CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-167

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey

Type 6 NDA 21-167

Vivelle® (estradiol transdermal system)

Patent Information

The U.S. patents covering Vivelle® (estradiol transdermal system) are as follows:

Patent Number:	4,814,168
Patent Expiration Date:	March 4, 2008
Claims:	Drug Product (Composition/Formulation),
Patent Owner:	Novartis AG

Patent Number:	4,994,267
Patent Expiration Date:	March 4, 2008
Claims:	Drug Product (Composition/Formulation),
Patent Owner:	Novartis AG

Patent Number:	4,994,278
Patent Expiration Date:	March 4, 2008
Claims:	Drug Product (Composition/Formulation),
Patent Owner:	Novartis AG

Patent Number:	5,300,291
Patent Expiration Date:	April 5, 2011
Claims:	Drug Product (Composition/Formulation),
Patent Owner:	Novartis AG

Author(s):	L. Mellor
Document type:	Patent Information
Document status:	Final
Release date:	July 28, 1999
Number of pages:	1

Exclusivity Checklist

NDA: 21-167				
Trade Name: Vivelle				
Generic Name: estradiol transdermal system				
Applicant Name: Novartis				
Division: HFD-510				
Project Manager: William C. Koch				
Approval Date: August 20, 2000				
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	
c. If yes, what type? (SE1, SE2, etc.)	SE1			
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	X	No	
If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.				
Explanation:				
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:				
Explanation:				
d. Did the applicant request exclusivity?	Yes	X	No	
If the answer to (d) is "yes," how many years of exclusivity did the applicant request?	Three			
IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS.				
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?	Yes		No	X
If yes, NDA #				
Drug Name:				
IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS.				
3. Is this drug product or indication a DESI upgrade?	Yes		No	X
IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS (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.	Yes	X	No	
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	X	No	
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).				
Drug Product	Vivelle			
NDA #	NDA 20-323			
Drug Product				
NDA #				
Drug Product				
NDA #				
2. Combination product.	Yes		No	X
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 <u>any one</u> 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).				
Drug Product				
NDA #				
Drug Product				
NDA #				
Drug Product				
NDA #				
IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS. IF "YES," GO TO PART III.				

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS				
To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."				
1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.	Yes	X	No	
IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.				

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	X	No	
If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCKS.				
Basis for conclusion:				
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	X
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	X
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 #:	035			
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	X
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:				
Investigation #1 -- NDA Number				
Investigation #2 -- NDA Number				
Investigation #3 -- NDA Number				

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	X
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:				
Investigation #1 -- NDA Number				
Investigation #2 -- NDA Number				
Investigation #3 -- NDA Number				
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 #1	035			
Investigation #2				
Investigation #3				
4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.				
a. For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?				
Investigation #1	Yes	X	No	
IND#:	40,773			
Explain:				
Investigation #2	Yes		No	
IND#:				
Explain:				
Investigation #3	Yes		No	
IND#:				
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		No	
IND#:				
Explain:				
Investigation #2	Yes		No	
IND#:				
Explain:				
Investigation #3	Yes		No	
IND#:				
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	X
If yes, explain:				

/S/ 08/11/00

Signature of PM Date:

/S/ 8/16/00

Signature of Division or Office Director Date:

cc:
Original NDA 21-167
HFD-510/Division File
HFD-93/Mary Ann Holovac
HFD-104/TCrescenzi

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	21167	**Trade Name:**	VIVELLE (ESTRADIOL TRANSDERMAL SYSTEM)
Supplement Number:	6	**Generic Name:**	ESTRADIOL TRANSDERMAL SYSTEM
Supplement Type:	SE1	**Dosage Form:**	FLM
Regulatory Action:	PN	**Proposed Indication:**	Prevention of post-menopausal osteoporosis

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No waiver and no pediatric data

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)

____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy	Does Not Apply
Formulation Status	-
Studies Needed	-
Study Status	-

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, WILLIAM C. KOCH

/S/ 08/14/00

Signature Date

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey

Type 6 NDA 21-167

Vivelle® (estradiol transdermal system)

Debarment Certification Statement (21 U.S.C.335a)

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

Novartis Pharmaceuticals Corporation hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

August 1, 1999
Date

Lynn Mellor
Associate Director
Drug Registration and Regulatory Affairs

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

Dec. Rm.

AUG 17 2000

Dear [redacted]

Between March 3 and March 15, 2000, [redacted] representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (Protocol #035) of the investigational drug, Vivelle® (estradiol matrix transdermal therapeutic system) performed for Novartis Pharmaceuticals, Inc. This inspection is part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you adhered to all pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator [redacted] during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

/S/

John R. Martin, M.D.
Branch Chief
Good Clinical Practice I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, Maryland 20855

cc:
HFA-224
HFD-510/Doc. Rm. NDA 21-167
HFD-510/Koch
HFD-510/Schneider
HFD-45/Reading File
HFD-46/Chron File
HFD-46/GCP File #010026
HFD- 46/Blay
HFD-46/Huff
HFD-46/Martin
HFR-PA250/Kozick
HFR-PA2565/
HFR-PA2535/

CFN #

Field Classification: VAI

Headquarters Classification:

_X_ 1)NAI
_____ 2)VAI no response required
_____ 3)VAI-R response requested
_____ 4)VAI-RR adequate response received prior to issuance of VAI-R letter
_____ 5)OAI-WL warning letter
_____ 6)OAI-NIDPOE

The 483 listed a lapse in IRB approval, a discrepancy on a case report form, the omission of a minor surgical procedure from the case report form, and the misdating of an ECG. After assessing the investigator's response to these deficiencies and the relative impact of these items on the overall quality of the study, this inspection has been reclassified as NAI.

L
drafted/rab/8.4.00
reviewed:/
final:mgk 8/9/00

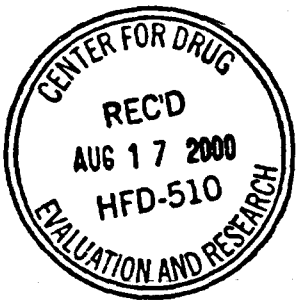
Note to Review Division and DSI Recommendation:

The field inspector reviewed the study-related records of 14 of the 26 subjects randomized to the study for protocol #035 at [redacted] site. The data appear acceptable for use in support of drug claims.

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

NOVARTIS



August 14, 2000

John Jenkins, M.D.
Acting Director
Division of Metabolism and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room #14B-19
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 21-167
Vivelle ® (estradiol transdermal system)

Amendment to a Pending Drug Application

Dear Dr. Jenkins:

Reference is made to our Type 3 New Drug Application for Vivelle® (estradiol transdermal system) dated October 19, 1999. This submission is for a labeling change to add a new indication for the prevention of postmenopausal osteoporosis. Vivelle is currently approved under NDA 20-323 for the treatment of patients with estrogen deficiency syndrome The osteoporosis submission also provides for additional dosage strength (Vivelle 0.025 mg/day).

Reference is also made to the August 3, 2000 FDA labeling teleconference to discuss the draft label for Vivelle. In addition, refererence is made to the telefacsimile sent to the agency dated August 10, 2000, that incorporated the revisions to the draft label discussed at the labeling teleconference. And reference is made to the telefacsimile sent to the agency dated August 11, 2000, that incorporated the revisions discussed on August 11, 2000 with the Division.

Enclosed is a draft label and an annotated label that includes the changes discussed on the dates referenced above and on August 14, 2000. Also included in this submission is a diskette containing these documents in Word format.

This information has alsc been submitted to the Division of Reproductive and Urological Drug Products.

The User Fee for this application (user fee ID 3766) was submitted on July 28, 1999.

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

Vivpmo9.doc
Attachments: Form 356h

Copy cover letter:
Diane Moore, Division of Reproductive and Urologic Drug Products

Novartis Pharmaceuticals Corporation

Fax

To:	Bill Koch	**From:**	Lynn Mellor
Fax:	301 443-9282	**Pages:**	50 (2parts 25pgs & 26pgs)
Phone:	301 827-6412	**Date:**	08/10/00
Re:	Vivelle NDA 21-167	**CC:**	

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

Dear Mr. Koch,

Attached is the draft and draft annotated label (Physician/ Patient) for Vivelle (estradiol transdermal system) NDA 21-167. This draft label incorporates the revisions requested by FDA at the August 3, 2000 labeling teleconfernece. Please provide a copy of the draft label to Diane Moore, Division of Reproductive and Urologic Drug Products.

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

Sincerely,

Lynn Mellor
Drug Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

24 page(s) of revised draft labeling has been redacted from this portion of the review.

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products

MEMORANDUM

Date: August 10, 2000 /S/

From: Bruce Schneider, M.D., Medical Reviewer

Subject: Second Safety Update

To: FILE: NDA 21-167

The 120-day safety update submitted by the applicant on February 14, 2000, is adequate for approval. A second safety update within 90 days of approval is not needed.

There are no new or ongoing trials with Vivelle and the reporting data base has been closed.

During the period of February 1999 through October 27, 1999, the _____ _____ prescriptions were written, exposing an estimated 98,500 patients to Vivelle.

There were no deaths and 8 serious adverse events reported with Vivelle in the last 4 years.

cc: Original NDA 21-167
HFD-510/Div. Files
HFD-510/CSO
HFD-510/reviewers

Drafted by: WKoch/08.08.00

filename: C:/Windows/Desktop/nda21167/MEMfileSU.doc

MEMO TO FILE

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products

MEMORANDUM

Date: August 10, 2000

From: Bruce Schneider, M.D., Medical Reviewer

Subject: Waiver of the Pediatric Study Requirement

To: FILE: NDA 21-167

I have reviewed the request for waiver of the pediatric study requirement submitted by the applicant on December 3, 1999, and the use of this product in pediatric populations has been addressed in the medical officer review of this application. Postmenopausal osteoporosis does not occur in the pediatric population. The requested waiver of the pediatric study requirement has, therefore, been granted.

ATTACHMENTS:

Applicant waiver request of December 3, 1999.

cc: Original NDA 21-167
HFD-510/Div. Files
HFD-510/CSO
HFD-510/reviewers

Drafted by: WKoch/08.08.00

filename: _____

MEMO TO FILE

Meeting Date: August 3, 2000 Time: 11:30 Location: PKLN Room #17B-43

NDA 21-167 Vivelle (estradiol transdermal system)

Type of Meeting: Labeling Telephone Conference

External Participant: Novartis Pharmaceuticals Corporation

Meeting Chair: Eric Colman, M.D. Acting Medical Team Leader

External Participant Lead: Lynn Mellor, Regulatory Affairs

Meeting Recorder: William C. Koch, R.Ph., Regulatory Project Manager

FDA Attendees and titles:

Eric Colman, M.D. Acting Medical Team Leader
Bruce Schneider, M.D., Medical Officer
Sue Jane Wang, Ph.D. Biometrics 2 Reviewer
Michael F. Ortwerth, Ph.D., Chemistry Reviewer (HFD-580)
Dornette Spell-Lesane, Regulatory Project Manager (HFD-580)
Margaret M. Kober, Regulatory Project Manager (HFD-42)
Lisa Stockbridge, Ph.D., Regulatory Reviewer (DDMAC; HFD-42)
Diane V. Moore, B.S., Regulatory Project Manager (HFD-580)
William C. Koch, R.Ph., Regulatory Project Manager

External participant Attendees (by phone) and titles:

Zeb Horowitz, M.D., Clinical Research
Fran Dapas, M.D., Medical Affairs
Judy Zander, M.D., Safety and Epidemiology
Maria Roberts, Clinical Research
Nathalie Ezzet, Ph.D., Biostatistics
Sumadha Jayawardene, Ph.D., Biostatistics
Mohammed Hossain, Ph.D., Clinical Pharmacology
Neal Sailer, Marketing
Stephanie Barba, Regulatory Affairs
Sheryl LeRoy, Regulatory Affairs
Lynn Mellor, Regulatory Affairs

Meeting Objectives:

- To discuss with the applicant the Division recommendations for the final product labeling For the proposed new indication of post-menopausal osteoporosis.

Discussion Points:

- Regarding the boxed warning on the first page the applicant reminded the Divisions that the pregnancy warning was moved to the **Information for the Patient** part of the label.
- In the **Special Populations** paragraph of the **PHARMACOKINETICS** section, the division Requested a sentence declaring that no studies were done with Vivelle in renally or hepatically impaired subjects. The first sentence was changed to include that approximately 90% of the postmenopausal women studied were caucasian.
- In the **Clinical Studies** paragraphs, the second and third paragraphs were accepted by the Division as proposed by the applicant.
- Figure was renamed to :

  Bone Mineral Density – AP Lumbar spine ——
  Last Post-Baseline Observation Carried Forward ————

- The Division requested that data presented in Figure 2 be formatted as a
- The changes recommended by the Division in the last paragraph in the **Clinical Studies** paragraphs was accepted by the applicant (refer to ATTACHMENT).
- The additions and changes to number four in **INDICATIONS AND USAGE** (refer to ATTACHMENT)section were accepted by the applicant with the understanding that competing products' labeling would be also changed.
- The Division recommended that the first sentence of the **Nursing Mothers** paragraph be deleted.
- The Division requested that distributor information be added to the last page of the professional part of the package insert in addition to retaining this information at the end of the patient package insert.
- The Division requested that all references in the text to the highest dose system would delete the zero following the 0.1 to avoid confusion.
- The Division requested that all references in the text to package insert sections be in bolded type.

Decisions (agreements) reached:

Unresolved or issues requiring further discussion:

- None

Action Items:

- None

Post-Meeting Activity:

- The applicant communicated to the Division on August 4, 2000, that the patient package insert is not separated from the professional portion of the labeling therefore it should not be necessary to include distributor information in two places.

- The chemistry reviewer, speaking for the Division, agreed with the applicant on the Necessity of having distributor information only at the end of the patient package insert.

Prepared by: /S/ 08/15/00, Meeting Recorder
William C. Koch, R.Ph. date
Regulatory Project Manager

APPEARS THIS WAY
ON ORIGINAL

ATTACHMENT:

Draft label based upon Division Revisions of August 3, 2000

cc: Original NDA 21-167
HFD-510/Div. Files
HFD-510/Meeting Minutes files
HFD-510/CSO
HFD-510/reviewers & attendees
HFD-580/DMoore/DSpellLesane/MOrtwerth
HFD-042/MKober/LStockbridge

Drafted by: WKoch/08.03.00
final: WKoch/08.15.00
filename: _____

MEETING MINUTES

APPEARS THIS WAY
ON ORIGINAL

23 page(s) of revised draft labeling has been redacted from this portion of the review.

TEAM LEADER MEMO

NDA: 21167

DRUG: Estradiol Transdermal System - Vivelle

COMPANY: Novartis

PROPOSED INDICATION: Prevention of Postmenopausal Osteoporosis

PRIMARY MEDICAL OFFICER: Bruce Schneider, MD

DATE: July 31, 2000

Vivelle is currently approved for the treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure. The doses approved include 0.0375mg, 0.05mg, and 0.10mg. The company sponsored a 2-year randomized, double-blind, placebo-controlled osteoporosis prevention trial which included 5 dosing arms (0.025mg, 0.0375mg, 0.05mg, 0.10mg, and placebo). Women with a uterus received 2.5mg of MPA. The primary efficacy variable was the change from baseline to Endpoint in lumbar spine (LS) bone mineral density (BMD).

A total of 261 women were randomized, in roughly equal allocation, to one of the 5 treatment groups. Baseline demographics were not significantly different among groups. The mean age was 52 years, the average BMI was 28 kg/m^2, 92% of the subjects were Caucasian, and 61% had had a hysterectomy. The average baseline LS T-score were all greater than –2.0 and similar among groups. Approximately 70% of the women completed the 2-year study; a slightly larger percentage of subjects discontinued prematurely from the highest Vivelle group.

As discussed in Dr. Schneider's review, the company mistakenly labeled the efficacy data presented in the tables and figures as ITT, but in fact the data were completers. It turns out that the results are similar for both analyses; however, for consistency with other approved estrogen compounds, the label should present true ITT data only (which the company has agreed to do).

Over the course of the study the placebo group had a mean percent reduction in LS BMD of about 2.0%. The mean percent increases in LS BMD for the four Vivelle groups were as follows: 0.025mg 1.8%, 0.0375mg 2.0%, 0.05mg 3.2%, and 0.10mg 6.0%. All changes in the Vivelle groups were statistically significantly greater than the change in the placebo group. The 0.10mg dose was the only Vivelle treatment group that differed significantly from the other active-treatment groups. The changes in femoral neck BMD was also significantly greater in the Vivelle groups relative to placebo.

No unexpected safety issue came to light in this trial. As one would predict, the rates of vaginal bleeding and breast pain were higher in the active-treatment arms compared with placebo (except for bleeding in the 0.025mg group, which was lower than placebo).

Comment

Novartis has submitted data from a 2-year trial in early postmenopausal women that demonstrates the BMD preserving effect of 4 doses of Vivelle. The highest dose — 0.10mg — was associated with the greatest increase in BMD, but was also associated with a larger number of adverse events. The lowest dose of

Vivelle — 0.025mg — increased LS BMD by about 4%. Whether this is the lowest effective dose for the prevention of postmenopausal osteoporosis is unknown. Presumably lower doses would lead to statistically significant increases in LS BMD relative to placebo; however, the question that still looms large for all estrogenic compounds is what is the minimum effective dose of estrogen that will confer risk reduction for osteoporotic fracture?

The sponsor has provided adequate data to support the approval of Vivelle (0.025mg, 0.0375mg, 0.05mg, and 0.10mg) for the prevention of postmenopausal osteoporosis, as defined by change in LS BMD.

/S/ 8/7/02

Eric Colman, MD

cc: NDA Arch

Novartis Pharmaceuticals Corporation

Fax

To:	Bill Koch	**From:**	Lynn Mellor
Fax:	301 443-9282	**Pages:**	
Phone:	301 827-6412	**Date:**	07/28/00
Re:	Vivelle NDA 21-167	**CC:**	

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

Dear Mr. Koch,

As requested attached is a copy of the Vivelle submission dated July 27, 2000. This submission was sent via Federal Express with delivery for the morning of July 28, 2000. Please let me know if you have received the Federal Express delivery. 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

Continued

39 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

NOVARTIS

Lynn Mellor
Associate Director

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

Tel 973 781-3665
Fax 973 781-3590

July 27, 2000

Susan Allen, 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

NDA No. 20-323
Vivelle® (estradiol transdermal system)

Amendment to Pending Labeling Supplement

Dear Dr. Allen:

Reference is made to our Type 3 New Drug Application for Vivelle® (estradiol transdermal system), NDA 21-167, dated October 19, 1999. This submission is for a labeling change to add a new indication for the prevention of postmenopausal osteoporosis and was submitted to the Division of Metabolism and Endocrine Drug Products. Vivelle is currently approved under NDA 20-323 for the treatment of patients with estrogen deficiency syndrome, specifically: treatment of moderate-to-severe vasomotor symptoms associated with menopause; treatment of vulval and vaginal atrophy; and treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure. The osteoporosis submission also provides for additional dosage strength (Vivelle 0.025 mg/day).

Reference is also made to the requests made by the Medical Reviewer and Biometrics Reviewer in the Division of Metabolism and Endocrine Drug Products, on July 20, 2000, pertaining to Protocol 035. Protocol 035 supports the indication for prevention of postmenopausal osteoporosis. The requested information was submitted to NDA 21-167.

The information submitted to NDA 21-167 includes the output of the primary efficacy analysis (lumbar spine bone mineral density [BMD]) for the intent-to-treat population (all patients with baseline and at least one post baseline lumbar spine BMD measurement) with last observation carried forward. In addition, the output of the secondary efficacy analysis (femoral neck BMD) for the intent-to-treat population (all patients with baseline and at least one post baseline femoral neck BMD measurement) with last observation carried forward was provided.

As these analyses affect the draft label, attached is an update of the Clinical Studies section of the package insert pertaining to osteoporosis. Attachment 1 provides for an update to the annotated draft label and draft label of the Clinical Studies section.

This information has also been submitted to the Division of Metabolism and Endocrine Drug Products as an Amendment to a Pending Drug Application.

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

Vivfda13.doc
Attachments: Form 356h

Copy cover letter:
Bill Koch, Division of Metabolism and Endocrine Drug Products

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

ORIG AMENDMENT

NOVARTIS

Lynn Mellor
Associate Director

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

Tel 973 781-3665
Fax 973 781-3590

July 27, 2000

John Jenkins, M.D.
Acting Director
Division of Metabolism and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room #14B-19
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 21-167
Vivelle ® (estradiol transdermal system)

Amendment to a Pending Drug Application

Dear Dr. Jenkins:

Reference is made to our Type 3 New Drug Application for Vivelle® (estradiol transdermal system) dated October 19, 1999. This submission is for a labeling change to add a new indication for the prevention of postmenopausal osteoporosis. Vivelle is currently approved under NDA 20-323 for the treatment of patients with estrogen deficiency syndrome, specifically: treatment of moderate-to-severe vasomotor symptoms associated with menopause; treatment of vulval and vaginal atrophy; and treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure. The osteoporosis submission also provides for additional dosage strength (Vivelle 0.025 mg/day).

Reference is also made to the requests made by Dr. Bruce Schnieder, Medical Reviewer, and Dr. Sue Jane Wang, Biometrics Reviewer, on July 20, 2000, pertaining to Protocol 035. Protocol 035 supports the indication for prevention of postmenopausal osteoporosis.

At this time we are providing the requested information for lumbar spine bone mineral density (BMD). In addition, the same approach was taken for the secondary endpoint femoral neck BMD, and the information is provided.

- The table in Attachment 1 provides the number of patients with baseline lumbar spine BMD measurements only, and the number of patients with baseline and at least one post-baseline lumbar spine BMD mesurement by treatment group.

- Attachment 2 provides the output of the primary efficacy analysis (lumbar spine BMD) for the intent-to-treat population (all patients with baseline and at least one post-baseline lumbar spine BMD measurement) with last observation carried forward. SND provides the output of the secondary efficacy analysis (femoral neck BMD) for the intent-to-treat population (all patients with baseline and at least one post-baseline femoral neck BMD measurement) with last observation carried forward

As these analyses affect the draft label, attached is an update of the Clinical Studies section of the package insert pertaining to osteoporosis.

- Attachment 3 provides for the annotated draft label and the draft label of the Clinical Studies section.

The labeling information has also been submitted to the Division of Reproductive and Urological Drug Products as an Amendment to a Pending Labeling Supplement.

The User Fee for this application (user fee ID 3766) was submitted on July 28, 1999.

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

Vivpmo8.doc
Attachments: Form 356h

Desk copy(s):
Dr. Bruce Schnieder, Medical Reviewer
Dr. Sue Jane Wang, Biometrics Reviewer
Mr. Bill Koch, Project Manager

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Copy cover letter:
Diane Moore, Division of Reproductive and Urologic Drug Products

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

Tel 973 781 7500
Fax 973 781 6325

NOVARTIS

26-Jul-00

NDA 21-167
Vivelle® (estradiol transdermal system)

Response to FDA June 30, 2000 letter – Chemistry, Manufacturing and Controls

John Jenkins, MD, Acting Director
Division of Metabolic and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-19
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Jenkins:

Please refer to our above-referenced New Drug Application for Vivelle (estradiol transdermal system). Reference is also made to FDA's June 30, 2000 letter outlining CMC concerns.

The attached documentation is provided in response to FDA's concerns. A copy of the FDA's June 30, 2000 letter is also provided in Attachment I, as a convenience to the reviewer.

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 Ms. 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

Desk copies to William Koch, project manager (2)

cc: Ms. Regina Brown
New Jersey District Office, North Brunswick Resident Post - Certified Field Copy

APPEARS THIS WAY
ON ORIGINAL

Meeting Date: July 18, 2000 Time: 12:00 pm Location: PKLN Room #14B-45

NDA 21-167 Vivelle (estradiol transdermal system)

Type of Meeting: Internal Labeling

Meeting Chair: Eric Colman, M.D. Acting Medical Team Leader

Meeting Recorder: William C. Koch, R.Ph., Regulatory Project Manager

FDA Attendees and titles:

Eric Colman, M.D. Acting Medical Team Leader
Bruce Schneider, M.D., Medical Officer
Hae-Young Ahn, Ph.D., Biopharmaceutics Team Leader
Robert Shore, Pharm.D., Biopharmaceutics Reviewer
Todd Sahlroot, Ph.D., Team Leader, Biometrics 2
Sue Jane Wang, Ph.D. Biometrics 2 Reviewer
Michael F. Ortwerth, Ph.D., Chemistry Reviewer (HFD-580)
Diane Moore, Regulatory Project Manager(HFD-580)
Margaret Kober, Consumer Safety Officer(DDMAC)
William C. Koch, R.Ph., Regulatory Project Manager

Meeting Objectives:

To discuss proposed Division labeling changes to this NDA.

Discussion Points:

- The Division proposed that the new dose be included in all revisions
- The Division proposed that the data presented in Figure 1 be modified to reflect the numbers of patients who actually contributed to the data at 104 weeks, or that the title of Figure 1 be changed accordingly.
- The Division proposed that the second paragraph of the Clinical Studies paragraphs be changed to the following:

  The study population comprised naturally (82%) or surgically (18%) menopausal, hysterectomized (61%) or nonhysterectomized (39%) women with a mean age of 52.0 years (range 27 to 62 years; the mean duration of menopause was 31.7 months (range 2 to 72 months) _____ of randomized subjects (– on active drug, - on placebo) _____ _____ contributed data to the analysis of percent change from

baseline in bone mineral density (BMD) of the AP lumbar spine, the primary efficacy variable. Patients were given supplemental dietary calcium (1000 mg elemental calcium/day) but no supplemental vitamin D. There was an increase in BMD of the AP lumbar spine in all Vivelle dose groups; in contrast to this a decrease in AP lumbar spine BMD was observed in placebo patients. All Vivelle doses were significantly superior to placebo ($p<0.05$) at all time points with the exception of Vivelle 0.05 mg/day at 6 months, [redacted]. The highest dose of Vivelle was superior to the three lower doses. There were no statistically significant differences in pairwise comparisons among the 3 lower doses.

- The Division proposed that the paragraph following Figure 1 be changed to:

  Analysis of percent change from baseline in femoral neck BMD, a secondary efficacy outcome variable , showed qualitatively similar results; all doses of Vivelle were significantly superior to placebo ($p<0.05$) at 24 months. [redacted] Again, the highest Vivelle dose was superior to the three lower doses, and there were no significant differences among the three lower doses at this skeletal site.

- The Division proposed that the first paragraph after Figure 2 be modified to the following:

  The mean serum osteocalcin (a marker of bone formation) and urinary excretion of cross-link N-telopeptides of type 1 collagen (a marker of bone resorption) decreased in most of the active treatment groups, relative to baseline. [redacted] However, the decreases in both markers were inconsistent across treatment groups and the differences between active treatment groups and placebo were not statistically significant.

- The Division proposed that the following paragraphs be added to the **INDICATIONS AND USAGE** section:

  White and Asian women are at higher risk for osteoporosis than black women, and thin women are at a higher risk than heavier women, who generally have a higher endogenous estrogen levels. Early menopause is one of the strongest predictors for the development of osteoporosis. Other factors associated with osteoporosis include genetic factors (small build, family history), lifestyle (cigarette smoking, alcohol abuse, sedentary exercise habits) and nutrition (below average body weight and dietary calcium intake)

  Essential to the prevention and management of osteoporosis are weight bearing exercise, adequate calcium intake, and, when indicated, estrogen. Postmenopausal women absorb dietary calcium less efficiently than premenopausal women and require and average of 1500 mg/day of elemental calcium to remain in neutral calcium balance. The average calcium intake in the USA is 400-600 mg/day. Therefore, when not contraindicated, calcium supplementation may be helpful for women with suboptimal dietary intake.

- In the third paragraph of the **ADVERSE REACTIONS** section, the Division proposed the addition of the following sentence:

  Vaginal bleeding and breast tenderness were more common in the highest dose group (0.1 mg/day) than in the three other active treatment groups or in placebo-treated patients.

- The Division proposed in the **DOSAGE AND ADMINISTRATION** section, the fourth Paragraph the addition of the following:

  Reproductive system-associated adverse events were encountered more frequently in the highest dose group (0.1 mg/day) than in other active treatment dose groups or in placebo-treated patients.

- In the patient package insert (PPI), the Division proposed that the word "helps" be inserted prior to all references to prevents osteoporosis.

- In the **SIDE EFFECTS** section of the PPI, the Division proposed the addition of "vaginal spotting or bleeding".

Unresolved or issues requiring further discussion:

- The above proposals will be presented to the applicant in a teleconference on August 3, 2000.

Action Items:

- None

Prepared by: /S/ 07/21/00, Meeting Recorder
William C. Koch, R.Ph. date
Regulatory Project Manager

ATTACHMENT:

Draft of Division proposals to label

cc: Original NDA 21-167
HFD-510/Div. Files
HFD-510/Meeting Minutes files
HFD-510/CSO
HFD-510/reviewers & attendees

Drafted by: WKoch/07.18.00
final: WKoch/07.21.00
filename: C:/Windows/desktop/nda21167/MTGlblTEAM071800.doc

MEETING MINUTES

APPEARS THIS WAY
ON ORIGINAL

Koch

NOVARTIS

Lynn Mellor
Associate Director

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

Tel 973 781-3665
Fax 973 781-3590

July 11, 2000

Susan Allen, 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

NDA No. 20-323
Vivelle® (estradiol transdermal system)

Amendment to Pending Labeling Supplement

Dear Dr. Allen:

Reference is made to our Type 3 New Drug Application for Vivelle® (estradiol transdermal system), NDA 21-167, dated October 19, 1999. This submission is for a labeling change to add a new indication for the prevention of postmenopausal osteoporosis and was submitted to the Division of Metabolism and Endocrine Drug Products. Vivelle is currently approved under NDA 20-323 for the treatment of patients with estrogen deficiency syndrome, specifically: treatment of moderate-to-severe vasomotor symptoms associated with menopause; treatment of vulval and vaginal atrophy; and treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure. The osteoporosis submission also provides for additional dosage strength (Vivelle 0.025 mg/day).

Reference is also made to our labeling supplement dated April 19, 2000, to provide draft labeling to include changes pertaining to prevention of osteoporosis. However, please note that in the HOW SUPPLIED section of the Prescribing Information the text pertaining to the Vivelle 0.025 mg/day dose was inadvertently omitted.

At this time we wish to amend the HOW SUPPLIED section of the draft label and annotated label to include the following:

Vivelle estradiol transdermal system 0.025 mg/day – each 7.25 cm^2 system contains 2.17 mg of estradiol USP for nominal* delivery of 0.025 mg of estradiol per day

Patient Calendar Pack of 8 systems.....NDC 0078-0348-42
Carton of 6 Patient Calendar Packs of 8 systems.....NDC 0078-0348-44

Identical information has also been submitted to the Division of Metabolism and Endocrine Drug Products as a Supplement to a Pending Application.

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

Vivfda12.doc
Attachments: Form 356h

Copy cover letter:
Bill Koch, Division of Metabolism and Endocrine Drug Products

APPEARS THIS WAY
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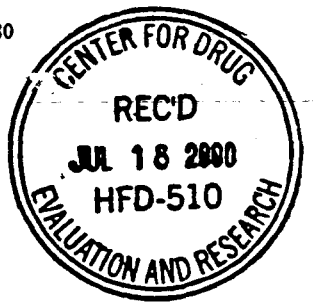
NOVARTIS

Lynn Mellor
Associate Director

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

Tel 973 781-3665
Fax 973 781-3590



July 11, 2000

John Jenkins, M.D.
Acting Director
Division of Metabolism and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room #14B-19
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 21-167
Vivelle ® (estradiol transdermal system)

Amendment to a Pending Drug Application

Dear Dr. Jenkins:

Reference is made to our Type 3 New Drug Application for Vivelle® (estradiol transdermal system) dated October 19, 1999. This submission is for a labeling change to add a new indication for the prevention of postmenopausal osteoporosis. Vivelle is currently approved under NDA 20-323 for the treatment of patients with estrogen deficiency syndrome, specifically: treatment of moderate-to-severe vasomotor symptoms associated with menopause; treatment of vulval and vaginal atrophy; and treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure. The osteoporosis submission also provides for additional dosage strength (Vivelle 0.025 mg/day).

Reference is also made to our submission dated April 19, 2000, to amend the pending application to provide for an updated annotated draft and draft label. Please note that in the HOW SUPPLIED section of the Prescribing Information the text pertaining to the Vivelle 0.025 mg/day dose was inadvertently omitted.

At this time we wish to amend the HOW SUPPLIED section of the draft label and annotated label to include the following:

Vivelle estradiol transdermal system 0.025 mg/day – each 7.25 cm^2 system contains 2.17 mg of estradiol USP for nominal* delivery of 0.025 mg of estradiol per day

Patient Calendar Pack of 8 systems.....NDC 0078-0348-42
Carton of 6 Patient Calendar Packs of 8 systems.....NDC 0078-0348-44

The User Fee for this application (user fee ID 3766) was submitted on July 28, 1999.

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

Vivpmo7.doc
Attachments: Form 356h

Copy cover letter:
Diane Moore, Division of Reproductive and Urologic Drug Products

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Novartis Pharmaceuticals Corporation

Fax

To:	Bill Koch	**From:**	Lynn Mellor
Fax:	301 443-9282	**Pages:**	
Phone:	301 827-6412	**Date:**	07/05/00
Re:	Vivelle NDA 21-167	**CC:**	

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

Dear Mr. Koch,

Attached is a copy of the letter dated November 23, 1999 to the Vivelle NDA 20-323 file. Novartis committed to submit information to support a Special Supplement – Changes Being Effected to provide for printing on the backing layer of the Vivelle transdermal system in July 2000.

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

Sincerely,

Lynn Mellor
Drug Regulatory Affairs

NDA 21-167

DISCIPLINE REVIEW LETTER

Novartis Pharmaceuticals Corporation
Attention: Sheryl LeRoy
Chemistry, Manufacturing and Controls
Drug Regulatory Affairs
59 Route 10
East Hanover, New Jersey 07936-1080

JUN 30 2000

Dear Ms. LeRoy:

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

We also refer to your submissions dated October 19, 1999, March 6 and June 15, 2000.

Our review of the Chemistry section of your submissions is complete, and we have identified the following deficiencies:

DEFICIENCIES:

1. Please provide a detailed sampling procedure for the finished drug product patches.

2. Please provide a rationale for weight changes made in —— testing during stability tests.

3. Please submit a shelf-life specification giving an acceptable range for drug product ——— testing and provide a rationale for selection of the specification.

4. Please provide a post-approval stability protocol and a post-approval stability commitment. (A cross-reference to NDA 20-323 is not acceptable for these items.) The post-approval stability commitment should include a statement that extension of expiration dating will be based on real-time data from three production batches.

5. Please replace the term ———— used throughout labeling with the approved term "estradiol".

6. Please provide labeling for the back panel of the drug product transdermal patch that includes the drug product tradename and delivery rate.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call William C. Koch, R.Ph., Regulatory Project Manager, at (301) 827-6412.

Sincerely,

/S/ 6/29/00

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader, for the
Division of Reproductive
and Urologic Drug Products (HFD-580),
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc:
Archival NDA 21-167
HFD-510/Div. Files
HFD-510/WKoch
HFD-510/Reviewers and Team Leaders
HFD-580/MOrtwerth/MRhee
HFD-820/DNDC Division Director
DISTRICT OFFICE

Drafted by: WKoch/June 29, 2000
Initialed by: MRhee/06.29.00
final: WKoch/06.29.00
filename: C:/WINDOWS/DESKTOP/NDA21167/LTRdr063000

DISCIPLINE REVIEW LETTER (DR)

FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS
5600 FISHERS LANE, HFD-510
ROCKVILLE, MARYLAND 20857-1706

DATE: June 30, 2000

Comments:

Attached is a copy, for your information, of the Discipline Review Letter from the Division's Chemistry Team. The original will be mailed directly.

Please don't hesitate to call with any questions.~Bill

TO:
Name: Sheryl LeRoy
Chemistry, Manufacturing and Controls
Fax No.: (973) 781-6325
Phone No.: (973) 781-2735
Location: Novartis Pharmaceuticals Corporation

FROM:
Name: William C. Koch, R.Ph.
Regulatory Project Manager
Fax No.: (301)-443-9282
Phone No.: (301)-827-6412

Pages (including this cover sheet): THREE (3)

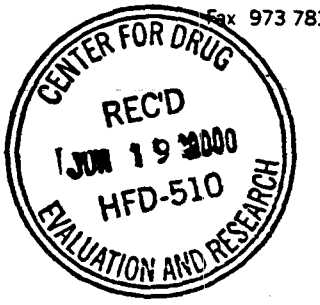
ORIGINAL

ORIG AMENDMENT
BC

NOVARTIS

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

Tel 973 781 7500
Fax 973 781 6325



/S/

27-JUN-2000
See Chemistry Review #1

15-Jun-00

NDA 21-167
Vivelle® (estradiol transdermal system)

Amendment to pending NDA: Response to FDA June 12, 2000 telephone call – Chemistry, Manufacturing and Controls

John Jenkins, MD, Acting Director
Division of Metabolic and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-19
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Dear Dr. Jenkins:

Please refer to our above-referenced New Drug Application for Vivelle (estradiol transdermal system). As a follow-up to the June 12, 2000 telephone conversation that Lynn Mellor of Novartis had with FDA Project Manager, Bill Koch, Novartis is providing additional CMC information to the above-referenced NDA.

Stability data
In summary, Mr. Koch asked Novartis to provide stability data for drug product batch 3A1410-A1. The stability data for + months at room temperature and – months at ——— were inadvertantly omitted from the NDA, and are now provided:

Attachment I

- Stability Summary Report - Estradiol transdermal; 7.25 sq. cm circles; 2.17 mg/unit, lot 3A1401-A1, manufactured 14-Jan-93

Please note that the month room temperature sample had — out of — out-of-specification results for potency. However, when averaged, the result passed, according to the Novartis Quality Standard. The follow-up investigation into the failures concluded that the out-of-specification results were due to non-uniform sampling procedures. Since the investigation, ——— sampling procedures have been modified to be more uniform over the length of the ——— Please also note that two higher strengths of Vivelle systems had been

manufactured from the same ——— and no failures were observed at — months for those batches.

Certificate of Analysis data
While reviewing the CMC section of this NDA, we noticed that the certificate of analysis for batch 6H2010-A1 was missing. We are also providing this certificate of analysis, to complete the NDA:

Attachment II

- Certificate of analysis – Lot 6H2010-A1, manufactured 31-Aug-96

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 Ms. 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 - Certified Field Copy

APPEARS THIS WAY
ON ORIGINAL