Electronic Mail Message

BEST POSSIBLE COPY

Date: 6/12/00 12:02:45 PM
From: Michael Ortwerth (ORTWERTHM)
To: William C. Koch (KOCHW)
Cc: Moo-Jhong Rhee (RHEEM)
Subject: Request for Stability Data; NDA 21167; Vivelle

Bill,

For NDA 21-167, Vivelle (estradiol transdermal system), I have found an error in the sponsors submission. In the stability section of volume 1.3 on page 4-119, the sponsor refers to Attachment 1 in which it's contents are defined as:

> Estradiol Transdermal System, (7.25 cm2) (0.025 mg.day), Lot Number 6H2010-A1
> Estradiol Transdermal System, (7.25 cm2) (0.025 mg.day), Lot Number 3A0601-A1
> Estradiol Transdermal System, (7.25 cm2) (0.025 mg.day), Lot Number 3A1401-A1

The last entry is actually NOT included in the sponsors submission. I will need this data for my review. Could you please request that the sponsor fax the information for "Estradiol Transdermal System, (7.25 cm2) (0.025 mg.day), Lot Number 3A1401-A1" to expedite my review and ask that they follow the facsimile with a formal amendment including this information.

If you have any questions, please give me a call at 7-7514 or if necessary I can drop by your office.

Thank you very much for attending to tnis request. If you would simply like me to contact the sponsor and request this information, please let me know. I thought I would go through you first so that you could handle it if you would like and to give you a heads-up on the issue.

Thanks again,

Michael Ortwerth
Review Chemist, HFD-560

CMC
Chantelle
973
781-2735

23773
973-741-8180
Ellen
Cutler

973-305-8145
Kimmel

Rob Clark
7005

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

[redacted]

MAY [redacted]

[redacted]

Dear [redacted]

Between March 2 and March 26, 2000, [redacted] representing the Food and Drug Administration (Agency), inspected your conduct as the investigator of record of a clinical study (Protocol #035) of Vivelle® (estradiol transdermal system) that you conducted for Ciba-Geigy (Novartis). This inspection is part of the Agency's Bioresearch Monitoring Program which includes inspections to determine the validity of clinical drug studies that may provide the basis for drug marketing approval and to assure that the rights and welfare of the human subjects who participated in those studies have been protected.

At the close of the inspection, [redacted] presented her inspectional observations (i.e., Form FDA 483) and discussed these observations with you. From our evaluation of the inspection report and your oral responses to the inspectional observations, we conclude that you did not adhere to all pertinent Federal regulations and good clinical practices governing your conduct of clinical studies of investigational new drugs and the protection of human subjects. We have noted the following specific instances in which you failed to maintain adequate and accurate records:

1. There were no source documents for subject #326 for Visit #2.

2. The Annual Progress Report, dated September 8, 1997, and submitted to the IRB did not report a serious adverse event (myocardial infarction) for subject #1615 even though the event was reported to the IRB at the time of its occurrence.

Additional recommendations:

1. A copy of the final screening log was not maintained in the files. A subsequent copy of the log was incomplete because it did not document the reasons for the exclusion of 38 of 52 subjects who were not randomized to the study. While not specifically required by the regulations, the maintenance of screening logs is recommended by the International Conference on Harmonization (ICH) as a part of Good Clinical Practice (GCP), [Federal Register: May 9, 1997; Volume 62, Number 90; page 25708, item 8.3.20]

2. While there was generally sufficient documentation of test article accountability, we note that study medication dispensing labels were missing from the Case Report Forms (CRFs) for various visits for eight subjects. In certain circumstances, lack of identifying labels could confound attempts to document drug disposition and/or accountability.

Please ensure that corrective actions will be taken to prevent similar problems in your current and future studies.

We appreciate the cooperation shown 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/

David A. Lepay, M.D., Ph.D.
Director
Division of Scientific Investigations, HFD-45
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Suite 103
Rockville, MD 20855

cc:
HFA-224
HFD-580/Doc. Rm.: NDA 21-167
HFD-510/Koch
HFD-510/Schneider
HFD-45/Reading File
HFD-46/Chron File
HFD-46/CIB file # 10049
HFD-46/Blay
HFD-46/Waterman
HFR-SW150/Thornburg
HFR-SW1540/Martinez
HFR-SW1535/[redacted]

CFN:
Field Classification: VAI
Headquarters Classification: VAI
_____1)NAI
__x__2)VAI (no response required)
_____3)VAI-R (30 day response requested)
_____4)VAI-RR (adequate response received)
_____5)OAI-WL

Deficiencies noted:
____inadequate consent form
____inadequate drug accountability
____deviation from protocol
__x_inadequate records
____failure to report ADRs
____failure to obtain IRB approval
____failure to personally conduct or supervise study
____other ( )

[redacted]
r/d: drafted/rab/4.25.00
reviewed/DAL/5.9.00
final:nlp/5.11.00

Note to Review Division:

The field investigator inspected the study-related records for 12 of the 24 subjects enrolled in protocol #035 at [redacted] site. The data appear acceptable for use in support of drug claims.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

MAY - 8 2000

Dear

Between March 22 and March 24, 2000, ——— representing the Food and Drug Administration (FDA), inspected your conduct as the investigator of record of a clinical study (Protocol #35) of Vivelle™ that you conducted for Ciba-Geigy Corporation. From our evaluation of the inspection report prepared by ——— we conclude that you conducted your study in compliance with applicable Federal regulations and good clinical investigational practices governing the conduct of clinical investigations and the protection of human subjects.

This inspection is part of FDA's Bioresearch Monitoring Program. This program includes inspections to determine the validity of clinical drug studies that may provide the basis for drug marketing approval and to assure that the rights and welfare of the human subjects who participated in those studies have been protected.

We appreciate the cooperation shown Investigator ——— 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,

/S/

David Lepay, M.D., Ph.D.
Director
Division of Scientific Investigations
Office of Medical Policy, HFD-45
Center for Drug Evaluation and Research,
7520 Standish Place, Suite 103
Rockville, Maryland 20855

cc:
HFA-224
HFD-510/Doc. Rm. NDA 21-167
HFD-510/Review Div. Dir.
HFD-510/Koch
HFD-510/Schneider
HFD-45/Reading File
HFD-46/Chron File
HFD-46/CIB File #00982
HFD- 46/Blay
HFD-46/Waterman
HFR-SE250/Chappell
HFR-SE2585/Torres
HFR-2585

CFN: #

Field Classification: NAI

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	

drafted/rab/4.21.00
reviewed:/
final:mgk 4/24/00

Note to Review Division and DSI Recommendation:

The field investigator inspected the study-related records for 8 of the 31 subjects enrolled in protocol #35 at [redacted] site. The data appear acceptable for use in support of drug claims.

APPEARS THIS WAY
ON ORIGINAL

ORIG AMENDMENT
BC

NOVARTIS

ORIGINAL

April 19, 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).

Enclosed is an updated annotated draft and draft label. The changes in the updated draft label pertaining to prevention of osteoporosis are identical to the changes submitted on October 19, 1999. However, on February 25, 2000 we received approval for our supplemental application (S-021 to NDA 20-323) from the Division of Reproductive and Urological Drug Products that included revisions to the Vivelle label. The approved label has an effective date of June 2000. Since the approved label has been revised and is the base for the prevention of osteoporosis label we are therefore submitting an updated draft prevention of osteoporosis label. Also included in this submission is a diskette containing these documents in Word format. The diskette provided has been virus scanned using Network Associates VirusScan version 4.0.3a (formerly known as McAfee Virus Scan). The diskettes were found to be virus free.

However, there is one minor difference between the approved Vivelle label, effective date June 2000, and the enclosed draft label. In the 'Information for the Patient' leaflet under the subsection 'When to Appl~ Vivelle' we have deleted the phrase '———' which refers to the location of the calendar checklist in the trade carton. The calendar checklist is currently in the Vivelle trade cartone rather than on the back. Enclosed is the trade carton for each dosage strength and the calendar checklist.

Identical information has also been submitted to the Division of Reproductive and Urological Drug Products as a 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

Vivpmo6.doc
Attachments: Form 356h

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

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ M[illegible]

CSO INITIALS DATE

APPEARS THIS WAY
ON ORIGINAL

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

Tel 973 781 7500
Fax 973 781 6323

NOVARTIS

BC

March 6, 2000

NDA 21-167
Vivelle® (estradiol transdermal system)

Amendment to pending NDA: Response to FDA Questions – November 18, 1999 phone call - Chemistry, Manufacturing and Controls

See Chemist's Review #1. dated 29-JUN-2000

FDA Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Metabolic and Endocrine Drug Products/HFD-510
Document Control Room 14B-19
5600 Fishers Lane
Rockville, Maryland 20857

Attention: John Jenkins, MD, Acting Director
Division of Metabolic and Endocrine Drug Products/HFD-510

Dear Dr. Jenkins:

Please refer to our above-referenced New Drug Application for Vivelle (estradiol transdermal system). As a follow-up to a November 18, 1999 telephone conversation that Lynn Mellor of Novartis had with the FDA chemistry reviewer, Dr. Michael Ortwerth, Novartis is providing additional CMC information to the above-referenced NDA.

In summary, Dr. Ortwerth asked Novartis to amend the above-referenced NDA to provide a listing of the current active drug master files (DMFs) referred to in the application. Dr. Ortwerth also mentioned that it would be helpful if Novartis provided letters of authorization for these DMFs. Additionally, Dr. Ortwerth requested that Novartis provide a statement addressing the reason that microbial limits testing is not necessary for the Vivelle 0.025 mg/day dose. He noted that reference should be made to Supplement S-022 in our Vivelle NDA 20-323, which provided for the deletion of microbial limits testing for the higher doses of Vivelle.

The following information is provided in response to Dr. Ortwerth's request:

Attachment I
- Listing of DMFs referenced in Vivelle NDA 20-323

Attachment II
- Respective letters of authorization for referenced DMFs

Please note that the above-referenced listing of DMFs notes currently active DMFs referenced in our NDA 20-323 for Vivelle. This list outlines the components that are currently used in the manufacture of Vivelle and the DMFs that support them. Please note that two of the components listed in the ——— DMF letter, ——— are no longer used in the manufacture of Vivelle.

Future updates to these DMFs will continue to be reported to NDA 20-323 and cross-referenced to NDA 21-167.

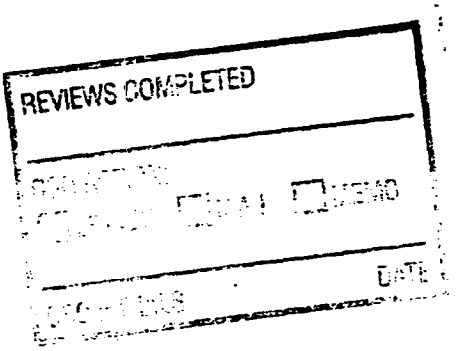
Attachment III
- Letter from ——— dated February 8, 2000

The above-referenced letter provides justification for not testing for microbial limits on the Vivelle 0.025 mg/day dose: 1) solvents used in the manufacture of the drug product provide an environment which is not conducive to microbial growth and 2) no microbial limits failures have been observed over 3 years of production of the higher Vivelle strengths nor in 11 non-commercial lots of the 0.025 mg/day strength.

Reference is also made to Supplement S-022 submitted to NDA 20-323 on July 14, 1999 and approved on October 29, 1999. This supplement provided for the deletion of microbial limits testing for all strengths of Vivelle transdermal systems (0.0375 mg/day, 0.05 mg/day 0.075 mg/day and 0.1 mg/day). Approval of this supplement, and the data therein, provides additional justification for not testing for microbial limits on the 0.025 mg/day Vivelle systems.

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, 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

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: HFD-580/Ortwerth 17B30			FROM: HFD-510 (Division of Metabolic and Endocrine Drug Products) William C. Koch, Regulatory Project Manager	
DATE: April 17, 2000	IND NO.:	NDA NO.: 21-167	TYPE OF DOCUMENT: CMC Amendment	DATE OF DOCUMENT: March 6, 2000
NAME OF DRUG: Vivelle (estradiol transdermal system)	PRIORITY CONSIDERATION: Standard		CLASSIFICATION OF DRUG: bone metabolism	DESIRED COMPLETION DATE: May 16, 2000

NAME OF FIRM: Novartis Pharmaceuticals Corporation

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ■ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE–NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER:	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER:

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILITY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Refer to attached enclosure: March 6, 2000, submission from applicant.
Note: UF10=08/20/00
cc: Original NDA 21-167
HFD-510/Div. Files
HFD-510/WKoch

SIGNATURE OF REQUESTER: /ST 7-6412	METHOD OF DELIVERY (Check one): ☐ MAIL ■ HAND
SIGNATURE OF RECEIVER: /ST 06/29/00	SIGNATURE OF DELIVERER: /ST 04/17/00 1440

NDA S AMEND

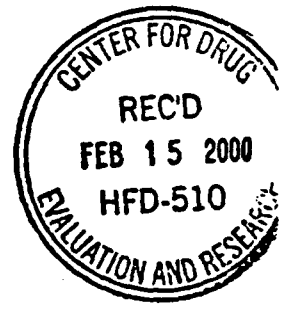
Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 7500
Fax 973 781 6325

NOVARTIS

ORIGINAL

February 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 - 120 Day Safety Update

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).

Enclosed is the Vivelle 120-Day Safety Update. This update summarizes the safety data on Vivelle from spontaneous reports received by Novartis and an update of the review of published literature on Vivelle, each from the respective cutoff dates indicated in the October 1999 NDA submission. There are no new or ongoing clinical trials being conducted with Vivelle.

In addition, Novartis received the rights from Rhone-Poulenc Rorer (RPR) to market Menorest (estradiol transdermal system) throughout the world, excluding the United States, Canada and Japan, effective September 30, 1999. Menorest is the identical transdermal system to Vivelle. Therefore, also included in this Vivelle 120-Day Safety

Update is safety data on Menorest that has been provided by RPR. This includes safety data from six Menorest Clinical Trial Reports and Periodic Safety Update Reports written by RPR.

In summary, the data in the 120-Day Safety Update confirms that Vivelle/Menorest is a well tolerated and safe transdermal estrogen replacement therapy.

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.

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

Vivpmo5.doc
Attachments: Form 356h
Volumes 1 – 11
Copy cover letter:
Regina Brown, NJ District Pre-Approval Inspection Coordinator
Diane Moore, Division of Reproductive and Urologic Drug Products

MEMORANDUM

DATE: January 21, 2000

FROM: Roy Blay, Ph.D., Good Clinical Practices Branch I, DSI
HFD-46, MPN1, Room 107,
Phone: 827-7378
Fax: 827-5290

TO: Enid Galliers, Project Manager, HFD-510
Bruce Schneider, M.D., Medical Officer, HFD-510

SUBJECT: Clinical Inspections for Pending NDA# 21-167

Clinical inspection assignment have been issued to verify data that were reported by clinical investigators from important study sites and were submitted by the sponsor in support of drug claims for this NDA.

Inspection assignments were issued for the following pending NDA:

Drug: Vivelle™ (estradiol transdermal system)

Sponsor: Novartis

NDA #: 21-167

The following investigators' clinical studies will be inspected:

Protocol #	Name of Investigator	Domestic	Foreign
035	Maria, Greenwald, M.D.	Palm Springs, CA	
035	Harris McIlwain, M.D.	Tampa, FL	
035	Leann Olansky, M.D.	Oklahoma City, OK	

Please notify me ASAP if you disagree with this selection.

When the inspection reports (EIRs) come in from the field, you will be notified only if there is a problem. Otherwise, you will not be notified again unless the PM requests a final summary.

NOVARTIS

NEW CORRESP
NC

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

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
DEC - 7 1999
HFD-510

December 3, 1999

Solomon Sobel, M.D.
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)

Response to Request for Information

Agree with waiver for pad study
S/S Sobel 1/6/00

12/15/99

Dear Dr. Sobel:

Reference is made to your letter dated October 29, 1999, acknowledging receipt of our Type 3 NDA submission 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 was studied under IND 40,773.

In addition, your letter makes reference to the pediatric study requirement for all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens unless the drug qualifies for a waiver of this requirement. Novartis believes that Vivelle qualifies for a waiver of the pediatric study requirement. At this time we are submitting a request for a waiver in accordance with the provisions of 21 CFR 314.55. Supporting information for this waiver of the pediatric study requirement follows.

The use of estradiol as hormone replacement therapy to mitigate the symptoms of menopause and to prevent postmenopausal osteoporosis is well established. Vivelle (estradiol transdermal system) is approved for the treatment of moderate to severe vasomotor symptoms and for vaginal atrophy associated with the menopause under NDA 20-323. It is currently available in four dosage strengths; 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1mg/day. In addition to these four dosage strengths, a 0.025 mg/day strength has been submitted for approval in this application.

NC
PW Stegwart
1/5/00

Vivelle should not be indicated for any osteoporosis condition or disease occurring in the pediatric population. Its use "off-label" would be an inappropriate therapeutic choice for prevention or treatment of pediatric osteoporosis and/or osteopenia. In the female pre-pubertal and pubertal pediatric patient use of an estrogen to prevent or treat bone loss can only produce negative consequences for sexual development and might conceivably increase the patients' lifetime risk for developing breast and/or uterine cancer. Estrogen does not have a place in the treatment of the male pediatric patient with osteopenia or osteoporosis.

- Post-menopausal osteoporosis does not occur in the pediatric population.

- The most important cause of secondary osteoporosis in pediatric patients, as in adults, is the chronic use of high dose corticosteroid therapy. Estrogen therapy will not prevent or treat corticosteroid-induced bone loss in estrogen-replete patients. Similarly, there is no data to suggest that bone loss associated with chronic anti-convulsive therapy can be mitigated by use of estrogen. Certain metabolic bone diseases may be associated with osteopenia in children, e.g. primary hyperparathyroidism, secondary hyper-parathyroidism, vitamin D deficiency rickets, rickets associated with 1-hydroxylase deficiency, intestinal resistance to 1,25 hydroxyvitamin D, osteopenia of prematurity, phosphopenic rickets, calciopenic rickets, and idiopathic juvenile osteoporosis. All of these conditions have specific therapies and none would be responsive to estrogen therapy because none is related to estrogen deficiency.

- The genetic diseases grouped under the heading "Osteogenesis Imperfecta" are also associated with osteopenia and osteoporotic fractures in the pediatric population. In these children osteopenia develops as a result of excessive turnover of an abnormal bone matrix (various collagen molecule defects) with diminished matrix mineralization and not as a result of estrogen deficiency. Treatment with bisphosphonates has been reported to be helpful, but use of estrogen would be inappropriate and has never been reported.

- Endocrinopathies associated with osteopenia in the pediatric population also have specific remedies, and all exclude estrogen treatment. These conditions include thyrotoxicosis, Cushing syndrome and disease, and diabetes mellitus.

- The pediatric gastrointestinal diseases associated with osteopenia require specific treatments, but exclude estrogen as a remedy. These are biliary atresia, gylcogen storage disease type I, hepatitis, and malabsorption.

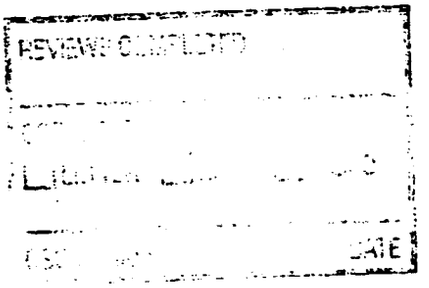
- Inborn errors of metabolism, e.g. homocysteinuria and lysinuric protein intolerance, and various miscellaneous conditions occurring in children, e.g. acute lymphoblastic leukemia, cyanotic congenital heart disease, and immobilization may also be associated with osteopenia. However, for each condition a specific therapy other than estrogen is required.

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

Vivpmo4.doc
Submitted in duplicate



APPEARS THIS WAY
ON ORIGINAL

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

November 23, 1999

Lisa Rarick, 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. 20-323
Vivelle®(estradiol transdermal system)

General Correspondence

Dear Dr. Rarick:

Reference is made to Vivelle ® (estradiol transdermal system) NDA 20-323 and to a request from Diane Moore, Project Manager, dated October 28, 1999. Ms. Moore requested that we commit to submit a supplement to provide for identifying information (printing) on the backing layer of the Vivelle transdermal system. Furthermore, this information can be submitted as a Special Supplement - Changes Being Effected.

At this time we commit to submit information to support a Special Supplement - Changes Being Effected to provide for identifying information (printing) on the backing layer of the Vivelle transdermal system in July 2000.

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

Submitted in duplicate

Attachments: Form 356h

Meeting Date: November 22, 1999 **Time:** 9:30 – 10:00 AM **Location:** PKLN 14-56

NDA 21-167 Vivelle (estradiol transdermal system) 0.025 mg/day

Type of Meeting: Filing/Planning

Meeting Chair: Ms. Galliers

Meeting Recorder: Ms. Galliers

FDA Attendees and Titles:

Dr. Solomon Sobel, Director, DMEDP (HFD-510)
Dr. Gloria Troendle, Deputy Director & Medical Team Leader, DMEDP
Dr. Bruce Schneider, Medical Officer, DMEDP
Dr. Leo Lutwak, Medical Officer, DMEDP
Dr. Ronald Steigerwalt, Pharmacology Team Leader, DMEDP
Dr. Moo-Jong Rhee, Chemistry Team Leader @ DRUDP
Dr. Michael Ortworth, Review Chemist @ DRUDP (HFD-580)
Dr. Robert Shore, Review Biopharmaceutist @ DMEDP
Dr. Todd Sahlroot, Statistics Team Leader @ DMEDP
Dr. Sue Jane Wang, Review Biostatistician @ DMEDP

Background: This Type 3 NDA provides for a new strength, 0.025 mg/day, of an already approved drug for a new indication, the prevention of postmenopausal osteoporosis. It also provides for the addition of this new indication to the four already approved higher strengths (0.0375, 0.05, 0.075, 0.1 mg/day) of Vivelle. This NDA has been submitted in electronic format.

Filing Date: December 19, 1999

Meeting Objectives: To determine if the application is adequate for filing and to establish timelines for its review.

Discussion and Decisions:

Clinical The application relies on a single, randomized, placebo-controlled, two-year study (Study # 035: placebo, 0.025 mg/day, 0.0375 mg/day, 0.1 mg/day Vivelle; n=250) with BMD and bone turnover markers plus some secondary endpoints. The NDA also contains literature reports of three studies with Menorest. No advisory committee is planned. The NDA is fileable.

- Statistics The NDA is fileable.

Biopharmaceutics The NDA is fileable.

Pharmacology There are no new animal studies and the labeling does not need to be modified. The NDA is fileable.

Chemistry The NDA is fileable. (Chemistry Filing Review is attached.)

Final review due date ***August 1, 2000***
(Date by which the review has been signed by the discipline team leader)

Status meeings: The first status meeting will be held in February, and then one will be held every two months. Medical officers from DRUDP will be invited.

Unresolved Issues: None.

Action Items: None

Signature, meeting chair & minutes preparer: /S/

ATTACHMENT

Cc: Orig. NDA 21-167 (+attachment)
HFD-510/Division File (+attachment)
HFD-510/EColman/BSchneider/LLutwak/RSteigerwalt/RShore/HAhn/TSahlroot/
HFD-510/EGalliers
HFD-715/SWang
HFD-580/MRhee/MOrtworth/DMoore

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 21-167

OCT 29 1999

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 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Vivelle® (estradiol transdermal system), 0.025 mg/day
Therapeutic Classification:	Standard (S)
Date of Application:	October 19, 1999
Date of Receipt:	October 20, 1999
Our Reference Number:	NDA 21-167

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 December 19, 1999, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be August 20, 2000, and the secondary user fee goal date will be October 20, 2000.

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 120 days of receipt of your pediatric drug development plan, we will notify you of the pediatric studies that are required under section 21 CFR 314.55.

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 notify you within 120 days of receipt of your response whether a waiver is granted. 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 proceed with the pediatric drug development plan that you submit and notify you of the pediatric studies that are required under section 21 CFR 314.55. 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 NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room, 14B-19
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, contact Enid Galliers, Chief, Project Management Staff, at (301) 827-6429.

Sincerely.

/S/

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc:
Archival NDA 21-167
HFD-510/Div. Files
HFD-510/E.Galliers
HFD-510/Reviewers and Team Leaders
DISTRICT OFFICE

Drafted by: ddk/October 25, 1999
Initialed by: Galliers 10.26.99
final: dk 10.26.99
filename: 21167AC

ACKNOWLEDGEMENT (AC)

NDA 21-167

Printed by Enid Galliers

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 28-Oct-1999 01:13pm
From: Enid Galliers
GALLIERS
Dept: HFD-510 PKLN 14B04
Tel No: 301-827-6429 FAX 301-443-9282

TO: Michael Jones (JONESM)
TO: Beverly Friedman (FRIEDMANB)
TO: Tawni Brice (BRICET)

CC: Lonnie Smith* (SMITHLO)
CC: Terri Rumble (RUMBLET)
CC: Diane Moore (MOORED)
CC: Randy Hedin (HEDINR)
CC: Gloria Troendle (TROENDLE)
Subject: NDA 21-167 Vivelle for prevention of PMO for FIVE strengths (+new strength, 0.025mg/dy)

Mike, Bev, Tawni:

This is a summary of the UF status and unbundling of NDA 21-167 from NDA 20-323 for Vivelle (estradiol transdermal system).

NDA 21-167 proposes to add a new strength dosage, 0.025 mg/day, to the already approved four higher strengths of Vivelle (NDA 20-323) and to add the new indication, prevention of postmenopausal osteoporosis (PMO) to all five strengths. (The other indications already approved are NOT proposed for the new lower strength.)

(NDA 20-323 is approved for 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 orvarian failure. DRUDP (HFD-580) is the "parent" division for NDA 20-323.)

The changes proposed in NDA 21-167 could have been submitted to the approved NDA as an efficacy supplement that requires clinical data, and the UF charge would have been $128,169 (supplement with clinical data). However, DMEDP (HFD-510) has the clinical expertise and jurisdiction for osteoporosis indications. Therefore, the applicant (Novartis) was requested to submit the changes to DMEDP as a Type 6 NDA for our administrative convenience. The fee is the same as it would be for a supplement with clinical data.

However, the "chemical" classification of this NDA will be type "3" because a new strength is involved as well as a new indication.

This summary is based on my conversations with Mike Jones.

/S/

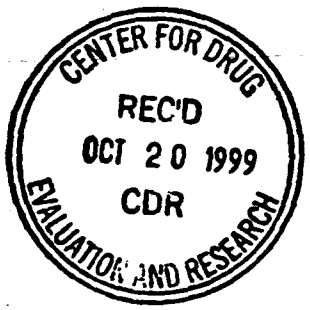
cc: Orig NDA 21-167
HFD-510/Div. Files

NOVARTIS

Lynn Mellor
Associate Director

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

Tel 973-781-3665
Fax 973-781-3590

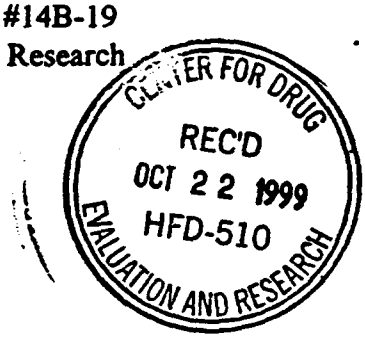


October 19, 1999

Solomon Sobel, M.D.
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
Document and Records Section
12229 Wilkins Avenue
Rockville, Maryland 20852

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

Type 6 NDA



Dear Dr. Sobel:

We are submitting this Type 6 NDA for Vivelle (estradiol transdermal system) for a labeling change to add a new indication for the prevention of postmenopausal osteoporosis. Vivelle was studied under IND 40,773. 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.

Four clinical studies performed with Vivelle (Protocols 035, 036, 037 and 038) are included in this Type 6 NDA. Study 035 was conducted in the target indication of prevention of postmenopausal osteoporosis, Study 036 in the treatment of menopausal symptoms. Two studies (Studies 037 and 038) evaluated skin tolerability and adhesion profile of Vivelle compared to Climara. In addition, data from published studies on Vivelle and Menorest (estradiol system identical to Vivelle marketed by Rhone-Poulenc Rorer outside the United States and Canada) are summarized in this dossier.

As discussed during the February 11, 1999 pre-NDA meeting and agreement communicated to us on June 1, 1999, the basis of the Type 6 NDA is the Protocol 035 clinical trial report. Also on June 1, 1999, the agency confirmed that the proposal not to have a separate Integrated Summary of Efficacy document was acceptable as Protocol 035 is the efficacy trial that the labeling registration will be based on and information from the literature is included in the clinical trial report for Study 035.

As requested by the Division at the pre-NDA meeting we are providing the clinical trial report for Protocol 035, the Integrated Summary of Safety and the labeling in Word format as well as a paper copy. These documents are provided in a Word 6 format.

In addition, on June 1, 1999, the Division agreed with our proposal not to submit the case report tabulations (data listings) in an electronic Word document for Protocols 036, 037, and 038 as was indicated at the pre-NDA meeting. As these clinical trial reports are legacy documents a Word file is not available at this time and scanning these documents into an electronic version would not allow for data manipulation and therefore essentially the same as the paper copy. A paper copy of these data listings is provided for these protocols. With regard to Protocol 035, case report tabulations are provided in a Word 6 document as well as a paper copy.

All Case report forms for this Type 6 NDA which are required under 21 CFR 314.50(f)(2) are only submitted electronically on CD-ROM according to the January 1999 FDA guidance document for regulatory submissions in electronic format. In addition, data files that support the efficacy analyses for Protocol 035 are provided in SAS (version 6.12) transport format. As agreed to at the pre-NDA meeting, no electronic SAS data files for Protocols 036, 037, or 038 will be provided since these trials do not support the efficacy claim for prevention of postmenopausal osteoporosis.

In addition, documentation to support a bioavailability waiver for the 0.025 mg/day dosage strength was provided in our May 7, 1999 submission and is resubmitted as part of the Human Pharmacokinetics and Bioavailability section of this application.

In accordance with CFR 314.50(j) Novartis Pharmaceuticals Corporation is claiming 3 years marketing exclusivity under CFR 314.108(b)(5) for Vivelle (estradiol transdermal system) Type 6 NDA for the prevention of postmenopausal osteoporosis. This Type 6 NDA contains a new clinical investigation (Protocol 035) that is essential to approval of the Type 6 NDA and the study was conducted by the applicant.

As specified in the FDA meeting minutes, as this application is submitted as a Type 6 NDA to the Division of Metabolism and Endocrine Drug Products Novartis should submit a labeling supplement to the Division of Reproductive and Urologic Drug Products. Novartis will submit the labeling supplement. The Type 6 NDA will be rolled over to the Division of Reproductive and Urologic Drug Products when the application is approved.

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

The FDA 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

vivpmo.doc
Attachments: Form 356h
Volumes 1 – 59

Copy cover letter:
Regina Brown, NJ District Pre-Approval Inspection Coordinator
Diane Moore, Division of Reproductive and Urologic Drug Products

APPEARS THIS WAY
ON ORIGINAL

NDA # 21-161 DOCUMENT ID/LETTER DATE 10.14.99 N Hrpd 136,144- 8/3/99

APPLICANT NAME Novartis Pharms

PRODUCT NAME VIVELLE (ESTRADIOL TRANSDERMAL SYSTEM)

FORM MUST BE COMPLETED ASAP UFd=3766

1. (YES) User Fee Cover Sheet Validated?

NOTE TO DOCUMENT ROOM:
PLEASE MAKE THE FOLLOWING CHANGES TO THE COMIS DATA ELEMENTS:

This Type 3 NDA could have been submitted as an efficacy supplement to DRUDP NDA 20-323. However, DMEDP needs to do the clinical review. Therefore, a separate NDA (UF = simple w/clinical data) was requested by FDA for our convenience.

2. (YES) NO CLINICAL DATA?
[Check YES if contains study reports or literature reports of what are explicitly or implicitly represented by the applicant to be adequate and well-controlled trials. "Clinical data do not include data used to modify the labelling 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?

3. (YES) NO NDA BEING SPLIT FOR ADMINISTRATIVE CONVENIENCE (OTHER THAN BUNDLING)? IF YES, list ALL NDA numbers, review divisions & indicate those for which application fees apply.

NDA #	DIVISION		
N_____	_____	FEE	NO FEE
N_____	_____	FEE	NO FEE

4. YES (NO) BUNDLING POLICY APPLIED CORRECTLY? NO DATA ENTRY REQUIRED FOR ELEMENT
[Check YES if application is properly designated as one application or is properly submitted as a supplement instead of an original application. Check NO if application should be split into more than one application or submitted as an original instead of a supplement. IF NO, list resulting NDA numbers, and review divisions.]

NDA #	DIVISION	NDA #	DIVISION
N_____	_____	N_____	_____

5. P (S) PRIORITY OR STANDARD? 1S 10/29/99

1S

6. CSO SIGNATURE/DATE SCSO CONCURRENCE SIGNATURE/DATE

COPY DISTRIBUTION: ORIGINAL TO ARCHIVAL AFTER DATA ENTRY, ONE COPY EACH TO DIVISION FILE AND CDER, ASSOCIATE DIRECTOR FOR POLICY HFD-5

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. XXXX-XXXX
Expiration Date: XX/XX/XX

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

[X] (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a ~~significant equity in the sponsor as defined in 21 CFR 54.2(b)~~ did not disclose any such interests. I ~~further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).~~

Clinical Investigators		
	See attached.	

[ ] (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)), had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

[ ] (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Peter Richardson, MD	TITLE Vice President Bone/Respiratory
FIRM/ORGANIZATION Novartis Pharmaceuticals Corporation	
SIGNATURE PC Richardson	DATE 13th August 1998

Paperwork Reduction Act Statement

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. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

Please DO NOT RETURN this form to this address.

FORM FDA 3454 (10/98) EF

Created by Electronic Document Services/USDHHS: (301) 443-2454

All studies were completed prior to February 2, 1999 therefore, the crossed out statements within (1) are not applicable.

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

TELEFAX

To: Ms. Lynn Meller
Novartis Pharmaceuticals Corp.

FAX: 973-781-3590
PHONE: 973-781-3665

From: Randy Hedin, R.Ph.

Food and Drug Administration
Division of Metabolism and Endocrine Drug Products
5600 Fishers Lane--HFD-510
Rockville, Maryland 20857-1706

FAX: (301) 443-9282
PHONE: (301) 827-6392

Date: February 17, 1999

Pages: __2__ (inclusive)

Food and Drug Administration
Division of Metabolism and Endocrine Drug Products
5600 Fishers Lane--HFD-510
Rockville, Maryland 20857-1706

NDA 20-323
Vivelle (estradiol transdermal system)

We have completed a review of your fax dated February 15, 1999, and have the following comment:

We can waive the bioavailability study for the 0.025 mg/day dosage form as long as you provide the following information:

1. The active and inactive ingredients of the 0.025 mg/day system is proportional to those of the marketed formulations.

2. The 0.025 mg/day system has the same release mechanism as the marketed formulation.

3. The 0.025 mg/day system is used in the clinical trials.

If you have any questions, contact Randy Hedin, R.Ph., Regulatory Management Officer, at (301) 827-6392.

Sincerely,

/S/

Dr. Hae-Young Ahn
Team Leader, OCPB DPE-2 for the
Division of Metabolic and Endocrine Drug Products (HFD-510)

Meeting Date: February 11, 1999 Time: 1:00 - 2:30 PM Location: Conf. Rm. "C"

IND 40,773 Vivelle (estradiol transdermal system)

Type of Meeting: Pre-NDA

External participant: Novartis Pharmaceuticals Corporation

Meeting Chair: Dr. Troendle

External participant lead: Ms. Lynn Mellor

Meeting Recorder: Mr. Randy Hedin

FDA Attendees and titles:

Dr. Gloria Troendle, Deputy Division Director, DMEDP
Dr. Leo Lutwak, Medical Reviewer, DMEDP
Dr. Bruce Schneider, Medical Reviewer, DMEDP
Dr. Joanna Zawadzki, Medical Reviewer, DMEDP
Dr. Todd Sahlroot, Team Leader, Division of Biostatistics
Ms. Diane Moore, Project Manager, DRUDP
Mr. Randy Hedin, Project Manager, DMEDP

External participant Attendees and titles:

Dr. Kim Andriano, Assistant Director, Biostatistics
Dr. Niroo Gupta, Associate Director, Clinical Research
Ms. Lynn Mellor, Associate Director, Drug Regulatory Affairs
Dr. Judith Zander, Senior Clinical Research Physician
Mr. Russ Hume, Regulatory Liason

Meeting Objectives:

Pre-NDA meeting requested by Novartis to discuss the submission of Vivelle (estradiol transdermal system) for an indication of prevention of postmenopausal osteoporosis.

Discussion Points and Decisions (agreements) reached:

- The following questions were submitted by Novartis Pharmaceutical Corporation in their background package dated January 26, 1999. The Division's answers follow the questions in bolded type.

  1. Is the content of the NDA acceptable for filing? We would like to obtain agreement on the following NDA content related issues:

We make the determination if an NDA is fileable after submission of the NDA.

2. We intend to include only Novartis sponsored Vivelle trials in this supplement. There have been some trials conducted by Novartis or RPR with the Menorest transdermal patch (e.g., trials in treatment of menopausal symptoms, prevention of bone loss in postmenopausal women, endometrial safety, and bioavailability/bioequivalence). The Menorest patch is identical to the Vivelle transdermal patch. Considering that this class of drugs has millions of patient years with regard to safety data, it is not felt that any new information would be added by including safety information from these non-Novartis trials in the supplement.

   Please submit all published data and all safety data you have access to.

3. Patient Narratives: patient narratives will not be provided for deaths as there have been no patient deaths. Patient narratives will be provided for serious adverse events (SAEs). However, we do not plan to provide narratives for patients that had an SAE that is definitely unrelated events (e.g., if a patient had elective surgery planned prior to the start of the trial). In addition, narratives will be provided for patients who had clinically significant adverse events (AEs), and for marked or clinically significant lab abnormalities.

   Please submit ALL serious adverse events.

4. CFR copies: will be provided for patients who dropped out due to an AE or SAE, had a clinically significant AE, or clinically significant lab abnormalities. Please note, there were no patient deaths. CRF copies will be provided electronically according to the April 1998 FDA guidance document for regulatory submissions in electronic format - NDAs.

   This is acceptable; however, submit all serious adverse events.

5. Electronic data file submission: we propose to provide electronic data files that support the efficacy analyses for Protocol 035. The files will be provided in a SAS (version 6.12) transport format and will include important baseline termination, and efficacy

measurements. No electronic data files for Protocols 036, 037, or 038 will be provided since these trials do not support the efficacy claim planned to be made from the postmenopausal osteoporosis trial (P035).

This is acceptable.

6. Case Report tabulations: for Protocols 035, 036, 037, and 038 data listings provided in an electronic document contain all the data collected on the CRFs and derived data used for analyses. The listings are sorted and presented by treatment, investigator center, patient, and visit for each domain (i.e., AEs, diary, vital signs, etc.). The termination listing is sorted by reason for termination. Laboratory data is sorted by investigator center, patient, and visit. We propose that these listings can be considered the case report tabulations and no electronic data files (SAS) be provided.

   This is acceptable.

7. Text files in Word 6.0 can be provided upon request.

   Please submit the integrated summaries of safety and efficacy, and the labeling in Word format.

- The firm presented an additional issue regarding human bioavailability. The Division replied that there is not a representative from biopharmaceutics at the meeting; therefore, we are not prepared to address the issue at this time. The Division asked the firm to submit the questions via facsimile for response at a later time. The firm agreed to this.

- The Division stated that this application should be submitted as a type 6 NDA to the Division of Metabolic and Endocrine Drug Products (DMEDP), and a labeling supplement should be submitted to the Division of Reproductive and Urologic Drug Products (DRUDP). The type 6 NDA would be rolled over to DRUDP when the application is approved.

- The firm plans to submit one small study in which safety and efficacy data will be provided on roughly 100 women who have not had a hysterectomy and who are concurrently taking a progestational agent. The Division questioned whether this one small study would be adequate to approve a drug which would be used to treat millions of women. The Division questioned whether the one small study the firm plans on submitting would be adequate to approve a drug which would be used to treat millions of women. The Division further stated that the original

protocol did not include women who had undergone hysterectomies and was powered accordingly. The protocol was amended subsequently and no adjustment was made for the number of patients in the study. Furthermore, the study is not powered to determine whether hysterectomy has an effect on safety/efficacy. The firm stated that the administrative record would show that the Agency agreed that the size of the study would be adequate. The Division replied that it would review the administrative record, and meet internally to determine if the one study would be adequate for the submission of an NDA.

Unresolved or issues requiring further discussion:

- None

Action Items:

- The Division will meet internally to determine if the one study is adequate.
- Ms. Diane Moore will search the IND for protocol comments, letters, and meeting minutes to clarify the administrative record, and determine what, if any, commitments the Agency made concerning the adequacy of this study.

Signature, minutes preparer: /S/

Concurrence Chair: /S/

cc: NDA Arch
HFD-510
Attendees
HFD-510/EGalliers
HFD-511/RHedin/2.16.99/I40773.MN1
Concurrences: BSchneider/LeoLutwak/2.16/DMoore/1.17/JZawadzki/TSahlroot/By Default

End

NOVARTIS

December 17, 1998

Lisa Rarick, 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)

Request for a Pre-sNDA Meeting

Dear Dr. Rarick:

Reference is made to our NDA for Vivelle (estradiol transdermal system), NDA 20-323. We wish to inform you that we plan to submit a supplement to NDA 20-323 in June 1999 for a labeling change to add the claim for the prevention of osteoporosis and remove restrictive language that some women taking the 0.0375 mg/day dosage may experience a delayed onset of efficacy. We are requesting a Pre-sNDA meeting with the Division of Reproductive and Urological Drug Products to discuss certain issues that we have identified associated with the upcoming submission.

The supplement will include the following Novartis clinical study reports: Protocol 035, prevention of postmenopausal bone loss; Protocol 036, low dose (0.0375 mg/day) transdermal patch in the treatment of moderate to severe postmenopausal vasomotor symptoms (Phase IV commitment); Protocol 037 and Protocol 038, skin irritation and adhesion comparison between Vivelle and Climara; and Protocol MA610, skin irritation study comparing Vivelle placebo and Estraderm placebo.

We would like to obtain agreement on the following sNDA content related issues:

- Rather than resubmit the pivotal vasomotor symptom trial reports (Study 1003-A and 1003-B) that were submitted in the Original NDA, we propose to resubmit the original ISE that encompasses the efficacy data regarding these trials. We will also resubmit the reanalyzes of the efficacy results for the 0.0375 and 0.05 mg/day doses in study 1003-A.

- We intend to include only Novartis sponsored Vivelle trials in this supplement. There have been some trials conducted by Noven or RPR with the Menorest transdermal patch (e.g., trials in treatment of menopausal symptoms, prevention of bone loss in postmenopausal women, endometrial safety, and bioavailability/bioequivalence). The Menorest patch is identical to the Vivelle transdermal patch. Considering that this class of drugs has millions of patient years with regard to safety data, it is not felt that any new information would be added by including safety information from these non-Novartis trials in the supplement.

• Patient narratives will be provided for deaths and serious adverse events (SAEs). However, we do not plan to provide narratives for patients that died or had an SAE that are definitely unrelated events (i.e., if patient died after signing consent and did not receive drug, elective surgery planned prior to the start of the trial). In addition, narratives will be provided for patients who had clinically significant adverse events (AEs), and for marked or clinically significant lab abnormalities (e.g., if a diabetic patient had a markedly elevated glucose that was due to non compliance with therapy, we plan not to include a narrative).

• CRF copies will be provided for patients who died, dropped out due to an AE, had a clinically significant AE, or clinically significant lab abnormalities. In addition, we propose not to submit CRFs that were previously submitted in the Original NDA, but cross reference to the previous submission (pertains to study 1003-A and 1003-B). CRF copies will be provided electronically according to the April 1998 FDA guidance document for regulatory submisions in electronic format - NDAs.

• Regarding electronic data file submission, we propose to provide electronic data files that support the efficacy analyses for Protocols 035 and 036. The files will be provided in a SAS (version 6.12) transport format and will include important baseline, termination, and efficacy measurements. No electronic data files for Protocols 037, 038, and MA610 will be provided since these are local skin irritation trials and no efficacy claims are planned to be made from these results.

• Regarding Case Report tabulations, for Protocols 035, 036, 037, 038, and MA610 data listings provided in an electronic document contain all the data collected on the CRFs and derived data used for analyses. The listings are sorted and presented by treatment, investigator center, patient, and visit for each domain (i.e., AEs, diary, vital signs, etc.). The termination listing is sorted by reason for termination. Laboratory data is sorted by investigator center, patient, and visit. We propose that these listings can be considered the case report tabulations and no electronic data files (SAS) be provided.

• In addition, text files in Word 6.0 ca be provided upon request.

We hope to be able to meet with the Division to discuss this supplemental application in early January 1999. We would also be agreeable to discussing this supplement by teleconference if deemed appropriate.

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

NDA 21-167 Filing Meeting

Vivelle (Estradiol Transdermal System) 0.025 mg/day

A. Facilities (Manufacturer, Testing, Packaging, Shipping, Labeling, etc.)

- **NDA Information:**

  - **FACILITIES ARE ACOUNTED FOR**
  - **A COMMITMENT TO SUBMIT DMF LETTERS OF AUTHORIZATION FOR REPORTED FACILITIES HAS BEEN RECEIVED (FACSIMILIE 19-NOV-1999).**

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

Establishment Information:

	Address	Function
DRUG SUBSTANCE	[redacted]	[redacted] DMF [redacted]
DRUG PRODUCT	[redacted]	[redacted]
	[redacted]	[redacted]
	Novartis Pharmaceuticals Suffern, NY	Cartoning of pouched product and release of finished goods and pouch stock only CFN#: 2416082
	[redacted]	[redacted]

Note: A Statement that all sites are ready for inspection by FDA investigators has NOT been received at this time.

B. Specifications/Test Methods

- **NDA Information:**

  - **SPECIFICATIONS: ONLY ONE CHANGES FROM CROSS-REFERENCED NDA 20-323 (Supplement SCS-022 for NDA 20-323 was approved for the deletion of the microbial limit test for all strengths of the finished product. – This also is the reasoning behind the omission of a Microbiology section from NDA 21-167. The sponsor has agreed to submit a statement to support the omission of a microbiology section from their application via amendment.)**
  - **VALIDATION METHODS: ALL METHODS ARE PROVIDED IN THE CROSS-REFERENCED NDA 20-323; THERE HAVE BEEN NO CHANGES TO THE VALIDATION METHODS SINCE THE APPROVED NDA.**
  - **EXPIRATION DATING: THE SPONSOR SEEKS 24 MO. EXPIRATION DATING AS WAS APPROVED IN THE CROSS-REFERENCED NDA 20-323.**

C. Content/Uniformity

- **NDA Information:** **NO CHANGES FROM CROSS-REFERENCED NDA 20-323**

D. Impurities

- NDA Information: NO CHANGES FROM CROSS-REFERENCED NDA 20-323

E. Stability

- NDA Information:
  - STABILITY DATA WHICH SUPPORT THE EXPIRATION DATING PERIOD ARE PROVIDED IN THE VIVELLE ANNUAL REPORT.
  - STABILITY TABLES IN SUPPORT OF Vivelle (Estradiol Transdermal System) 0.025 mg/day ARE PROVIDED CONTAINING
    - Two (2) years real time data
    - Three (3) and Six (6) months accelerated data
    - Cross-reference to historical data for the other 4 strengths of Vivelle found in NDA 20-323.

F. Formulation

- NDA Information: NO CHANGES FROM CROSS-REFERENCED NDA 20-323

G. Packaging

- NDA Information: NO CHANGES FROM CROSS-REFERENCED NDA 20-323

H. Labeling

- NDA Information:
  - LABELS ARE PROVIDED FOR PHYSICIAN/PATIENT PACKAGE INSERT AND CONTAINERS AND CARTONS

Other Info:

Foreign Marketing History:

Vivelle marketing authorization was received from the Canadian Health Authority on January 4, 1996 and launched in Canada in May 1996. In Canada it is indicated for the relief of menopausal and postmenopausal symptoms occurring in naturally or surgically induced estrogen deficiency states.

Note: Menorest™ (estradiol transdermal system) is identical to Vivelle and is marketed by Rhone Poulenc Rorer outside the U.S. and Canada in postmenopausal osteoporosis as well as for treatment of patients with estrogen deficiency syndrome.

NO ADVISORY COMMITTEE MEETING

APPEARS THIS WAY
ON ORIGINAL

NO FEDERAL REGISTER NOTICES;
OTC OR DESI DOCUMENTS

APPEARS THIS WAY
ON ORIGINAL

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-167 /SE_____ - _____

Drug Vivelle (estradiol transdermal system) Applicant Novartis

RPM William C. Koch Phone (301) 827-6412

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

☐Fast Track ☐Rolling Review Review priority: X S ☐P

Pivotal IND(s) 40,773

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

PDUFA Goal Dates:
Primary 08/20/00
Secondary 10/20/00

Arrange package in the following order:

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

GENERAL INFORMATION:

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

- Action Letter..... ☐AP ☐ 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.....
  Has DDMAC reviewed the labeling? ..... ☐ Yes (include review) ☒ No
  Immediate container and carton labels X
  Nomenclature review ..... N/A

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

Continued ⇨

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

- Post-marketing Commitments
  - Agency request for Phase 4 Commitments..... X
  - 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)] ..... N/A
  - 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 — X
  - No disclosable information .....
  - Disclosable information – indicate where review is located .....

- Correspondence/Memoranda/Faxes X

- Minutes of Meetings X
  - Date of EOP2 Meeting _____
  - Date of pre NDA Meeting 02/11/99
  - Date of pre-AP Safety Conference N/A

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

- 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

Continued ⇨

- ◆ Safety Update review(s) X

- ◆ Pediatric Information
  X Waiver/partial waiver (Indicate location of rationale for waiver) ☐ Deferred
  Pediatric Page..... X
  ☐ Pediatric Exclusivity requested? ☐ Denied ☐ Granted ☐ Not Applicable

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

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

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

- ◆ DSI Audits X
  ☐Clinical studies ☐ bioequivalence studies .....

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 X

- ◆ DMF review(s) ..... N/N

- ◆ Environmental Assessment review/FONSI/Categorical exemption X

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

- ◆ Facilities Inspection (include EES report) X
  Date completed _____ ..... X Acceptable ☐ Not Acceptable

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

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

- ◆ Pharm/Tox review(s) and memoranda X

- ◆ Memo from DSI regarding GLP inspection (if any) ..... N/N

Continued ⇨

- Statistical review(s) of carcinogenicity studies ..... N/A
- CAC/ECAC report ..... N/A