

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-048

**ADMINISTRATIVE
DOCUMENTS/CORRESPONDENCE**

PATENT INFORMATION UNDER SECTION 505(b)

TRADEMARK, (17 β -estradiol transdermal system) is covered by claims in U.S. Patent 5,252,334 which covers a transdermal drug delievery device and by U.S. Patent 5,770,219 which covers a drug containing matrix for transdermal drug delivery. Both patents expire October 12, 2010. The parent company of applicant is licensed under these patents. In the opinion of applicant and to the best of applicant's knowledge, there are no other U.S. patents containing claims which cover the drug for which applicant has sought approval or which claims the use of the drug for which applicant has sought approval.

WYETH-AYERST LABORATORIES

By: _____

Arnold Milowsky
Senior Patent Attorney

September 28, 1998

Patent/Exclusivity Information

- | | | |
|----|---|---|
| 1) | Active ingredient(s) | 17 β -estradiol |
| 2) | Strength(s) | 13.5 cm ² , 20 cm ² , and 27 cm ² with a nominal delivery of 50, 75, and 100 μ g per day, respectively. |
| 3) | Trade Name | TRADEMARK |
| 4) | Dosage Form
(Route of Administration) | Transdermal System |
| 5) | Applicant Firm Name | Wyeth-Ayerst Laboratories |
| 6) | NDA Number | 21-048 |
| 7) | Approval Date | - |
| 8) | Exclusivity - Date first ANDA could be submitted or approved and length of exclusivity period | Pursuant to Section 505(j)(4)(D)(ii) and 505(c)(3)(D)(ii) of the Federal Food, Drug, and Cosmetic Act, no ANDA may be approved with an effective date which is prior to 3 years after the date of approval of this NDA. |
| 9) | Applicable patent numbers and expiration date of each | 5,252,334 expires October 12, 2010
5,770,219 expires October 12, 2010 |

INDEX

ITEM 1

EXCLUSIVITY SUMMARY FOR NDA # 21-048 SUPPL # _____

Trade Name Trademark Generic Name estradiol transdermal system

Applicant Name Wyeth-Averst HFD # 580

Approval Date If Known _____

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 question about the submission.

a) Is it an original NDA?
YES /X/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /___/

If yes, what type? (SE1, SE2, etc.) _____

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

YES /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.

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:

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

NDA# _____

NDA# _____

NDA# _____

2. Combination product.

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

YES / ___ / NO / ___ /

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

NDA# _____

NDA# _____

NDA# _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. 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 / / NO / /

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

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

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

YES / / NO / /

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

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

YES / / NO / /

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

YES /___/ NO /___/

If yes, explain: _____

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

YES /___/ NO /___/

If yes, explain: _____

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

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

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

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

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

Investigation #1 !

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

Investigation #2 !

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

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

Investigation #1 !

YES / ___ / Explain _____ ! NO / ___ / Explain _____
 !
 _____ ! _____
 !
 _____ ! _____

Investigation #2 !

YES / ___ / Explain _____ ! NO / ___ / Explain _____
 !
 _____ ! _____
 !
 _____ ! _____

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

YES /__/

NO /__/

If yes, explain: _____

David Spellman 9/20/99
Signature Date
Title: Project Manager

Alan 9/20/99
Signature of Office/ Date
Division Director

cc: Original NDA Division File HFD-93 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	<u>21048</u>	Trade Name:	<u>ESTRADIOL TRANSDERMAL SYSTEM (E2 III TS)</u>
Supplement Number:		Generic Name:	<u>ESTRADIOL TRANSDERMAL SYSTEM (E2 III TS)</u>
Supplement Type:		Dosage Form:	<u>TDP</u>
Regulatory Action:	<u>PN</u>	Proposed Indication:	<u>Hormone Replacement Therapy</u>

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 product is indicated for use in post-menopausal women and does not have pediatric implications.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, DORNETTE SPELL-LESANE

Dornette Spell-Lesane
 Signature

9/16/99
 Date

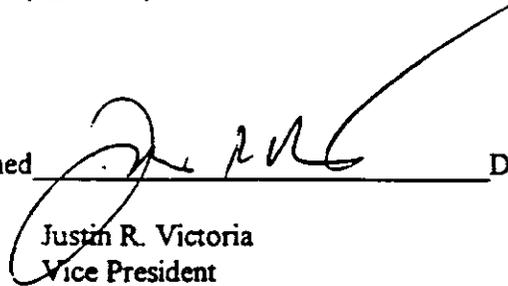
**17 β -Estradiol Transdermal System
E₂ III TS**

NDA No. 21-048

Item 16. Debarment Certification

The undersigned certifies that Wyeth-Ayerst did not and will not knowingly use in any capacity the services of any person debarred under subsection (a) or (b) of section 306 of the Federal Food, Drug, and Cosmetic Act in connection with NDA No. 21-048 for 17 β -Estradiol Transdermal System (E₂ III TS).

Signed



Date 11/10/98

Justin R. Victoria
Vice President
Worldwide Regulatory Affairs

CONFIDENTIAL



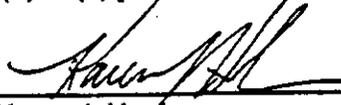
Item 16

DEBARMENT CERTIFICATION SECTION

Certification Statement

In compliance with 21 U.S.C § 335a (k) (1) (2), Cygnus, Inc. hereby certifies that it has not and will not use, in any capacity, the services of any person debarred under subsections (a) or (b) [Section 306 (a) or (b)], in connection with this Drug Master File.

Signed By: _____


Karen J. Harder

Title:

VP, Regulatory and Clinical Affairs

Date:

2 October 1998

SEP 20 1999

Teleconference Minutes

Date: September 20, 1999

Time: 11:00-11:15 a.m.

Location: Parklawn; 17B45

NDA 21-048

Drug Name: 17 β -estradiol transdermal system

Indication: Hormone Replacement Therapy

Type of Meeting: labeling

Meeting Chair: Dornette Spell-LeSane, NP-C

External Lead: Joseph Sobecki

Meeting Recorder: Dornette Spell-LeSane

FDA Attendees

Dornette Spell-LeSane, NP-C, Project Manager, Division of Reproductive and Urologic Drug Products
DRUDP (HFD-580)

External Attendees:

Joseph Sobecki, Associate Director, US Regulatory Affairs

Meeting Objectives:

To discuss labeling changes

Background:

Wyeth-Ayerst submitted draft labeling on September 16, 1999 for review by the division for a September 20, 1999 action date.

FDA comments:

1. **DESCRIPTION** section,
Replace chemical structure to reflect that of estradiol shown in the "USP Dictionary of drug names". by adding a hydrogen atom to carbon-17.
2. _____ section,
Remove ~~←~~ elevated blood pressure and add it to the *Precautions* section making it #3 after cardiovascular risk.
3. **CLINICAL PHARMACOLOGY** section,
CLINICAL STUDIES subsection,
The second sentence should read: "On average, these patients had approximately (12-13) hot flushes per day upon study entry." After 4 weeks.....
4. **CLINICAL PHARMACOLOGY** section
CLINICAL STUDIES subsection,
Figure 3 and 4 should be changed to show points only at weeks 4, 8 and 12 in line graph and on x axis.

SEP 17 1999

Memorandum

To: NDA 21-048, 17 β -Estradiol Transdermal System (E₂III TS)
From: David Lin, Ph.D. *DL* for M.J. Rhee
Date: September 17, 1999 *9/17/99*
Re: Proprietary Name

The sponsor has not submitted a proprietary name for their drug product. However, this NDA can be approved without one. When the sponsor wishes to market their drug product, their proposed proprietary name will require review by this Division.

cc:
Orig. NDA #21-048
HFD-580/Division File
HFD-580/Dspell-LeSane
HFD-580/MRhee

Filename: nda21048mem.nam (doc)

Memo

NDA: 21-048
Drug 17 β -Estradiol transdermal system
Sponsor: Wyeth Ayerst
Date: 09/17/99

SAFETY UPDATE

For safety update see page 29 of Medical Officers review.



OFFICES OF DRUG EVALUATION
ORIGINAL NDA/NDA EFFICACY SUPPLEMENT
ACTION PACKAGE CHECKLIST

NDA # 21-048 Drug 17β-estradiol transdermal system DATE 9/17/99

Applicant Wyeth-Ayerst CSO Dornette-Spell-LeSane /Phone 301-4260

User Fee Goal Date: _____

Arrange package in the following order:

- | | <u>Check or Comment</u> |
|--|---|
| 1. ACTION LETTER with supervisory signatures
Are there any Phase 4 commitments? | AP _____ AE _____ NA _____
Yes _____ No <u>X</u> |
| 2. Have all disciplines completed their reviews?
If no, what review(s) is/are still pending? | Yes _____ No _____ |
| 3. Completed copy of this CHECKLIST in package | Chem/Ther Types _____ |
| 4. LABELING (package insert <u>and</u> carton and container labels).
(If final or revised draft, include copy of previous version with ODE's
comments and state where in action package the Division's review
is located. If Rx-to-OTC switch, include current Rx Package insert
and HFD-312 and HFD-560 reviews of OTC labeling.) | Draft <u>X</u>
Revised Draft <u>X</u>
Final _____ |
| 5. PATENT INFORMATION | _____ <u>X</u> |
| 6. EXCLUSIVITY CHECKLIST | _____ <u>X</u> |
| 7. PEDIATRIC PAGE | _____ <u>X</u> |
| 8. DEBARMENT CERTIFICATION (Copy of applicant's certification for all NDAs submitted on or after June 1, 1992). | _____ <u>X</u> |
| 9. Statement on status of DSI's AUDIT OF PIVOTAL CLINICAL STUDIES
If AE or AP ltr, explain if not satisfactorily completed. Attach a COMIS printout of DSI status.
If no audits were requested, include a memo explaining why. | _____ <u>X</u> |
| 10. REVIEWS: | |
| DIVISION DIRECTOR'S MEMO If more than 1 review for any | _____ |
| GROUP LEADER'S MEMO 1 discipline, separate reviews | _____ <u>X</u> |
| MEDICAL REVIEW with a sheet of colored paper. | _____ <u>X</u> |
| SAFETY UPDATE REVIEW Any conflicts between reviews | _____ <u>X</u> |
| STATISTICAL REVIEW must have resolution documented | _____ <u>X</u> |
| BIOPHARMACEUTICS REVIEW | _____ <u>X</u> |
| PHARMACOLOGY REVIEW (Include pertinent IND reviews) | _____ <u>X</u> |
| Statistical Review of Carcinogenicity Study(ies) | _____ |
| CAC Report/Minutes | _____ |
| CHEMISTRY REVIEW | _____ <u>X</u> |
| Labeling and Nomenclature Committee Review Memorandum | _____ N/A |
| Date EER completed <u>9-15-99</u> (attach signed form or CIRTS printout) | OK _____ No _____ |
| FUR needed _____ FUR requested _____ | |
| Have the methods been validated? | Yes (attach) _____ No <u>X</u> |
| Environmental Assessment Review / FONSI | Review <u>X</u> FONSI _____ |
| MICROBIOLOGY REVIEW | Yes <u>X</u> |
| What is the status of the monograph? | _____ <u>N/A</u> |
| 11. CORRESPONDENCE, MEMORANDA OF TELECONS, and FAXes | _____ <u>X</u> |
| 12. MINUTES OF MEETINGS | |
| Date of End-of-Phase 2 Meeting <u>6/27/95</u> | _____ |
| Date of pre-NDA Meeting <u>none</u> | _____ |
| 13. ADVISORY COMMITTEE MEETING MINUTES
or, if not available, 48-Hour Info Alert or pertinent section of transcript. | Minutes _____ Info Alert _____
Transcript _____ No mtg _____ |
| 14. FEDERAL REGISTER NOTICES; OTC or DESI DOCUMENTS | _____ N/A _____ |

CONTINUE TO NEXT PAGE

15. If approval letter, has ADVERTISING MATERIAL been reviewed? Yes _____ No X _____
If no and this is an AP with draft labeling letter, has advertising material already been requested? Yes, documentation attached _____
No, included in AP ltr _____
16. INTEGRATED SUMMARY OF EFFECTIVENESS X _____
17. INTEGRATED SUMMARY OF SAFETY X _____

revision: 3/7/96

SEP 16 1999

Addendum to Labeling Review

SEP 20 1999

Reference is made to draft labeling submitted by Wyeth-Ayerst dated September 16, 1999. Reference is also made to Wyeth-Ayerst facsimile transmissions of September 9 and 10, 1999 with alternative proposals to some of the aspects of the labeling in response to the Division's comments on August 26, 1999 and September 10, 1999.

The sponsor has submitted revised draft labeling that incorporates changes that have been discussed and agreed upon: These changes are:

Physician's label prior to Clinical Studies, Adhesion subsection:

The sponsor now includes the number and percentage of patients in each TRADENAME arm (0.05, 0.075, 0.10 mg) who required replacement of their patch due to inadequate adhesion. The paragraph reads:

In two 12-week, double blind, placebo-controlled studies, a total of 442 patients received 0.05, 0.075, or 0.1 mg TRADENAME. The percent adhesion of the patch at weeks 4, 8, and 12 was assessed. Among the TRADENAME recipients, 88% to 90% of the patches observed were 90% to 100% adherent. One patient in the 0.05 mg/day TRADENAME arm discontinued therapy during these clinical trials because of adhesion failure. In these trials, 4.1% (71/1730), 3.9% (74/1883) and 4.6% (83/1814) of the 0.05, 0.075, and 0.1 mg patches, respectively, required replacement due to inadequate adhesion.

Physician's Labeling

Under Indications

_____ has been deleted.

Under Contraindications

Active thrombophlebitis or thromboembolic disorders or a history of these conditions with previous estrogen use is retained. The sentence _____ has been deleted.

Under Adverse Reactions

The paragraph concerning the _____ had been deleted.

Under Administration

The text, "The sites of application *must be rotated*" is retained since it is consistent with the labeling for other marketed estradiol patches.

Under Administration, therapeutic regimen, the following text is agreed upon:

TRADENAME may be given continuously in patients who do not have an intact uterus. In those patients with an intact uterus, TRADENAME may be given *continuously or on a cyclic schedule* (e.g., 3 weeks on drug followed by 1 week off drug). In patients with an intact uterus, concomitant progestin therapy is recommended.

Patient Labeling**Under Risks of Estrogens**

The text _____ has been deleted.

This sentence is now placed in the section **Side Effects**.

The text "A spotty darkening of the skin, particularly on the face, which may persist when drug is discontinued" is retained under **Side Effects**.

As previously stated, all of the above changes have been agreed upon, therefore, draft labeling is now acceptable to this reviewer, with the exception of the pharmacology/pharmacokinetic section. This section is being discussed with the sponsor by the appropriate reviewer.

Phill H. Price, M.D.

September 16, 1999

Manic M.D.
9/20/99

Second Addendum to Draft Labeling

In a final review of the label it was noted that in the sponsor's draft figures 3 and 4 reported mean changes in the daily number of flushes by weeks _____ on the x axis and the percent of mean change on the y axis for the two pivotal studies. The sponsor has agreed that changes to the x axis will show mean changes by weeks 4, 8, and 12, which were the primary efficacy endpoints of the study, not the changes from weeks _____

Phill H. Price, M.D.

September 20, 1999

Manic M.D.
9/20/99

Memorandum

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

Date: SEP 13 1999
From: David Hoberman, Ph.D., HFD-715
Subject: Estradiol Transdermal System
To: File (NDA# 21-048)

In talking with Dr. Price about review of this NDA, it was decided that no formal statistical review would be necessary unless he indicated that there were major issues that arose during his medical review. Since that has not occurred, there is no formal statistical review of this application.


David Hoberman, Ph.D.

Concur: Dr. Kammerman *JK 9/13/99*

Dr. Nevius *892 9/13/99*

cc:
Arch NDA# 21-048
HFD-580
HFD-580/PPrice
HFD-715/DHoberman, DOB2, Chron

**FACSIMILE TRANSMISSION
WYETH-AYERST RESEARCH
170 RADNOR-CHESTER ROAD
ST. DAVIDS, PA 19087
Telefax Number: (610) 964-5973**

DATE: September 10, 1999

TO: Dornette Spell-LeSane
Division of Reproductive and Urologic Drug Products

FACSIMILE No: 1-301-827-4267

FROM: Joseph J. Sobecki, US Regulatory Affairs
(610) 902-3737

No. of PAGES: 1 (including cover page)

Re: NDA NO. 21-048, 17 β -Estradiol Transdermal System (E₂ III TS)

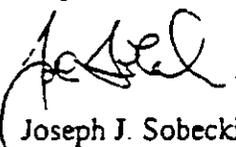
We agree to revise the draft labeling for 17 β -Estradiol Transdermal System in accord with the Division's comments which you provided by telephone yesterday (September 9, 1999) in response to the labeling proposals we faxed earlier that day. However, upon further review of the labeling, we discovered the omission of two words from the Therapeutic Regimen subsection of DOSAGE AND ADMINISTRATION. Specifically, while we accept the FDA's request to state that for patients with an intact uterus, the product may be given on a cyclic schedule, we believe that the dosing recommendation should also include the possibility of continuous therapy in these women. This is supported by the fact that the dosing regimen used for this product in the Phase 3 clinical trials was continuous for all patients, regardless of whether they had an intact uterus. Clearly, the dosing regimens recommended in the labeling should include the one studied in the clinical program.

Thus, we propose the following revised text, which replaces item #6 of our September 9, 1999 proposal (added text shown in boldface):

Under THERAPEUTIC REGIMEN in DOSAGE AND ADMINISTRATION:
TRADENAME may be given continuously in patients who do not have an intact uterus. In those patients with an intact uterus, TRADENAME may be given **continuously or on a cyclic schedule** (e.g., 3 weeks on drug followed by 1 week off drug). In patients with an intact uterus, concomitant progestin therapy is recommended (see PRECAUTIONS).

We would appreciate the Division's concurrence with this proposal prior to finalizing the draft labeling. If you have any questions or comments, please don't hesitate to call me at (610) 902-3737.

Regards,


Joseph J. Sobecki
Associate Director, US Regulatory Affairs

Teleconference Minutes

Date: September 10, 1999

Time: 3:00-3:15 p.m. Location: Parklawn: 17B45

NDA 21-048

Drug Name: 17 β -estradiol transdermal system

Indication: Hormone Replacement Therapy

Type of Meeting: labeling

Meeting Chair: Dornette Spell-LeSane, NP-C

External Lead: Joseph SobECKi

Meeting Recorder: Dornette Spell-LeSane

FDA Attendees

Dornette Spell-LeSane, NP-C, Project Manager, Division of Reproductive and Urologic Drug Products
DRUDP (HFD-580)

External Attendees:

Joseph SobECKi, Associate Director, US Regulatory Affairs

Meeting Objectives:

To discuss labeling changes

Background:

Wyeth-Ayerst submitted draft labeling on August 5, 1999; FDA conveyed comments to the sponsor regarding the draft label August 26, 1999. The sponsor faxed a response to FDA's comments September 9, 1999. Sponsor initiated phone call to convey acceptance of proposed labeling changes.

Wyeth-Ayerst's Comments

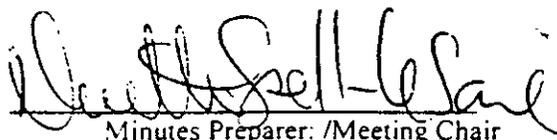
See attached faxed comments from Wyeth-Ayerst submitted September 10, 1999.

Decision Reached:

- sponsor declined teleconference for September 10, 1999
- sponsor to begin producing final draft labeling after response from FDA regarding attached information received by fax dated September 10, 1999.

Action Items:

- FDA to review sponsors responses and return a decision by September 13, 1999
- meeting minutes to be conveyed to sponsor within 30 days



Minutes Preparer: /Meeting Chair

cc:

Original NDA 21-048

HFD-580/Div. Files

HFD-580/Mann/Slaughters/Price/Mitra/Rhee/Parekh/Haidar/Rumble/

Drafted by: Spell-LeSane September 13, 1999

Concurrences: Rumble, 9.16.99, Mann, 9.16.99

Final: Spell-LeSane, 9.20.99

NDA/21048/label rev 9.10.99

TELECONFERENCE MINUTES

Teleconference Minutes

Date: September 9, 1999

Time: 2:20-2:50 p.m. Location: Parklawn: 17B45

NDA 21-048

Drug Name: 17 β estradiol transdermal system

Indication: Hormone Replacement Therapy

Type of Meeting: labeling

Meeting Chair: Dornette Spell-LeSane, NP-C

External Lead: Joseph Sobecki

Meeting Recorder: Dornette Spell-LeSane

FDA Attendees

Dornette Spell-LeSane, NP-C, Project Manager, Division of Reproductive and Urologic Drug Products
DRUDP (HFD-580)

External Attendees:

Joseph Sobecki, Associate Director, US Regulatory Affairs

Meeting Objectives:

To discuss Sponsor's response to the proposed labeling changes offered by the Division.

Background:

Wyeth-Ayerst submitted draft labeling on August 5, 1999; FDA conveyed comments to the sponsor regarding the draft label August 26, 1999. The sponsor faxed a response to FDA's comments September 9, 1999. This t-con is to convey FDA's response to the sponsor's proposal.

See attached comments from Wyeth-Ayerst submitted September 9, 1999.

FDA Comments:

Physician Labeling

1. Adhesion Subsection:

The Division concurs with the sponsors' proposal and further would like to include the number of patches as well as the percentages.

2. Indications:

The Division has not accepted indications for which there are no clinical studies to support efficacy for HRT products approved in the past year. There are no data provided by the sponsor to support the indication:

~~therefore, the division is firm that the indication:~~
~~_____ must be deleted.~~

3. *Contraindications:*

The Division feels strongly that ERT is contraindicated in patients who have had previous thromboembolic events occurring in association with previous estrogen use. Therefore, the Division wishes to retain the FDA proposed language. The sponsor may provide for review clinical data that suggest that this should not be a contraindication.

4. *Adverse Reactions:*

The Division recommends deleting all references to _____ in the label. The most relevant data regarding skin irritation comes from the controlled clinical trials, and is already in the label. Adding information from the _____ is not relevant.

5. *Administration:*

The Division concurs with the sponsors' proposal.

6. *Therapeutic Regimen:*

The Division concurs with the sponsors' proposal.

Patient Labeling:

7. *Risk of Estrogens:*

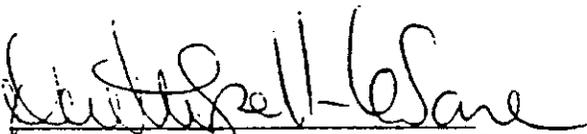
Any reference to "inflammation of the Pancreas" in the patient labeling should be listed as a side effect, and not as a : _____

8. *Side Effects:*

The Division concurs with the sponsor proposal to retain "spotty darkening of the skin":

Action Items:

- sponsor to review FDA responses and return a decision within 2 days
- sponsor to confirm need for teleconference, scheduled September 10, 1999, to discuss further labeling requests
- meeting minutes to be conveyed to sponsor within 30 days



Minutes Preparer / Meeting Chair

cc:

Original NDA 21-048

HFD-580/Div. Files

HFD-580/Mann/Slaughters/Price/Mitra/Rhee/Parekh/Haidar/Rumble/

Drafted by: Spell-LeSane September 13, 1999

Concurrences: Mann, 9.16.99, Rumble, 9.16.99

Final: Spell-LeSane, 9.20.99

filename: NDA/21048/label rev.9999

MEETING MINUTES

**FACSIMILE TRANSMISSION
WYETH-AYERST RESEARCH
170 RADNOR-CHESTER ROAD
ST. DAVIDS, PA 19087**

Telefax Number: (610) 964-5973

DATE: September 9, 1999

TO: **Dornette Spell-LeSane**
Division of Reproductive and Urologic Drug Products

FACSIMILE No: 1-301-827-4267

FROM: Joseph J. Sobecki
US Regulatory Affairs
(610) 902-3737

No. of PAGES: 3 (including cover page)

Re: NDA NO. 21-048, 17 β -Estradiol Transdermal System (E₂ III TS)

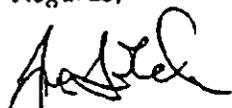
Dornette,

Attached are Wyeth-Ayerst's proposals in response to your August 26, 1999 facsimile providing FDA's suggested revisions to the draft labeling for 17 β -Estradiol Transdermal System, submitted by Wyeth-Ayerst on August 5, 1999.

We would appreciate the Division's concurrence or further comments concerning these proposals, prior to finalizing the draft labeling.

If you have any questions or comments, please don't hesitate to call me at (610) 902-3737.

Regards,



Joseph J. Sobecki
Associate Director
US Regulatory Affairs

3 Page(s) Withheld

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

 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

MEETING MINUTES

Date: August 18, 1999

Time: 1:00-2:30 p.m.

Location: Parklawn, 17B43

NDA: 21-048

Drug: estradiol transdermal system

Sponsor: Wyeth-Ayerst

Indication: Hormone Replacement Therapy

Type of meeting: 9-month status /Labeling (internal)

FDA lead: Dr Marianne Mann

Meeting Recorder: Dornette Spell-LeSane

Participants:

Marianne Mann, M.D., Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP HFD-580)

Amit Mitra, Ph.D. Chemist, New Drug Chemistry II, @ DRUDP (HFD-580)

David Hoberman, Statistician, DBII @ DRUDP (HFD-580)

Sam Haidar, R.P.H., Ph.D., Pharmacokinetics Reviewer, DPE II @ DRUDP (HFD-580)

Lisa Stockbridge, Ph.D., Division of Drug Marketing and Advertising

Dornette Spell-LeSane, NP-C, Regulatory Project Manager, DRUDP (HFD-580)

Meeting Objective

To discuss the status of reviews and review draft labeling

Background:

The sponsor submitted revised draft labeling August 5, 1999.

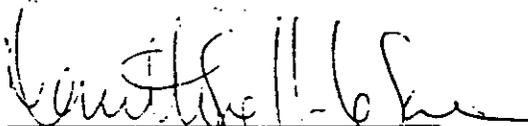
Discussion

See attached recommended changes to revised draft labeling labeling.

Action Items:

- Send copy of FDA recommendations to draft labeling to sponsor within 5-7 days

NOTE: Comments to draft labeling was faxed to sponsor August 26, 1999.


Minutes Preparer


Chair Concurrence 9/22/99

Cc: Original

HFD/Div Files

HFD-580/Spell-Lesane

HFD-580/Rarick/Mann/Price/Slaughter/Rhee/Mitra/Jordan/Parekh/

Kammerman/Hoberman/Haidar/

Concurrence: Rumble, 9.20.99, Mann, 9.21.99

Draft: Spell-LeSane 9.16.99

Final: Spell-LeSane, 9.21.99

16 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

SEP 20 1999

MEETING MINUTES

Date: July 12, 1999 **Time:** 9:33-9:45 a.m. **Location:** Parklawn; 17B45

NDA: 21-048 **Drug:** Estradiol Transdermal System

Indication: Hormone Replacement Therapy

Type of meeting: 8-month status/Labeling

FDA lead: Dornette Spell-LeSane, NP-C

Meeting Recorder: Dornette Spell-LeSane, NP-C

Participants:

Dornette Spell-LeSane, NP-C, Regulatory Project Manager, DRUDP (HFD-580)

Meeting Objective

Meeting was scheduled to discuss sponsor's revised draft labeling.

Background: On July 2, 1999, a request was made to the sponsor to review and compare their current label with that of Esclim making changes were applicable then submit a revised label for review.

Discussion Points:

8-Month status consisted of phone calls to reviewers for updates. Labeling meeting rescheduled awaiting draft labeling from sponsor.

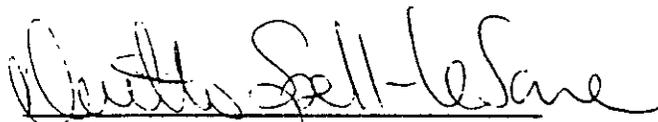
Status of Reviews:

Ongoing

Action:

- determine from sponsor when label will be completed for review
- schedule label meeting for mid-August

Note: Revised draft label submitted August 5, 1999. Meeting scheduled for August 18, 1999.


Minutes Preparer/Chair Concurrence
9/20/99

NDA 21048

Page 2

Cc: Original

HFD/Div Files

HFD-580/Spell-Lesane

HFD-580/Rarick/Mann/Price/Slaughter/Rhee/Mitra/Jordan/Parekh/
Kammerman/Hoberman/

Concurrence: Rumble, 9.20.99

Draft: Spell-LeSane September 13, 1999

Final:

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved OMB No. 0310-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

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

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

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Wyeth-Ayerst Laboratories	DATE OF SUBMISSION September 16, 1999
TELEPHONE NO. (include Area Code) (610) 902-3739	FACSIMILE (FAX) Number (include Area Code) (610) 964-5973
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): P O. Box 8299 Philadelphia, PA 19101-8299	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued) NDA No. 21-048

ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Estradiol Transdermal System (E2 HTS)	PROPRIETARY NAME (trade name) IF ANY N/A	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any) Estradiol-1,3,5 (10)-inone-3,17 beta-diol	CODE NAME (if any)	
DOSEAGE FORM: Patch	STRENGTHS: 0.05, 0.075, and 0.1mg per day	ROUTE OF ADMINISTRATION: Transdermal
(PROPOSED) INDICATION(S) FOR USE. Hormone Replacement in Menopausal Women		

APPLICATION INFORMATION

APPLICATION TYPE (check one)
 NEW DRUG APPLICATION (21 CFR 314.50) ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 31.94)
 BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE 505 (b) (1) 505 (b) (2) 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
 Name of Drug: _____ Holder of Approved Application: _____

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

REASON FOR SUBMISSION: Approval to market a new drug product

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

NUMBER OF VOLUMES SUBMITTED: 1 THIS APPLICATION IS PAPER PAPER AND ELECTRONIC ELECTRONIC

ESTABLISHMENT INFORMATION

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

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

IND No. 44,168 DMF Nos. _____

This application contains the following items: (Check all that apply)

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

DECLARATION

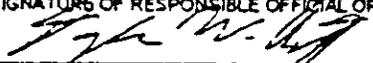
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA.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

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 608, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

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

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

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

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Mr. Douglas W. Bitt, Director, U.S. Regulatory Affairs	DATE 3/16/99
--	--	-----------------

ADDRESS (Street, City, State, and ZIP Code) P.O. Box 8299, Philadelphia, PA 19101-8299	Telephone Number (610) 902-3739
---	------------------------------------

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

OHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
270 Independence Avenue, S.W.
Washington, DC 20201

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.

Please DO NOT RETURN this form to this address.

WYETH-AYERST  RESEARCH

PO BOX 8270 - PHILADELPHIA PA 19101-8270
TEL: 610 964 5973

Division of American Home Products Corporation

September 16, 1999

U.S. REGULATORY AFFAIRS

NDA No. 21-048
17 β -Estradiol Transdermal System (E₂ III TS)

Amendment to a Pending New Drug Application:
Revised Draft Labeling

Response to FDA Request for Information

Lisa Rarick, MD, Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Rarick:

Reference is made to NDA No. 21-048 for 17 β -Estradiol Transdermal System (E₂ III TS), submitted on November 20, 1998.

Further reference is made to the Division's facsimile transmissions dated August 26, 1999 and September 10, 1999, providing comments on the revised draft physician and patient package insert labeling submitted on August 5, 1999. We further refer to Wyeth-Ayerst's facsimile transmissions of September 9 and 10, 1999 with alternative proposals to some aspects of the labeling, in response to the Division's comments. Based on telephone conversations between Mr. Joseph Sobocki of Wyeth-Ayerst and Ms. Dornette Spell-LeSane of FDA on September 9, 13, and 16, 1999, we are providing revised draft labeling which incorporates all of the changes that have been discussed and agreed upon.

Accordingly, enclosed are four (4) copies of revised draft labeling for the physician and patient package insert. One additional "desk copy" has been provided for Ms. Spell-LeSane.

With reference to the agreement to express the product dosage strengths in milligrams _____), as reflected in the enclosed package insert, please also be advised that Wyeth-Ayerst hereby commits to make this change to all of the labels for the patch backing, foil pouch, and carton

09/16/99 12:00 PM FAX 902 373 3310
REGULATORY AFFAIRS
0000

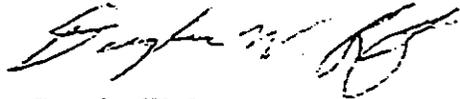
NDA No. 21-048

September 16, 1999
Page 2

If you have any questions on the revised draft labeling or need any additional information, please contact Mr. Joseph Sobocki at (610) 902-3737, or Miss JoAnne Bissinger at (610) 902-3731.

Sincerely,

WYETH-AYERST LABORATORIES



Douglas W. Bitz
Director, US Regulatory Affairs

Desk Copy: Ms. Domette Spell-LeSane, Project Manager

24 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

NDA 21-048
ESTRADIOL TRANSDERMAL SYSTEM
WYETH AYERST

DRAFT LABELING CHANGES FROM 8/18/99
(COMMENTS FROM FDA)

Faxed to sponsor: August 26, 1999

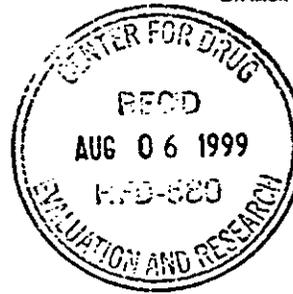
CC: Mann
Price
Haidar
Mitra
Hoberman

NOTE: Status meeting September 10, 1999 8:30 a.m.
May use for t-con with Sponsor if needed

70 BOX 8299 • PHILADELPHIA, PA 19101-8299 • (610) 902-3710
FAX: (610) 964-5973

15V
Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS



August 5, 1999

NDA No. 21-048
17 β -Estradiol Transdermal System (E₂ III TS)

Amendment to a Pending New Drug Application:
Revised Draft Labeling

Response to FDA Request for Information

Lisa Rarick, MD, Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Rarick:

Reference is made to NDA No. 21-048 for 17 β -Estradiol Transdermal System (E₂ III TS), submitted on November 20, 1998.

I further refer to a telephone call on July 6, 1999 from Ms. Dornette Spell-LeSane (Project Manager, FDA) to Mr. Joseph Sobecki of Wyeth-Ayerst, requesting a submission of revised draft labeling. Wyeth-Ayerst was advised to model the NDA No. 21-048 draft labeling, in terms of content and format, after that of Esclim[®] (estradiol transdermal system). Esclim was approved as NDA No. 20-847 on August 3, 1998 and, according to Ms. Spell-LeSane, is the most recently approved transdermal estradiol product.

In accordance with the FDA request, attached please find four (4) copies of revised draft labeling (prescribing information for physicians and patient labeling). One additional "desk copy" has been provided for Ms. Spell-LeSane. We have provided both a "clean" copy of the revised draft labeling and a version which details the changes (via "redline" and "strikeout" text) from the draft labeling submitted in the November 20, 1998 original NDA. The revised draft labeling (both versions) is also provided electronically in WORD 97 on the attached disk.

NOTE: Figures 1 and 2 of the electronic version of the labeling may not appear on the screen since they are in EPS (or Encapsulated Post Script) format, but will print from the attached disk.

34 Page(s) Withheld

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

 § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

4 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

MEETING MINUTES

Date: June 9, 1999

Time: 1:30pm

Location: Parklawn; 17B45

NDA: 21-048

Drug: Estradiol Transdermal System

Indication: Hormone Replacement Therapy

Type of meeting: 7-month status (internal)

FDA lead: Dr. Marianne Mann

Meeting Recorder: Dornette Spell-LeSane

Participants:

Marianne Mann, M.D., Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP HFD-580)

Phill Price, M.D. Medical Officer, DRUDP (HFD 580)

Amit Mitra, Ph.D. Chemist, New Drug Chemistry II. @ DRUDP (HFD-580)

Ameeta Parekh, Ph.D., Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) DPE II; (HFD-870) @ DRUDP (HFD-580)

David Hoberman, Statistician, DBII @ DRUDP (HFD-580)

Terri Rumble, BSN, Chief Project Management Staff, DRUDP (HFD-580)

Dornette Spell-LeSane, NP-C, Regulatory Project Manager, DRUDP (HFD-580)

Meeting Objective

To discuss the status of reviews for NDA 21-048

Background: This NDA sponsored by Wyeth-Ayerst is being submitted to

This HRT patch is a 7-day patch available in three sizes with normal delivery rates of 50, 75, and 100 µg. NDA was submitted November 20, 1998, with a Goal date of September 20, 1999. A 6-month status meeting was held May 11, 1999, with the following action items:

1. send microbiology consult-- sent May 21, 1999, completed July 20, 1999
2. call sponsor to inquire regarding trade name- completed May 12, 1999, no tradename established
3. chemistry to request EER inspections requested Jan 1999
4. schedule two internal labeling meetings July 12, 1999 8-mo status mtg. & labeling August 18, 1999 labeling mtg. August 23, 1999 labeling mtg.

Discussion

Clinical pharmacology:

- review is underway

Clinical:

- review is underway

Chemistry:

- review is underway

Biometrics

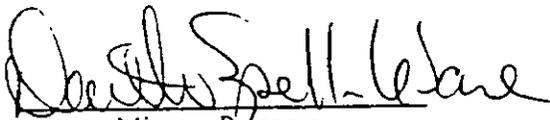
- will review as needed at request of Medical Officer

Unresolved Issues:

- none

Action Items:

- Biopharm to identify if adhesion data is acceptable or if phase 4 commitment is necessary.
- give sponsor heads up that division will begin labeling discussions July 12, 1999.
completed 6/10/99
- schedule tentative teleconference with sponsor 1-2 weeks after labeling meeting.-
September 8, & 10, 1999 reserved
- schedule next meeting for 1-1½ hrs. completed 6/9/99
- include copies of label as meeting package for July 12, 1999 meeting


Minutes Preparer


Chair Concurrence 9/20/99

Cc: Original
HFD/Div Files
HFD-580/Spell-LeSane
HFD-580/Rarick/Mann/Price/Slaughter/Rhee/Mitra/Jordan/Parekh/
Kammerman/Hoberman/
Concurrence: Mann, 9.17.99
Draft: Spell-LeSane 7.9.99
Final: 9.20.99

SQL> START COMISEXE:SINSPECT N 021048

IND AND NDA INVESTIGATOR DATA

SNAME	CITY	ST	IN	ASSIGN	RECD DATE	ACTN DATE	CLASS	REVIEWER
HOPKINS	WINTER PK	FL	DA	10-MAR-99	03-MAY-99	12-MAY-99	NAI	GDT
LIVINGSTON	WEST PALM BCH	FL	DA	10-MAR-99	19-MAY-99	01-JUN-99	NAI	GDT
MCCLUSKEY	MOGADORE	OH	DA	10-MAR-99	12-APR-99	14-MAY-99	NAI	GDT
RIPLEY	SOUTH YARMOUTH	MA	DA	10-MAR-99	24-MAY-99	01-JUN-99	VAI	GDT

SQL> SPOOL OFF

VIEW THE REPORT AGAIN? <Y,N>

JUN - 3 1999

Peter M. Ripley, M.D.
Clinical Studies Cape Cod
23H White's Path
South Yarmouth, MA 02664

Dear Dr. Ripley:

Between April 12-14, 1999, Ms. Elizabeth B. Griffin and Mr. George T. Allen, representing the Food and Drug Administration (FDA), conducted an inspection of your conduct, as investigator of record, of a clinical study (protocol #0802E1-316-US) of the investigational drug Estradiol Transdermal System, performed for Wyeth Ayerst Research. This inspection is a 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 an evaluation of the inspection report and of the documents collected during the inspection, we conclude that you did adhere to most Federal regulations and/or good clinical practices governing your conduct of clinical investigations and the protection of human subjects. At the close of the audit the FDA inspectors issued you Form FDA 483 which listed their observations including failure to report accurately to the IRB. Your letter of April 28, 1999 responding to the observations listed in form FDA 483 was reviewed and will be made part of the inspection file.

We appreciate the cooperation shown Ms. Griffin and Mr. Allen during the inspection.

Sincerely yours,

Bette L. Barton, Ph.D., M.D.
Chief
Good Clinical Practice Branch I
Division of Scientific
Investigations, HFD-344
Office of Medical Policy
Center for Drug Evaluation
and Research
7520 Standish Place
Rockville, MD 20855

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
344	-1	Tan			6/2/99
344	1002	Barton			
	18	17			

FILE
COPY

Page 2 - Peter M. Ripley, M.D.

bcc:

HFA-224
HFD-580 Doc. Rm. NDA #21-048
HFD-580 Review Div. Dir. Rarick
HFD-580 MO Price
HFD-580 PM Spell-LeSane
HFD-340/R/F
HFD-344/Chron File
HFD-344/CIB File #9406
HFD-344/Turner
HFR-NE-252 DIB Kraychuck
HFR-NE-250 BIMO MONITOR Kelley
HFR-NE-250 FIELD INVESTIGATOR Allen

CFN:1283955

Field Classification:VAI

Headquarters Classification:

- 1)NAI
- 2)VAI-no response required
- 3)VAI-response requested
- 4)OAI

If the Field and Headquarters classifications are different,
explain
why:

Deficiencies noted:

- inadequate consent form
- inadequate drug accountability
- deviations from protocol
- inadequate records
- failure to report ADRs
- other (specify)

M.O. notes:30 subjects were randomized at this site. The auditors reviewed 10 of the 30 subjects. No major problems were found and DSI would recommend that the data be used in support of the NDA.

r/d:GDTurner: 5/26/99
finald:slk:5/27/99

Stephen H. Livingston, M.D.
Hill Top Research Inc.
2051 45th Street, Suite 200
West Palm Beach, FL 33407

JUN -1 1999

Dear Dr. Livingston:

Between April 26-30, 1999, Mr. Jose R. Rodriguez, representing the Food and Drug Administration (FDA), conducted an inspection of your conduct, as investigator of record, of a clinical study (protocol #0802E1-317-US) of the investigational drug Beta Estradiol Transdermal System, performed for Wyeth-Ayerst Research. This inspection is a 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 an evaluation of the inspection report and of the documents collected during the inspection, we conclude that you did adhere to all Federal regulations and/or good clinical practices governing your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Mr. Rodriguez during the inspection.

Sincerely yours,

Bette L. Barton, Ph.D., M.D.
Chief
Good Clinical Practice Branch I
Division of Scientific
Investigations, HFD-344
Office of Medical Policy
Center for Drug Evaluation
and Research
7520 Standish Place
Rockville, MD 20855

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
3-4	-1	5/25/99			
3/11	1/2	128 May 99			

FILE
CCF:

Page 2 - Stephen H. Livingston, M.D.

bcc:

HFA-224
HFD-580 Doc. Rm. NDA #21-048
HFD-580 Review Div. Dir. Rarick
HFD-580 MO Price
HFD-580 PM Spell-Lesane
HFD-340/R/F
HFD-344/Chron File
HFD-344/CIB File #9782
HFD-344/Turner
HFR-SE-250 DIB Chappell
HFR-SE-2585 BIMO MONITOR Torres
HFR-SE-2585 FIELD INVESTIGATOR Rodriguez

CFN:1064061

Field Classification: NAI

Headquarters Classification:

- 1) NAI
- 2) VAI-no response required
- 3) VAI-response requested
- 4) OAI

If the Field and Headquarters classifications are different,
explain
why:

r/d:GDTurner: 5/24/99
finaled:slk:5/25/99

M.O. notes: 32 subject completed the study. The records from 6 subjects were reviewed. No problems were found and DSI would recommend that the study be used in support of the NDA.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

MAY 14 1999

Dennis C. McClusky, M.D.
Hill Top Research LTD.
754 S. Cleveland Ave, Suite 200
Mcgradore, OH 44260

Dear Dr. McClusky:

Between March 30-April 6, 1999, Ms. Karen M. Kondas, representing the Food and Drug Administration (FDA), conducted an inspection of your conduct, as investigator of record, of a clinical study (protocol #0802E1-317-US) of the investigational drug Estradiol Transdermal System, performed for Wyeth-Ayerst Research. This inspection is a 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 an evaluation of the inspection report and of the documents collected during the inspection, we conclude that you adhered to the Federal regulations and/or good clinical practices that govern your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Ms. Kondas during the inspection.

Sincerely yours,

B. L. Barton for BLB
Bette L. Barton, Ph.D., M.D.
Chief
Good Clinical Practice Branch.I
Division of Scientific
Investigations, HFD-344
Office of Compliance
Center for Drug Evaluation
and Research

Page 2 - Dennis C. McClusky, M.D.

bcc:

HFA-224
HFD-580 Doc. Rm. NDA #21-048
HFD-580 Review Div. Dir. Rarick
HFD-580 MO Price
HFD-580 PM Spell-Lisane
HFD-340/R/F
HFD-344/Chron File
HFD-344/CIB File #3442
HFD-344/Turner
HFR-CE-450 DIB Fielden
HFR-CE-450 BIMO MONITOR Grelle
HFR-CE-450 FIELD INVESTIGATOR Kondras

CFN:152804S

Field Classification:NAI

Headquarters Classification:

1)NAI
 2)VAI-no response required
 3)VAI-response requested
 4)OAI

If the Field and Headquarters classifications are different,
explain
why:

r/d:GDTurner:5/6/99
finaled:slk:5/7/99

M.O. notes: Records for 20 of the 36 subjects randomized into
this study were audited. No problems were found and DSI would
recommend that this study be used in support of the NDA.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

Lynne Hopkins, M.D.
Clinical Studies LTD.
2100 Aloma Ave.
Winter Park, FL 32792

MAY 12 1999

Dear Dr. Hopkins:

Between April 6-9, 1999, Ms. Brunilda Torres, representing the Food and Drug Administration (FDA), conducted an inspection of your conduct, as investigator of record, of a clinical study (protocol #0802EI-316-US) of the investigational drug Beta Estradiol TS, performed for Wyeth-Ayerst Research. This inspection is a 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 an evaluation of the inspection report and of the documents collected during the inspection, we conclude that you did adhere to all Federal regulations and/or good clinical practices governing your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Ms. Torres during the inspection.

Sincerely yours,

Bette L. Barton, Ph.D., M.D.
Chief
Good Clinical Practice Branch I
Division of Scientific
Investigations, HFD-344
Office of Medical Policy
Center for Drug Evaluation
and Research
7520 Standish Place
Rockville, MD 20855

Page 2 - Lynne Hopkins, M.D.

bcc:

HFA-224
HFD-580 Doc. Rm. NDA #21-048
HFD-580 Review Div. Dir. Rarick
HFD-580 MO Price
HFD-580 PM Spell-Lesane
HFD-340/R/F
HFD-344/Chron File
HFD-344/CIB File #9768
HFD-344/Turner
HFR-HFR-SE-250 DIB Chappell
HFR-SE-2585 BIMO MONITOR Torres
HFR-SE-2585 FIELD INVESTIGATOR B.Torres

CFN:1064060

Field Classification: NAI

Headquarters Classification:

1) NAI
 2) VAI-no response required
 3) VAI-response requested
 4) OAI

If the Field and Headquarters classifications are different,
explain
why:

r/d:GDTurner: 5/10/99
finaled:slk:5/11/99

M.O. notes: 53 subjects were screened for this study and 26
completed the study. No problems were found during the audit. DSI
would recommend that the study be used in support of the NDA.

MEETING MINUTES

Date: May 11, 1999

Time: 3:30-4:15pm

Location: Parklawn: 17B45

NDA: 21-048

Drug: estradiol transdermal system

Sponsor: Wyeth-Ayerst

Indication: Hormone Replacement Therapy

Type of meeting: 6-month status (internal)

FDA lead: Dr Marianne Mann

Meeting Recorder: Dornette Spell-LeSane

Participants:

Marianne Mann, M.D., Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP HFD-580)

Amit Mitra, Ph.D. Chemist, New Drug Chemistry II, @ DRUDP (HFD-580)

Ameeta Parekh, Ph.D., Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) DPE II; (HFD-870) @ DRUDP (HFD-580)

Terri Rumble, BSN, Chief Project Management Staff, DRUDP (HFD-580)

Diane Moore, Regulatory Project Manager, DRUDP (HFD-580)

Dornette Spell-LeSane, NP-C, Regulatory Project Manager, DRUDP (HFD-580)

David Hoberman, Statistician, DBII @ DRUDP (HFD-580)

Meeting Objective

To discuss the status of reviews for NDA 21-048

Background:

This NDA sponsored by Wyeth-Ayerst is being submitted to treat

This HRT patch is a 7-day patch available in three sizes with normal delivery rates of 50, 75, and 100 µg. The NDA was submitted November 23, 1998, with a Goal date of September 23, 1999.

Discussion

Clinical pharmacology:

- review is underway

Pharm tox:

- review is completed; recommend approval

Clinical:

- review is underway

DSI:

- inspections underway

Chemistry:

- minor deficiencies have been identified
- no non-approval issues noted at this time
- the proposed shelf-life of 36 months may not be appropriate
- a trade name for this drug has not yet been established

Biometrics

- will review as needed at request of Medical Officer

Unresolved Issues:

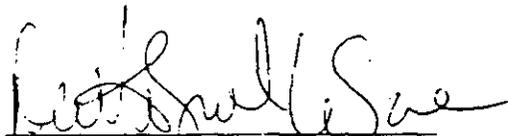
Dr. Mann will inquire regarding any information in the draft HRT Guidance that can be communicated to the sponsor to enable them to propose revised labeling.

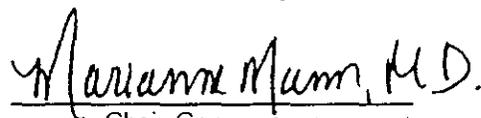
Action Items:

- Send consult to Microbiology
- Call Sponsor to inquire regarding trade name of drug
- Chemistry to request EER inspections
- Schedule two internal labeling meetings
- Schedule two labeling meetings with sponsor

NOTE: The 7-month status meeting scheduled for June 9, 1999 at 1:30 p.m. will include discussions on labeling.

Addendum: The most recent draft guidance (4/99) is not available for the sponsors' review until after announced in the federal register and available on-line.


Minutes Preparer


Chair Concurrence
9/16/99

NDA 21048

Page 2

Cc: Original

HFD/Div Files

HFD-580/Spell-Lesane

HFD-580/Rarick/Mann/Price/Slaughter/Rhee/Mitra/Jordan/Parekh/

Kammerman/Hoberman/

Concurrence: Rumble, 6.1.99/Moore, 6.1.99/Mann, 6.1.99/Hobberman, 6.2.99/Mitra, 6.3.99/

Draft: Spell-LeSane 5.20.99

Final: 5.27.99, 9.9.99

50

TEL 8299 • PHILADELPHIA, PA 19101-8299 • (610) 902-3710
FAX (610) 964-5973

Division of American Home Products Corporation

AJ 4/2/99

REGULATORY AFFAIRS

March 24, 1999

Estradiol Transdermal System (E₂ III TS)

NDA No. 21-048

**Amendment to a Pending New Drug Application:
Safety Update Report**

Lisa Rarick, MD, Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

*Noted
4/1/99*

*noted
4-3-99*

Dear Dr. Rarick:

Reference is made to NDA No. 21-048 for Estradiol Transdermal System (E₂ III TS), submitted on November 20, 1998.

In accord with 21 CFR 314.50(d)(5)(vi)(b), this letter serves as the Safety Update Report for NDA No. 21-048 (NDA Item 9).

All available safety information for this product was reported in the original NDA. There are no ongoing preclinical or clinical studies; all studies were completed prior to the time of NDA submission. Accordingly, there is no additional safety information to report.

If there are any questions, please contact our representative, Miss JoAnne Bissinger, at (610) 902-3731, or Mr. Joseph Sobacki, at (610) 902-3737.

Sincerely,

WYETH-AYERST LABORATORIES

[Handwritten Signature]

Douglas W. Bitz
Director
U.S. Regulatory Affairs



JJS/lm:111

REVIEWS COMPLETED
CSO ACTION:
<input type="checkbox"/> LETTER <input checked="" type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
DSL 4/5/99
CSO INITIALS
DATE

NEW CORRESP

Division of American Home Products Corporation

NC

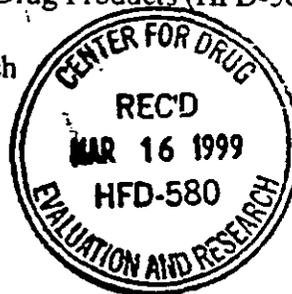
PO BOX 8299 • PHILADELPHIA, PA 19101-8299 • (610) 902-3710
FAX: (610) 964-5973

US REGULATORY AFFAIRS

ORIGINAL

March 15, 1999

Dornette Spell-LeSane, Project Manager
Division of Reproductive and Urologic Drug Products (HFD-580)
Room 17B-45
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



Dear Ms. Spell-LeSane:

Reference is made to your February 26, 1999 telephone conversation with Mr. Douglas Bitz of Wyeth-Ayerst, in which you indicated that the Division is unable to locate the CD-ROM that Wyeth-Ayerst provided with the original submission of NDA No. 21-048. You requested that another copy of the CD-ROM be sent to your attention.

Enclosed is the requested CD-ROM for NDA No. 21-048. As noted in our cover letter for the original NDA submission dated November 20, 1998, this CD-ROM contains the following information:

- PDF files of Items 11 and 12 (Case Report Tabulations and Case Report Forms)
- SAS Datasets for Item 11 and Item 6 (Human Pharmacokinetics & Bioavailability)
- Files providing text (in WORD 7) for the following NDA documents:
 - Integrated Summary of Safety
 - Integrated Summary of Efficacy
 - Application Summary
 - Study reports for the pivotal studies (General Medical Reports, or GMRs)

If you have any questions, please contact me at (610) 902-3737.

Sincerely,

WYETH-AYERST LABORATORIES

Joseph J. Sobecki
Joseph J. Sobecki
Associate Director
US Regulatory Affairs

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

Enclosure: CD-ROM
JJS/am:110

4 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

ORIGINAL

WYETH-AYERST  RESEARCH

P.O. BOX 8299, PHILADELPHIA, PA 19101-8299 • (610) 902-3710
FAX: (610)964-5973

Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

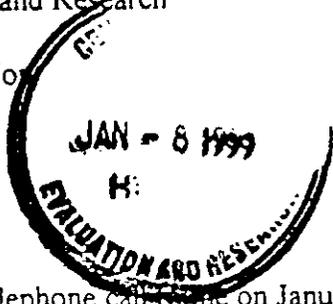
JJ 1/13/99

January 7, 1999

Additional Desk Copies
for NDA No. 21-048

[Handwritten signatures and initials]
1/13/99

Diane Moore, Project Manager
Division of Reproductive and Urologic Drug Products (HFD-580)
Center for Drug Evaluation and Research
Room 17B-45
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



Dear Diane:

As you requested in your telephone call on January 4, 1999, enclosed are two additional Desk Copies of certain volumes of NDA No. 21-048 for Estradiol Transdermal System, as follows:

- Volume 1.001 (containing the Index, Labeling, and Items 13, 14, 15, 16, 17, 18 and 19)
- Volume 1.026 (which includes the List of Clinical Investigators and Clinical Overview)
- Volume 1.038 (the Integrated Summary of Efficacy)
- Volumes 1.039-1.040 (the Integrated Summary of Safety)

If you have any questions or need any additional information, please contact me at (610) 902-3737.

Sincerely,

WYETH-AYERST LABORATORIES

[Handwritten signature]

Joseph J. Sobecki
Associate Director, US Regulatory Affairs

REVIEWS COMPLETED
CSO ACTION:
<input type="checkbox"/> LETTER <input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS
DATE

Enclosures (10 volumes)

Meeting Minutes

Date: January 5, 1999

Time: 10:00 – 10:12 AM

Location: Parklawn; Room 17B-43

NDA: 21-048

Drug Name: 17 β -estradiol Transdermal System

Type of Meeting: Filing

Indication: Treatment of moderate to severe vasomotor symptoms associated with menopause; vulval and vaginal atrophy

Sponsor: Wyeth-Ayerst Research

Meeting Chair: Dr. Lisa Rarick

Meeting Recorder: Ms. Diane Moore

FDA Attendees:

Lisa Rarick, M.D. - Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Marianne Mann, M.D. - Deputy Director, DRUDP (HFD-580)

Diane Moore - Project Manager, DRUDP (HFD-580)

Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)

Amit Mitra, Ph.D. - Chemist, DNDC II @ DRUDP (HFD-580)

Sam Haidar, R.Ph., Ph.D. - Pharmacokinetics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)

Lisa Kammerman, Ph.D. - Team Leader, Division of Biometrics II (DBII) @ DRUDP (HFD-580)

Meeting Objective: To discuss the fileability of NDA 21-048.

Discussion Points:

- an electronic version of the NDA data is available on the Division drive
- the User Fee Goal Date is September 20, 1999

Decisions reached:

- Clinical: Approved for Filing (AF)
- Pharmacology: AF
- Chemistry: AF
 - a tradename has not been submitted
 - the sponsor requested a — shelf-life for this product; the data may only support a — shelf-life
- Clinical Pharmacology and Biopharmaceutics: AF
- Biometrics: AF

Action Items: none

Diane Moore 2/17/99
Signature, recorder

Marulyn 2/18/99
Signature, Chair

drafted: dm/1.14.99/N21048FM1599.doc

cc:

NDA Arch:

HFD-580/LRarick/MMann/SSlaughter/PPrice/AMitra/MRhee/AParekh/SHaidar/LKammerman

HFD-580/AJordan/DHoberman

HFD-580/DMoore

Concurrence:

TRumble 01.18.99/MRhee, MMann 1.20.99/AMitra, SHaidar, LRarick 01.21.99

LKammerman 01.25.99

NDA: 21-048

**45 Day Filing Meeting Checklist
CLINICAL**

ITEM	YES	NO	COMMENT
1) Is the clinical section of the NDA clearly organized?	✓		
2) Is the clinical section of the NDA adequately indexed and paginated?	✓		
3) Is the clinical section of the NDA legible?	✓		
4) Is there an adequate rationale for selection of dose and dosing schedule?	✓		
5) Are the requisite number of adequate and well controlled studies submitted in the application?	✓		
6) Are the pivotal efficacy studies of appropriate design and duration to assess approvability of this product for its proposed indication?	✓		
7) Are electronic data sets (with adequate documentation for their use) provided for pivotal efficacy studies?			
8) Has the applicant submitted line listings in a format to allow review of individual patient data?			
9) Has the applicant submitted a rationale for assuming the applicability of foreign trial results to the U.S. population?			N/A
10) Has the applicant submitted all required case report forms (i.e., deaths, drop-outs due to ADEs and any other CRFs previously requested by the Division)?	✓		
11) If appropriate, have stratified analyses of primary safety and efficacy parameters been conducted for age, gender and race?	✓		
12) Has the applicant presented the safety data in a manner previously agreed to by the Division?	✓		
13) If approved in other countries, have a summary and assessment of foreign post-marketing experience been provided?	✓		
14) Has draft labeling been submitted?	✓		
15) Have all special studies/data requested by the Division during pre-submission discussions with the sponsor been submitted?			N/A
16) From a clinical perspective, is this NDA fileable? If "no", please state in item #17 below why it is not.	✓		

17) Reasons for refusal to file:

None

Shelley Bruce

Reviewing Medical Officer / Date

1/5/99

\45dfile

**45 Day Meeting Checklist
MANUFACTURING AND CONTROLS**

Estradiol Transdermal system (NDA 21-048)

AMIT K MITRA

ITEM	YES	NO	COMMENT
1) On its face, is the M&C section of the NDA organized in a manner to allow substantive review to begin?	√		
2) Is the M&C section of the NDA indexed and paginated in a manner to allow substantive review to begin?	√		
3) On its face, is the M&C section of the NDA legible so that substantive review can begin?	√		
4) Are all the facilities (manufacturing, packaging, testing, sterilization, etc.) appropriately delineated with full address?	√		
5) Has the applicant submitted a complete environmental impact assessment?		√	Categorical exclusion request was filed
6) Has the applicant developed appropriate controls assessment procedures that are presently ready for FDA verification?	√		
7) For an antibiotic, has the applicant submitted an appropriate validation package and committed to the readiness of exhibit samples?	NA		
8) Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor?	√		

ITEM	YES	NO	COMMENT
9) Has the applicant submitted draft labeling consistent with 201.56 and 201.57, current divisional labeling policies, and the design of the development package?	√		
10) Has the applicant submitted stability data to support and justify the proposed expiry?			The sponsor requested a three years expiry based on 3 years stability data. Since the batch size is small (pilot) for the stability lots, I would recommend a shelf life of two years. The extension from 2 years would be given from stability of commercial production lots.
11) From a manufacturing and controls perspective, is this NDA fileable? If "no", please state in item #12 below why it is not.	√		

**45 Day Meeting Checklist
PROJECT MANAGEMENT**

ITEM	YES	NO	COMMENT
1) Do any of the following apply to this application (i.e., if YES, the application MUST BE REFUSED TO FILE under 314.100 (e) and there is no filing over protest):		X	
a. Is the drug product already covered by an approved application?		X	
b. Does the submission purport to be an abbreviated application under 314.55; however the drug product is not one for which FDA has made a finding that an abbreviated application is acceptable under 314.55(b)?		X	
c. Is the drug product subject to licensing by FDA under the Public Service Act and Subchapter F of Chapter I of Title 21 of the CFR?		X	
2) Do any of the following apply to this application (i.e., if NO, the application MAY BE REFUSED TO FILE under 314.100 (d) and there is the potential for filing over protest):			
a. Does the application contain a completed application form as required under 314.50 or 314.55?	X		

ITEM	YES	NO	COMMENT
b. On its face, does the application contain the sections of an application required by regulation and Center guidelines?	X		no Clinical Microbiology section (see DMF)
c. Has the applicant submitted a complete environmental assessment which addresses each of the items specified in the applicable format under 25.31 or has the applicant submitted evidence to establish that the product is subject to categorical exclusion under 25.24 of the CFR?	X		
d. On its face, is the NDA formatted in compliance with Center guidelines including integrated efficacy and safety summaries?	X		
e. Is the NDA indexed and paginated?	X		
f. On its face, is the NDA legible?	X		
g. Has the applicant submitted all required copies of the submission and various sections of the submission?	X		
h. Has the sponsor submitted all special studies/data requested by the Division during pre-submission discussion with the sponsor?	X		

ITEM	YES	NO	COMMENT
i. Does the application contain a statement that all nonclinical laboratory studies was conducted in compliance with the requirements set forth in Part 58 or a statement why a study was not conducted in compliance with those requirements?	X		See individual safety reports
j. If required, has the applicant submitted carcinogenicity studies?			none conducted by W/A not required -
k. On its face, does the application contain at least two adequate and well-controlled clinical trials?	X		
l. Does the application contain a statement that all clinical trials were conducted in accord with the IRB/Declaration of Helsinki provisions of the CFR?	X		
m. Have all articles/study reports been submitted either in English or translated into English?	X		
n. Has the applicant submitted draft labeling in compliance with 210.56 and 210.57 of the CFR?	X		
3. From a project management perspective, is this NDA fileable? If "no", please state on reverse why it is not.	X		

ITEM	YES	NO	COMMENT
4. Reasons for refusal to file:			



Project Manager

Supervisory Project Manager

APPEARS THIS WAY
ON ORIGINAL

D. Moore

NDA 21-048

DEC 30 1998

Wyeth-Ayerst Laboratories
Attention: Mr. Douglas W. Bitz
Director, U.S. Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Mr. Bitz:

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:	Estradiol Transdermal System (E ₂ III TS)
Therapeutic Classification:	Standard (S)
Date of Application:	November 20, 1998
Date of Receipt:	November 20, 1998
Our Reference Number:	21-048

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 January 19, 1998, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be September 20, 1999, and the secondary user fee goal date will be November 20, 1999.

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/Courier/Overnight Mail:

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

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

Sincerely,



Lana L. Pauls, M.P.H.
Acting Associate Director
Division of Reproductive and Urologic Drug
Products (HFD-580)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:

Archival NDA 21-048
HFD-580/Div. Files
HFD-580/D.Moore
HFD-580/LRarick/MMann/SSlaughterPPrice/MRhee/AMitra
HFD-580/KRaheja/AJordan/SHaidar/AParekh/LKammerman
DISTRICT OFFICE

Drafted by: dm/December 21, 1998

Concurrence:

TRumble 12.28.98



filename: N21048AK.DOC

ACKNOWLEDGEMENT (AC)



U.S. REGULATORY AFFAIRS

November 2, 1998

17 β -Estradiol Transdermal System

Original New Drug Application

NDA No. 21-048

Lisa Rarick, MD, Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Center for Drug Evaluation and Research
Attention: Document Control Room 17B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



Dear Dr. Rarick:

In accordance with 21 CFR \S 314.50, Wyeth-Ayerst Laboratories is submitting a New Drug Application (NDA) for 17 β -Estradiol Transdermal System (E₂ III TS), NDA No. 21-048.

Marketing approval is being sought for E₂ III TS delivering 50, 75 and 100 mcg, per day, for the treatment of moderate to severe vasomotor symptoms associated with menopause, vulval and vaginal atrophy

Clinical studies contained in this NDA were conducted under IND No. 44,168, submitted by Cygnus, Inc. on December 17, 1993. On November 9, 1995, Cygnus submitted a letter to the FDA stating that the sponsorship of IND No. 44,168 had been transferred to Wyeth-Ayerst Laboratories.

The primary evidence for safety and efficacy in this NDA consists of two 3-month, Phase III, randomized, double-blind, placebo-controlled studies, Protocol Nos. 0802E1-316-US and 0802E1-317-US. In addition, an open-label, Phase III, non-IND, ex-US study (Protocol No. 0802E1-330-EU) was also conducted and is provided as supportive information. Six pharmacokinetic studies and one skin sensitization study were also conducted.

An End-of-Phase II Meeting was held on June 27, 1995 to obtain FDA concurrence that the proposed clinical development plan for E₂ III TS was sufficient to support an NDA for E₂ III TS. Clinical and statistical requests from the FDA were incorporated into the clinical program. Primarily, FDA indicated the need in the clinical trials for a two-week pretreatment period to establish a baseline for vasomotor symptoms; after two weeks of treatment, a statistical trend in

favor of treatment was to be shown over placebo, with a statistically significant difference from placebo by week four. There was agreement that analyses posttreatment would be done at 2 weeks (for a trend) and at 4, 8 and 12 weeks. Both pivotal studies, 0802E1-316-US and 0802E1-317-US, comply with this requirement and demonstrate efficacy in this regard. In response to the FDA's suggestion that some comparator data be included, study 0802E1-317-US contains an open-label group which provides descriptive data for Climara®. Final FDA concurrence with the design of Protocol No. 0802E1-317-US was received on February 1, 1996 (via a telecon with Ms. Christina Kish, Project Manager).

A Pre-NDA Meeting was not held.

Submission Information

NDA No. 21-048 and User Fee ID No. 3553 have been preassigned to this application. This submission is being provided primarily in paper format (55 Volumes), with some information in electronic format. The NDA Contents are as follows:

Item No.	Description	Volume No.
1	Index	Volume 1.001
2	Labeling	Volume 1.001
3	Application Summary	Volume 1.002
4	Chemistry, Manufacturing and Controls	Volume 1.003
5	Nonclinical Pharmacology and Toxicology	Volume 1.004 - 1.014
6	Human Pharmacokinetics and Bioavailability	Volume 1.015 - 1.025
7	Microbiology	Not Applicable
8	Clinical	Volume 1.026 - 1.040
9	Safety Update	Not Applicable
10	Statistical	Volume 1.041 - 1.054
11	Case Report Tabulations	Electronic Submission
12	Case Report Forms	Electronic Submission
13	Patent Exclusivity Information (see Item 1)	Volume 1.001
14	Patent Certification with Respect to any Patent which Claims the Drug (see Item 1)	Volume 1.001
15	Establishment Description (see Item 1)	Not Applicable
16	Debarment Certification (see Item 1)	Volume 1.001
17	Field Copy Certification (see Item 1)	Volume 1.001
18	User Fee Cover Sheet (see Item 1)	Volume 1.001
19	Other (see Item 1)	Not Applicable

Electronic Information

Paper copies of Items 11 (Case Report Tabulations) and 12 (Case Report Forms) are not included in this submission, but are provided on tape, in accordance with the FDA guidance *Providing Regulatory Submissions in Electronic Format* (September 1997).

In addition, a CD-ROM is provided, which consists of PDF files of Items 11 and 12, SAS datasets for Item 11 and Item 6 (Human Pharmacokinetics and Bioavailability), and the text in WORD 7 for the following NDA documents: Integrated Summary of Safety, Integrated Summary of Efficacy, Application Summary, and final study reports (General Medical Reports, or GMRs) for the pivotal studies.

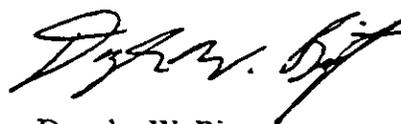
In compliance with 21 CFR § 314.50(k)(3), Cygnus, Inc. has provided to the FDA San Francisco District Office a true and exact copy of Drug Master File 10,651, which is incorporated into this NDA by reference, and which contains the complete Chemistry, Manufacturing, and Controls⁴ information for NDA No. 21-048. Wyeth-Ayerst has provided copies of the 356h application form and Application Summary of the NDA to both the Philadelphia, PA and the San Francisco, CA District Offices. The Field Copy Certifications are contained in Item 17.

Regarding the User Fee Payment, a check for \$256,846 (the required 1998 application fee) was sent to Mellon Bank, PO Box 360909, Pittsburgh, PA 15251-60909 for this NDA (User Fee ID No. 3553), on November 17, 1998. It is our understanding that when the fiscal year 1999 application fees are determined, if the new fee exceeds this amount, Wyeth-Ayerst will be billed for any remaining application fee due.

If you have questions regarding this submission, please contact our representative, Miss JoAnne M. Bissinger, at (610) 902-3731 or Mr. Joseph J. Sobeki, at (610) 902-3737.

Sincerely,

WYETH-AYERST LABORATORIES



Douglas W. Bitz
Director, US Regulatory Affairs

Enclosure: 55 Volumes

Desk Copy (letter only):

Mrs. Diane Moore, Project Manager,
Division of Reproductive and Urologic Drug Products

9 Page(s) Withheld

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

 § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

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

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

<p>1. APPLICANT'S NAME AND ADDRESS Wyeth-Ayerst Laboratories P.O. Box 8299 Philadelphia, PA 19101-8299</p>	<p>3. PRODUCT NAME 17β-Estradiol Transdermal System</p>
<p>2. TELEPHONE NUMBER (Include Area Code) (610) 902-3739</p>	<p>4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA).</p>
<p>5. USER FEE I.D. NUMBER 3553</p>	<p>6. LICENSE NUMBER / NDA NUMBER NDA No. 21-048</p>

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)	<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)	<input type="checkbox"/> THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)	

FOR BIOLOGICAL PRODUCTS ONLY

<input type="checkbox"/> WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION	<input type="checkbox"/> A CRUDE ALLERGENIC EXTRACT PRODUCT
<input type="checkbox"/> AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY	<input type="checkbox"/> AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT
<input type="checkbox"/> BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92	

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? YES NO
(See reverse side if answered YES)

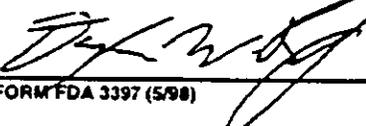
A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0297)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

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.

Please DO NOT RETURN this form to this address.

<p>NATURE OF AUTHORIZED COMPANY REPRESENTATIVE  Douglas W. Bitz</p>	<p>TITLE Director, U.S. Regulatory Affairs</p>	<p>DATE November 17, 1998</p>
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**INSTRUCTIONS FOR COMPLETING USER FEE COVER SHEET
FORM FDA 3397**

Form FDA 3397 is to be completed for and submitted with each new drug or biologic product original application or supplemental application submitted to the Agency on or after April 27, 1998. Form 3397 should be placed in the first volume of the application with the application form. A copy of Form 3397 should be included with the fee payment.

ITEM NOS.

INSTRUCTIONS

1-2. Self-explanatory

3. PRODUCT NAME - Include generic name and trade name, as applicable.

4. CLINICAL DATA - The definition of 'clinical data' for the assessment of user fees is found in Interim Guidance: Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees under the Prescription Drug User Fee Act of 1992.

5. USER FEE I.D. NUMBER - PLEASE INCLUDE THIS NUMBER ON THE APPLICATION PAYMENT CHECK. If the application is exempted from a fee, a User Fee I.D. Number is not required. To obtain the appropriate User Fee I.D. Number, read and complete the following:

FOR DRUG PRODUCTS - A unique identification number will be assigned to each submission. This individual identification number may be obtained by calling the Center for Drug Evaluation and Research, Central Document Room, at (301) 827-4210.

FOR BIOLOGIC PRODUCTS - The first 4 characters are the U.S. License Number, including leading zeros; the next 4 characters are the product code (2 letters followed by 2 numbers); and the last 7 characters are the date on the cover letter of the submission, in the format: DDMONYR. If the facility is unlicensed, or the product code is unknown, a number can be obtained by calling the Center for Biologics Evaluation and Research, at (301) 827-3503.

EXAMPLE: For U.S. License Number 4, product code XX01, with a document submission date of 8/3/93, the number would be: 0004XX0103AUG93.

6. LICENSE NUMBER / NDA NUMBER

FOR BIOLOGIC PRODUCTS - Indicate the U.S. License Number. If the facility is unlicensed, leave this section blank.

FOR DRUG PRODUCTS - Indicate the NDA number, including a leading zero. NDA numbers can be obtained by calling the Center for Drug Evaluation and Research, Central Document Room, at (301) 827-4210.

EXAMPLE: For NDA 99999, the number would be: NO99999.

7. EXCLUSIONS:

Section 505(b)(2) applications, as defined by the Federal Food, Drug, and Cosmetic (FD&C) Act, are excluded from application fees if: they are NOT for a new molecular entity which is an active ingredient (including any salt or ester of an active ingredient); or NOT a new indication for use.

The application is for an orphan product. Under section 736(a)(1)(E) of the FD&C Act, a human drug application is not subject to an application fee if the proposed product is for a rare disease or condition designated under section 526 of the FD&C Act (orphan drug designation) AND the application does not include an indication that is not so designated. A supplement is not subject to an application fee if it proposes to include a new indication for a rare disease or condition, and the drug has been designated pursuant to section 526 for a rare disease or condition with regard to the indication proposed in the supplement.

The submission is a supplement for a new pediatric indication. Under section 736(a)(1)(F) of the FD&C Act, a supplement to a "human drug application" proposing to include a new indication for use in pediatric populations is not subject to a fee.

8. WAIVER - Complete this section only if a waiver of user fees, including the small business waiver, has been granted for this application. A copy of the official FDA notification that the waiver has been granted must be provided with the submission.

Memorandum of Meeting

Industry Participants:

Ms. Joanne Bissinger, Senior Regulatory Coordinator, Wyeth-Ayerst
Jim Ermer, Ph.D.; Senior Pharmacokineticist, Wyeth-Ayerst
Phil Maya, Ph.D.; Director of Clinical Pharmaceutics, Wyeth-Ayerst
Mr. Allan Russell; Senior Vice President, Cygnus
Ms. Carol Karp; Regulatory Affairs, Cygnus
Ms. Sally Naish, Project management, Wyeth-Ayerst
Ms. Louise Johnson, Regulatory Affairs, Cygnus
Judith Nadelmann, Ph.D.; Principal Statistician, Wyeth-Ayerst
James Pickar; Clinical Research, Wyeth-Ayerst
Mary Zrimer; Clinical Research, Wyeth-Ayerst

FDA Staff:

Dr. Corfman	Mr. Hunt (HFD-426)	Dr. Pian (HFD-713)
Dr. Cropp	Dr. Dorantes (HFD-426)	Ms. Kish
Dr. Price	Dr. Nevius (HFD-713)	

Discussion and Conclusion:

Cygnus began the meeting by stating that the IND (presently held by Cygnus) will be transferred to Wyeth-Ayerst who will perform all of the clinical research. Cygnus will remain responsible for the DMF and CMC sections of any resulting NDA.

Wyeth Ayerst then presented their proposed clinical program. They noted that they had chosen the study doses to have a blood serum level of approximately 40 pg/ml and higher, but that they did not want to go above the serum levels of Ciba Geigy's patch (which is 74 pg/ml above baseline). Dr. Price stated that 100 pg/ml might not be safe (as suggested by pellet and European data). Dr. Price suggested that sponsors use as a high dose approximately 80 pg/ml, but noted that this would not be a requirement.

Cygnus presented a very brief overview of the toxicology and pharmacokinetic studies. They noted that a minor formulation change had taken place due to a yellowing which occurred with some of the ingredients. The sponsor noted that all tests which had been performed with the original formulation had been repeated with the new formulation. The sponsor noted that both the skin and the patch will control the rate of drug release. In release tests approximately ten percent of drug is released over seven days. The sponsor said that total E₂ will be analyzed both before and after the patch is worn, and noted that an assay was available to perform this test.

Cygnus outlined the first pharmacokinetic study which was performed on the upper arm to look at adhesion and irritation. The second study was a four way crossover of patches sized 10, 15 and 20 cm² on the abdomen for seven days. Samples were assayed at

claims they are able to detect levels as low as _____ Cygnus noted that in this test, performed under controlled conditions, in house, the subjects were not allowed to use tape to keep the patch on unless the patch came off completely. A third pharmacokinetic study was

performed because of the lower than expected blood levels which came out of the second study. The patch size in the third study was increased. The sponsors are only seeking a single application site for this patch (abdomen). Cygnus noted that two more pharmacokinetic studies are planned the first a single dose (8 day) application. The second would compare their patch to Climara. In both of these studies they will be measuring estradiol and estrone. Estrone sulfate would be monitored in the multiple dose study. These studies will be carried out concurrently with the phase III trials, but utilizing a different group of subjects (due to blood volume required). Mr. Hunt suggested the sponsor report the ongoing obtained data to his division, noting that there might be a chance that the number of blood draws could be decreased. Mr. Hunt further noted that he would like to review the protocols prior to their initiation, and that intersubject as well as intrasubject variability should be determined.

Cygnus stated three studies were planned for phase III, two for safety and efficacy, and one for adhesion. Diaries would be kept and turned in on weeks four, eight, and twelve. A blood serum level would be taken at baseline and again at week twelve. Cygnus planned on enrolling 216 women into nine sites (approximately 24 women per site) with over 50 % having a uterus. Dr. Price noted that if the women had had twelve months of amenorrheic, then their FSH level could be 40 pg/ml; however if the woman had been amenorrhea for less than twelve months, their FSH levels have to be 50 pg/ml. The sponsor noted that the primary endpoint will be the number and severity of hot flushes, severity judged on a scale of one to three (none to severe), with a secondary endpoint of vaginal tissue changes and quality of life indicators.

Dr. Price noted that we would require a two week baseline run in of VMS symptoms. He stated that after two weeks of treatment a statistical trend in favor of the treatment should be shown over placebo and there should be a clear statistical significance over placebo by week four. He requested that both days and weeks be averaged separately.

Dr. Nevius requested a copy of the protocol for statistical review when submitted.

Cygnus proposed a Draize skin sensitization study to be performed on the upper back utilizing 200 subjects. The sponsor requested that the number of subjects be lowered. An internal meeting will be held to discuss the appropriateness of the back as a test site, and the number required for the Draize study.

Dr. Price suggested that for the pivotal trials he would like to see one trial placebo controlled and one comparing a reference patch, such a Climara. Wyeth-Ayerst noted that this would be possible as long as an open label study would be accepted. Dr. Price agreed that an open label study would be acceptable. Dr. Price added that if the sponsors did not want to utilize a reference patch study a good objective study (similar to Howard Judd's) would be acceptable. Wyeth Ayerst asked which Climara patch should be used as a reference. An internal meeting will be required to discuss which Climara patch should be used. Dr. Price further suggested that all protocols be submitted for review prior to initiating any study. He also said that fasting glucose could go as high as 140.

The Division of Biopharmaceutics requested that estrone sulfate be analyzed and PK/PD and populatin PK be studied considering covariants such as body weight, clearance, age, race, smoking habits, etc. They also requested the sponsor to monitor women with poor adhesion. Wyeth Ayerst agreed that the individual variables could be analyzed but noted that the total study size was small, they also noted that they had a rating scale for patch adhesion.

Dr. Price reminded the sponsors that two independent readers with a third adjudicating over conflicting results would be required. Wyeth-Ayerst suggested that this was not necessary as hyperplasia was not a primary endpoint. Dr. Corfman suggested an internal meeting to discuss this once their final protocol was submitted. Dr. Nevius reminded the sponsors that centers were taken into account during statistical review usually by a two way analysis. He noted that he may have further comments on this once he has seen the protocol to be submitted.

Action Items:

An internal meeting to discuss both the Draize study design, and which strength Climara patch should be used in an active control study is to be held. Also, once the sponsors' final protocol was submitted a decision regarding whether biopsies will be necessary for monitoring hyperplasia will be made.


Christina Kish, CSO
8/7/95

cc:

Orig IND

HFD-510

MEETING ATTENDEES

HFD-510/SSobel/YJohnson

HFD-510/CKish/7.3.95/i44168.mm

Concurrences: Adorantes 7.7.95/JHunt 7.10.95/PPrice 7.19.95/CCropp 7.10.95/PCorfman
7.19.95/LPian 7.20.95/ENevius 8.1.95/EGalliers 8.7.95

344 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling