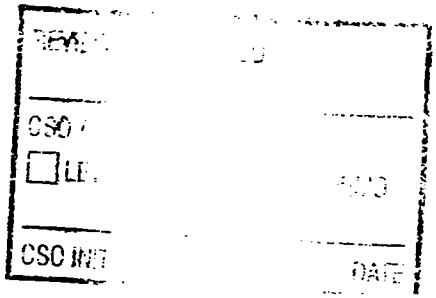
Reference is made to a request from Ms. Diane Moore on November 7, 2001 to provide the draft labeling on a diskette. Enclosed are diskettes that contain the draft annotated and draft physician and patient information labeling for Vivelle-Dot that was previously submitted in a paper copy on November 6, 2001. The diskettes provided have been virus scanned using Network Associates VirusScan NT. The diskettes were found to be virus free.

If you have any questions or comments concerning this submission, please contact me at (973) 781-3665.

Sincerely yours,

Lynn Mellor
Associate Director
Drug Regulatory Affairs

LM/tln
Vivdotlabeldiane.doc
Attachments: Form 356h
20538-S012 request for information.doc



DUPLICATE

NOVARTIS NDA SUPP AMEND

SIR-012-BL
SE8-014-BL
SE7-015-BL

November 6, 2001

Susan Allen, MD
Director
Division of Reproductive and Urological
Drug Products/HFD-580
Office of Drug Evaluation II
Attn: Document Control Room 17B-20
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 20-538/S-012, S-014,S-015

Vivelle-Dot™ (estradiol transdermal system)

Amendment to a Pending Labeling/Efficacy Supplements - Draft Labeling

Dear Dr. Allen:

Reference is made to our efficacy supplements for Vivelle-Dot™ (estradiol transdermal system), S-014 submitted on January 18, 2001 and S-015 submitted on January 22, 2001. In addition reference is made to your letter received on October 25, 2001 which provided combined labeling comments to our physician package insert and patient information insert for these supplements.

Reference is also made to a telephone conversation with Ms. Diane Moore the week of October 22, 2001 concerning combining the labeling changes and taking action on S-014 and S-015 as well as S-012 at the same time. Supplement 012 dated November 13, 2000 was a "Changes Being Effected in 30 days" supplement to incorporate safety information requested by the Agency in a letter dated August 10, 2000.

Attached is a draft annotated Vivelle-Dot physician package insert and patient information that incorporates the changes outlined in the October 25, 2001 FDA letter. In addition, attached is a draft label. However, points that we wish to discuss with the Agency are highlighted by bolded/italic text within the document.

Following are the points we wish to discuss:

Physician package insert

- Indications and usage.
- Warnings, a. Endometrial cancer. We wish to include the last sentence

- Warnings, 2. Thromboembolic disorders. Venous thromboembolism. Add to the first sentence: [redacted]

- Warnings, 3. Gallbladder disease. We request the references be provided to us for the 2- to 4-fold increase in the risk of gallbladder disease.....
- Precautions. 3. Elevated blood pressure. We propose to add to the end of the statement, [redacted]

- Precautions. Nursing Mothers. Revised text to add emphasis and be consistent with global labeling for this product.
- Adverse Reactions. Vivelle-Dot AE data from clinical trials is limited as Vivelle-Dot was approved based on BE to Vivelle, therefore we wish to retain the specific Vivelle-Dot AE text. We propose to include 2 AE tables from Vivelle clinical trial databases. The first table will summarize AEs reported in $\geq$ 2% of patients in the pivotal symptom trials (Protocol 1003A and 1003B - 3 months duration). The second table will summarize the AEs reported in $\geq$ 2% of patients in the pivotal PMO trial (Protocol 035 - 2 year duration). It is not possible to combine all studies into a single table as Protocol 1003A and 1003B used the CoStar dictionary and Protocol 035 used the IMN dictionary as defined by WHO as defined by Novartis.
  In addition, dependent on the AEs listed in the tables, we will propose to list AEs from the current "class labeling AE" list that are not included in the tables in text format.
  We will provide the AE tables and text to the Agency as soon as available.

Patient Information

- Vivelle-Dot is approved for use in the following ways. Add to end of first bullet: [redacted] the majority of women do not need estrogen replacement for longer than 6 months. We feel that it is important to be clear that this recommendation refers to the reducing menopausal symptoms indication.
- [redacted]

- [redacted]

- [redacted]

- Less common but serious effects include. We have included text under each serious effect in order to provide adequate information to the patient.

- What can I do to lower my chances of getting a serious side effect with Vivelle-Dot? If you use Vivelle-Dot you can reduce your risks by _____

- Other Information. _____

If you have any questions or comments concerning this submission, please contact me at (973) 781-3665.

Sincerely yours,

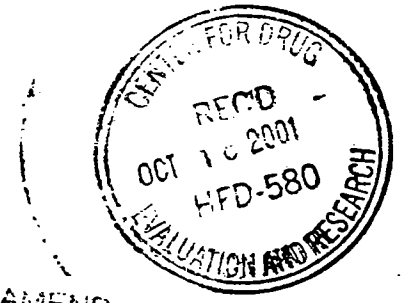
Lynn Mellor
Associate Director
Drug Regulatory Affairs

Vivdotlabel.doc
Attachments: Form 356h

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 7500
Fax 973 781 6525

NOVARTIS



October 16, 2001

NDA 20-538/S-015
Vivelle-Dot™
(estradiol transdermal systems)

NDA SUPP AMEND

Response - Chemistry, Manufacturing and Controls

S015-12C

Daniel Shames, MD, Acting Director
Division of Reproductive and
Urological Drug Products/HFD-580
Office of Drug Evaluation II
Attn: Document Control Room 17B-20
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Shames:

Please refer to our above-referenced New Drug Application for Vivelle-Dot™ (estradiol transdermal systems) and our pending Supplement, S-015, submitted on January 22, 2001. Additional reference is made to our July 17, 2001 amendment, providing a corrected stability protocol and commitment and our October 1, 2001 CMC response which provided for an updated drug product control document and stability data.

The attached documentation is provided in response to FDA Project Manager, Diane Moore's, October 15, 2001 telephone request to Lynn Mellor of Novartis.

The following document contains the expected introductory concentration (EIC) calculation for Vivelle-Dot and is provided:

Attachment I
- Vivelle-Dot – Confidential documentation in support of a Claim of Categorical Exclusion, dated 16-Oct-01

This calculation includes peak estimates of the amount of estradiol that will be marketed within the next 5 years for all of the affected Novartis products. Ownership of Combipatch was transferred to Novartis, as of March 30, 2001 and therefore, estimates for estradiol in this product are also included in this calculation. The estradiol amounts for the following products are included in the EIC calculation:

Vivelle-Dot, NDA 20-538	Estraderm, NDA 19-081
Vivelle, NDA 20-323	Combipatch, NDA 20-870

Since the EIC (aquatic) is significantly less than the threshold of [redacted], a categorical exclusion has been requested for Vivelle-Dot, NDA 20-538.

Should you have any comments or questions regarding this submission or any other Chemistry, Manufacturing and Controls issue please contact me directly at (973) 781-2735. If there are any general or Clinical related issues please contact Lynn Mellor, the DRA Therapeutic Area representative at (973) 781-3665.

Sincerely,

Sheryl LeRoy
Chemistry, Manufacturing and Controls
Drug Regulatory Affairs

Attachments
Submitted in Duplicate

cc: Ms. Regina Brown
New Jersey District Office, North Brunswick Resident Post (letter only)

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 7500
Fax 973 781 6325

NOVARTIS

ORIGINAL

NDA SUPP AMEND

October 1, 2001

NDA 20-538/S-014 and S-015
Vivelle-Dot™
(estradiol transdermal systems)

Response - Chemistry, Manufacturing and Controls

Susan Allen, MD, Director
Division of Reproductive and
Urological Drug Products/HFD-580
Office of Drug Evaluation II
Attn: Document Control Room 17B-20
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

REVIEWS COMPLETED
☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS DATE

Dear Dr. Allen:

Please refer to our above-referenced New Drug Application for Vivelle-Dot™ (estradiol transdermal systems) and our pending Supplements, S-014 and S-015, submitted on January 18 and 22, 2001, respectively. Additional reference is made to our July 17, 2001 amendment, providing a corrected stability protocol and commitment.

The attached documentation is provided in response to FDA Project Manager, Diane Moore's, September 6, 2001 telephone request to Lynn Mellor of Novartis.

The following drug product specification has been updated to include the specification for _____; and is provided:

Attachment I
- Estradiol Second Generation Transdermal, Rounded Rectangle, revision 6

The following updated stability data for the 0.025 mg/day strength of Vivelle-Dot, are provided:

Attachment II
- Second Generation Transdermal System (0.025 mg/day), Lot Number 9A2203-E3
- Second Generation Transdermal System (0.025 mg/day), Lot Number 0K2502-A1

Real time stability data for lot 9A2203-E3 were updated to include the 18 and 24 month timepoints. Accelerated and real time stability data are provided for lot 0K2502-A1 for up to and including 6 months.

As noted in our original supplement, the laminate for batch 6G1201-E8 (stability data provided in the original supplement) was manufactured in July 1996. However, the 0.025 mg/day systems were not packaged (cut into systems and pouched) until October 1997, 15 months after the date of manufacture of the laminate. Subsequently, the stability study for this batch began 15 months into the expiration period of the drug product. Therefore, since the stability study for batch 6G1201-E8 ended at the 9 month (24 months from the date of laminate manufacture) timepoint, there are no new data.

Data generated for all 3 stability batches, meet all stability specifications for this product.

Should you have any comments or questions regarding this submission or any other Chemistry, Manufacturing and Controls issue please contact me directly at (973) 781-2735. If there are any general or Clinical related issues please contact Lynn Mellor, the DRA Therapeutic Area representative at (973) 781-3665.

Sincerely,

Sheryl LeRoy
Chemistry, Manufacturing and Controls
Drug Regulatory Affairs

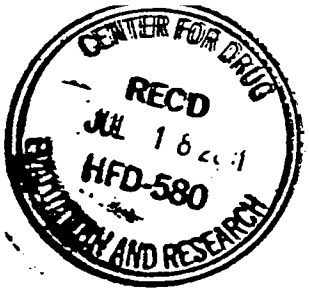
Attachments
Submitted in Duplicate

cc: Ms. Regina Brown
New Jersey District Office, North Brunswick Resident Post (letter only)

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 7500
Fax 973 781 6325

NOVARTIS



July 17, 2001

ORIGINAL

NDA 20-538/S-015
Vivelle-Dot™
(estradiol transdermal system)

Amendment - Chemistry, Manufacturing and Controls

NDA SUPP AMEND

S015 BC

Susan Allen, MD, Director
Division of Reproductive and Urological
Drug Products/HFD-580
Office of Drug Evaluation II
Attn: Document Control Room 17B-20
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Allen:

Please refer to our above-referenced New Drug Application for Vivelle-Dot™ (estradiol transdermal systems) and our pending Supplement, S-015, submitted on January 22, 2001 for the prevention of postmenopausal osteoporosis. This supplement included documentation on a new 0.025 mg/day strength of Vivelle-Dot.

The attached documentation is provided to correct CMC information that was previously submitted with the original submission of S-015. The following documentation replaces the stability protocol and commitment, dated December 19, 2000 on pages 4-93 and 4-94 of the original supplement:

- Drug product – Stability protocol and comitment dated June 29, 2001

The replacement stability protocol and commitment were revised to include [redacted] microbial limits testing.

Should you have any comments or questions regarding this submission or any other Chemistry, Manufacturing and Controls issue please contact me directly at (973) 781-2735. If there are any

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

general or Clinical related issues please contact Lynn Mellor, the DRA Therapeutic Area representative at (973) 781-3665.

Sincerely,

Sheryl LeRoy
Chemistry, Manufacturing and Controls
Drug Regulatory Affairs

Attachments
Submitted in Duplicate

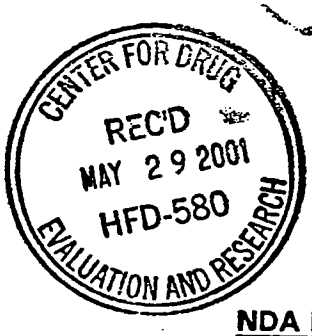
cc: Ms. Regina Brown
New Jersey District Office, North Brunswick Resident Post – Letter only

ORIGINAL

NOVARTIS

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 7500
Fax 973 781 6325



NDA SUPP AMEND
Sel-15-SU

May 25, 2001

Susan Allen, MD
Director
Division of Reproductive and Urological
Drug Products/HFD-580
Office of Drug Evaluation II
Attn: Document Control Room 17B-20
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 20-538/S-015

Vivelle-Dot™ (estradiol transdermal system)

Amendment to a Pending Supplement – 120 Day Safety Update

Dear Dr. Allen:

Reference is made to our efficacy supplement for Vivelle-Dot™ (estradiol transdermal system), S-015 submitted on January 22, 2001. The supplement is to incorporate the labeling changes that were approved on August 16, 2000 for Vivelle® (estradiol transdermal system) NDA 21-167/NDA 20-323 (S-023) to add the claim for prevention of postmenopausal osteoporosis. Approval of Vivelle-Dot was based on demonstrating bioequivalence to Vivelle. FDA approved this supplement (NDA 20-538/S-006) on January 8, 1999. Therefore, we wish to update the Vivelle-Dot label to be consistent with the Vivelle labeling changes approved on August 16, 2000.

Enclosed is the Vivelle-Dot 120-Day Safety Update. This update summarizes the safety data on Vivelle-Dot from spontaneous reports received by Novartis and an update of the review of published literature, each from the respective cutoff dates indicated in the January 2001 sNDA submission. There is no new clinical trial information reported on in this update.

In summary, the data derived from the postmarketing experience and from recent publications do not exhibit any new or unknown aspects that lead to a changing of the safety profile for Vivelle-Dot. All observations are in accordance with already recorded and described data from previous experiences.

There is no new Chemistry, Manufacturing and Controls information being submitted in this Safety Update, therefore a Field Copy will not be provided to the New Jersey District Office.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

If you have any questions or comments concerning this submission, please contact me at (973) 781-3665.

Sincerely yours,

Lynn Mellor

Lynn Mellor
Associate Director
Drug Regulatory Affairs

Vivdot120.doc
Attachments: Form 356h

Copy cover letter:
Regina Brown, NJ District Pre-Approval Inspection Coordinator

NOVARTIS

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 7500
Fax 973 781 3590

ORIGINAL

May 18, 2001

Susan Allen, MD
Director
Division of Reproductive and Urological
Drug Products/HFD-580
Office of Drug Evaluation II
Attn: Document Control Room 17B-20
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 20-538/S-015

Vivelle-Dot™ (estradiol transdermal system)

NDA SUPP AMEND

Amendment to a Pending Supplement

Dear Dr. Allen:

Reference is made to our efficacy supplement for Vivelle-Dot™ (estradiol transdermal system), S-015 submitted on January 22, 2001. The supplement is to incorporate the labeling changes that were approved on August 16, 2000 for Vivelle® (estradiol transdermal system) NDA 21-167/NDA 20-323 (S-023) to add the claim for prevention of postmenopausal osteoporosis. Approval of Vivelle-Dot was based on demonstrating bioequivalence to Vivelle. FDA approved this supplement (NDA 20-538/S-006) on January 8, 1999. Therefore, we wish to update the Vivelle-Dot label at this time to be consistent with the Vivelle labeling changes approved on August 16, 2000.

As requested by the Division attached is an updated financial disclosure attachment for the clinical investigators for the trials included in this supplement. The attachment now includes the number of subjects enrolled in each study by center.

If you have any questions or comments concerning this submission, please contact me at (973) 781-3665.

Sincerely yours,

Lynn Mellor
Associate Director
Drug Regulatory Affairs

LM/tln

Attachments: Form 356h
Sent in Duplicate

REVIEWS COMPLETED

CSO ACTION:

☐ LETTER ☐ E.A.I. ☐ MEMO

CSO INITIALS DATE

NOVARTIS

Lynn Mellor
Associate Director
Drug Regulatory Affairs

Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936-1080

Tel: 973-781-3665
Fax: 973-781-3590
Internet: lynn.mellor@pharma.novartis.com

ORIGINAL

NDA SUPP AMEND

SC1-015-BM February 12, 2001

Susan Allen, MD, Director
Division of Reproductive and Urological
Drug Products/HFD-580
Office of Drug Evaluation II
Attn: Document Control Room 17B-20
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 20-538/S-015

Vivelle-Dot™ (estradiol transdermal system)

Amendment to Pending Application

Dear Dr. Allen:

Reference is made to your January 30, 2001, letter notifying us of receipt of our supplemental drug application (S-015) for Vivelle-Dot (estradiol transdermal system) dated January 22, 2001. This supplement proposes to revise the labeling to incorporate the labeling changes that were approved on August 16, 2000, for Vivelle (estradiol transdermal system) NDA 21-167 and NDA 20-323/S023, to add the claim for prevention of postmenopausal osteoporosis.

Your letter advises that all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR 66632*). The request for a waiver to assess this product in pediatric patients was included in the supplemental application (S-015) for the prevention of postmenopausal osteoporosis submitted on January 22, 2001, volume 1 and page 20-1. The document is entitled 'Waiver Request of Pediatric Study Requirement'.

If you have any questions or comments concerning this submission, please contact me at (973) 781-3665.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Sincerely yours,

Lynn Mellor

Lynn Mellor
Associate Director
Drug Regulatory Affairs

VivdotS015.doc

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 7500
Fax 973 781 6325

NOVARTIS

NDA NO. 20538 REF NO. 015
NDA SUPPL FOR SE8-SE1

January 22, 2001

Susan Allen, MD
Director
Division of Reproductive and Urological
Drug Products/HFD-580
Office of Drug Evaluation II
Attn: Document Control Room 17B-20
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 20-538

Vivelle-Dot™
(estradiol transdermal system)

Efficacy Supplement

Dear Dr. Allen:

At this time we are submitting an efficacy supplement for Vivelle-Dot™ (estradiol transdermal system) to incorporate the labeling changes that were approved on August 16, 2000 for Vivelle® (estradiol transdermal system) NDA 21-167/NDA 20-323 (S-023) to add the claim for prevention of postmenopausal osteoporosis. Approval of Vivelle-Dot was based on demonstrating bioequivalence to Vivelle. FDA approved this supplement (NDA 20-538/S-006) on January 8, 1999. Therefore, we wish to update the Vivelle-Dot label at this time to be consistent with the Vivelle labeling changes approved on August 16, 2000.

The supplement seeks approval for Vivelle-Dot 0.025 mg/day to 0.1 mg/day in the indication for the prevention of postmenopausal osteoporosis based on bioequivalence between Vivelle-Dot and Vivelle and dose proportionality over the entire dosing range of 0.025 mg/day to 0.1 mg/day. Information to support a waiver for a bioequivalence study for the new lower strength of Vivelle-Dot (0.025 mg/day) is provided. Please note with regard to the bioequivalence waiver, the same approach was acceptable to FDA for the approval of the Vivelle 0.025 mg/day strength.

In addition, safety and local tolerability data from three bioavailability studies performed with Vivelle-Dot are presented in the documentation. Also, adhesion data, with Vivelle-Dot, from these studies is discussed. As confirmed by Ms. Diane Moore, FDA project manager, on December 12, 2000, a user fee in not required as this supplement is based solely on bioequivalence or bioavailability studies which are not considered to contain clinical data for the purposes of assessing user fees, even if the studies include clinical endpoints.

The annotated draft label enclosed identifies all of the changes which are consistent with the Vivelle NDA 21-167/NDA 20-323 (S-023) approved changes. In addition, there are minor editorial changes that have been made to the Vivelle-Dot draft label and these are identified as such in the annotated draft label. Also, this supplement will be amended to incorporate any pending labeling changes that are approved prior to the action date on this supplement.

In addition to a paper copy, the draft annotated and draft labeling is being submitted on diskettes. The draft annotated labeling is provided on two diskettes, one contains the physician labeling and the other the patient information labeling. In addition, the draft labeling is provided on two diskettes, one contains the physician labeling and the other the patient information labeling. The diskettes are in the archival copy of the submission. The diskettes provided have been virus scanned using Network Associates VirusScan NT. The diskettes were found to be virus free.

A Field Copy will be provided to the New Jersey District Office.

If you have any questions or comments concerning this submission, please contact me at (973) 781-3665.

Sincerely yours,

Lynn Mellor
Associate Director
Drug Regulatory Affairs

vivdotpmodraft.doc
Attachments: Form 356h
Volumes 1 – 19

cc: Letter Only Regina Brown, NJ District Pre-Approval Inspection Coordinator

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICATION INFORMATION

NAME OF APPLICANT
NOVARTIS PHARMACEUTICALS CORPORATION

DATE OF SUBMISSION
January 22, 2001

TELEPHONE NO. (*Include Area Code*)
(973) 781-3665

FACSIMILE (FAX) Number (*Include Area Code*)
(973) 781-3590

APPLICANT ADDRESS (*Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued*):

59 Route 10
East Hanover, New Jersey 07936-1080

AUTHORIZED U.S. AGENT NAME & ADDRESS (*Number, Street, City, State, ZIP Code, telephone & FAX number*) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (*If previously issued*) **20-538**

ESTABLISHED NAME (*e.g., Proper name, USP/USAN name*)
estradiol transdermal system

PROPRIETARY NAME (*trade name*) IF ANY
Vivelle DOT™

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (*If any*)

CODE NAME (*If any*)

DOSAGE FORM:
Transdermal delivery system

STRENGTHS:
0.025, .0.0375, 0.05, 0.075, 0.1 mg/day

ROUTE OF ADMINISTRATION:
Transdermal

(PROPOSED) INDICATION(S) FOR USE:

APPLICATION INFORMATION

APPLICATION TYPE (*check one*)

☐ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)

☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION (*check one*)

☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☒ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
SUPPLEMENTAL NEW DRUG APPLICATION - EFFICACY SUPPLEMENT

PROPOSED MARKETING STATUS (*check one*) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 19

THIS APPLICATION IS ☒ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

NOVEN PHARMACEUTICALS CORPORATION, MIAMI, FLORIDA
CFN 1058171

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: (*Check all that apply*)	
X	1. Index
X	2. Labeling *(check one)* ☒ Draft Labeling ☐ Final Printed Labeling
X	3. Summary (21 CFR 314.50 (c))
X	4. Chemistry section
X	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50 (d)(1); 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g., 21 CFR 314.50 (e)(2)(i); 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50 (d)(2); 21 CFR 601.2)
X	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50 (d)(3); 21 CFR 601.2)
	7. Clinical Microbiology (e.g., 21 CFR 314.50 (d)(4))
X	8. Clinical data section (e.g., 21 CFR 314.50 (d)(5); 21 CFR 601.2)
	9. Safety update report (e.g., 21 CFR 314.50 (d)(5)(vi)(b); 21 CFR 601.2)
X	10. Statistical section (e.g., 21 CFR 314.50 (d)(6); 21 CFR 601.2)
	11. Case report tabulations (e.g., 21 CFR 314.50 (f)(1); 21 CFR 601.2)
	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
X	13. Patent information on any patent which claims the drug (21 U.S.C 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b)(2) or (j)(2)(A))
	15. Establishment description (21 CFR Part 600, if applicable)
X	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k)(3))
	18. User Fee Cover Sheet (Form FDA 3397)
X	19. Financial Information (21 CFR Part 54)
X	20. OTHER *(Specify)* Pediatric Rule Waiver Request

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowlegde are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Lynn Mellor	Lynn Mellor, Associate Director Drug Regulatory Affairs	1/22/01

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
59 Route 10 East Hanover, New Jersey 07936-1080	(973) 781-3665

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Document Information Page

This page is for FDA internal use only. **Do NOT send this page with the letter!**

Application #(s):	NDA 20-538/S-014, S-015
Document Type:	Supplement Letter
Document Group:	Information Request Letters
Document Name:	Information request letter for pending supplement(s)
Shortcut ID Code:	SNDA-E1
COMIS Decision:	IR (INFORMATION REQUEST)
COMIS Data Entry:	
Drafted by:	dm/October 19, 2001
Revised by:	
Initialed by:	P.Price, S.Slaughter, D.Shames 10.23.01/A.Parekh, T.Rumble 10.24.01
Finalized:	October 24, 2001
Filename:	C:\My Documents\NDALETTERS2001\Novartis\N20538S15ir.doc
DFS Key Words:	
Notes:	
Linking Instructions:	Link this letter to the incoming document for the supplement containing the information requiring further clarification.

END OF DOCUMENT INFORMATION PAGE

The letter begins on the next page

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-538\S-014 and S-015

INFORMATION REQUEST LETTER

Novartis Pharmaceuticals Corporation
Attention: Lynn Mellor
Associate Director, Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Dear Ms. Mellor:

Please refer to your supplemental new drug application (S-014) dated January 19, 2001, received January 23, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vivelle-Dot™ (estradiol transdermal system) 0.0375, 0.05, 0.075 and 0.1 mg/day.

We also refer to your supplemental new drug application (S-015) dated January 22, 2001, received January 23, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vivelle-Dot™ (estradiol transdermal system) 0.0275, 0.0375, 0.05, 0.075 and 0.1 mg/day.

We have completed our review of the physician package insert and patient information insert for your submissions and have the following comments. Revisions have been incorporated directly into the enclosed package insert. Additions have been noted with underlining, deletions have been noted as ~~strikeouts~~. Additional comments requiring response are in **14 pt bold face type**. A clean version copy has also been provided.

Please submit your revised package insert (in hard copy and in electronic format) as soon as available so that we can continue the evaluation of your supplemental NDA.

If you have any questions, call Diane Moore, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Terri Rumble
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Revised package insert

54 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

__X__ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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

/s/

Terri F. Rumble
10/24/01 12:48:05 PM

Document Information Page

This page is for FDA internal use only. **Do NOT send this page with the letter.**

Application #(s):	NDA 20-538/S-015
Document Type:	Supplement Letter
Document Group:	Acknowledgement Letters
Document Name:	Prior approval supplement acknowledgment letter
Letter Code:	SNDA-A1
COMIS Decision:	No Decision Code *(PRIOR APPROVAL SUPPLEMENT ACKNOWLEDGEMENT)*
Drafted by:	dm/January 27, 2001
Revised by:	
Initialed by:	
Finalized:	
Filename:	N20538S15AK.DOC
DFS Key Words:	HRT
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Linking Instructions:	Link the outgoing letter to the first incoming document for the supplemental application. If the submission being acknowledged is being submitted in response to a Refusal-to-File action, then link this outgoing letter to the corresponding RS coded incoming document for the supplement.

END OF DOCUMENT INFORMATION PAGE

The letter begins on the next page.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-538/S-015

PRIOR APPROVAL SUPPLEMENT

Novartis Pharmaceuticals, Corporation
Attention: Lynn Mellor, Associate Director
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Dear Ms. Mellor:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Vivelle-Dot™ (estradiol transdermal system)
NDA Number:	20-538
Supplement Number:	S-015
Review Priority Classification:	Standard (S)
Date of Supplement:	January 22, 2001
Date of Receipt:	January 23, 2001

This supplement proposes the following change: to incorporate the labeling changes that were approved on August 16, 2000, for Vivelle® (estradiol transdermal system) NDA 21-167 and NDA 20-323/S-023, to add the claim for prevention of postmenopausal osteoporosis.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on March 24, 2001 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be November 23, 2001, and the secondary user fee goal date will be January 23, 2002.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt

of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Diane Moore, BS, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Terri Rumble
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

/s/

Terri F. Rumble
1/30/01 09:58:00 AM

54 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

__X__ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Lynn Mellor
Associate Director
Drug Regulatory Affairs

Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936-1080

Tel: 973-781-3665
Fax: 973-781-3590
Internet: lynn.mellor@pharma.novartis.com

NOVARTIS

ORIGINAL

NDA [illegible] AMEND

[illegible] BM February 12, 2001

Susan Allen, MD, Director
Division of Reproductive and Urological
Drug Products/HFD-580
Office of Drug Evaluation II
Attn: Document Control Room 17B-20
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 20-538/S-015

Vivelle-Dot™ (estradiol transdermal system)

Amendment to Pending Application

Dear Dr. Allen:

Reference is made to your January 30, 2001, letter notifying us of receipt of our supplemental drug application (S-015) for Vivelle-Dot (estradiol transdermal system) dated January 22, 2001. This supplement proposes to revise the labeling to incorporate the labeling changes that were approved on August 16, 2000, for Vivelle (estradiol transdermal system) NDA 21-167 and NDA 20-323/S023, to add the claim for prevention of postmenopausal osteoporosis.

Your letter advises that all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR 66632*). The request for a waiver to assess this product in pediatric patients was included in the supplemental application (S-015) for the prevention of postmenopausal osteoporosis submitted on January 22, 2001, volume 1 and page 20-1. The document is entitled 'Waiver Request of Pediatric Study Requirement'.

If you have any questions or comments concerning this submission, please contact me at (973) 781-3665.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A. ☐ MEMO

CSO INITIALS DATE

Sincerely yours,

Lynn Mellor

Lynn Mellor
Associate Director
Drug Regulatory Affairs

VivdotS015.doc

NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey

Vivelle-Dot (estradiol transdermal system) sNDA
Waiver Request of Pediatric Study Requirement

Author(s):	Patricial Ibarra de Palacios
Document type:	Waiver Request of Pediatric Study Requirement
Document status:	Final
Release date:	13-Nov-00
Number of pages:	3

46 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process