CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-258

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

13. PATENT INFORMATION

Pursuant to 21 CFR 314.50(h) and to 21 CFR 314.53(a), (b), (c)(1) and (2), the undersigned declares that the patents identified below cover the composition of Estradiol/Levonorgestrel Transdermal System, the subject of NDA 21-258 for ClimaraPro™ for which approval is being sought.

Type of Patent	Patent Number	Patent Owner	Expiration Date
Composition	U.S. 5,676,968	Schering AG	10/14/2014
Composition	U.S. 5,393,529	LTS Lohmann and Schwarz Pharma	2/28/2012
Composition	U.S. 5,252,334	Cygnus Inc.	10/12/2010
Composition	U.S. 5,770,219	Cygnus Inc.	10/12/2010

BERLEX LABORATORIES, INC.

Ted Ikeda

Ted Ikeda
General Counsel Intellectual Properties

June 5, 2000

Date

gab/patents/clmpropt/049

14. PATENT CERTIFICATION

A patent certification pursuant to 21 U.S.C. 355(b)(2) or (j)(2)(A) is not applicable to NDA 21-258 for ClimaraPro™ [Estradiol/Levonorgestrel Transdermal System].

BERLEX LABORATORIES, INC.

Ted Ikeda

Ted Ikeda
General Counsel Intellectual Properties

June 5, 2000

Date

EXCLUSIVITY SUMMARY for NDA # 21-258_____ SUPPL #

Trade Name Climara Pro™_____Generic Name estradiol/levonorgestrel
Applicant Name Berlex Laboratories, Inc. HFD-580
Approval Date November 21, 2003

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

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

      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:

d) Did the applicant request exclusivity?

YES /_X__/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request? 3 years

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

YES /___/ NO /_X__/

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

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

YES /___/ NO /_X__/

If yes, NDA # _____ Drug Name

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

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

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

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

YES /___/ NO /___/

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

NDA #

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the 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 /_X__/ NO /___/

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

NDA # 20-870 Combipatch

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

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

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X__/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications

(i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

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

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

YES /_X__/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

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

YES /___/ NO /_X__/

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

YES /___/ NO /_X__/

If yes, explain:

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

YES /___/ NO /_X__/

If yes, explain:

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

Investigation #1, Study # _96042A

Investigation #2, Study # 96043A

Investigation #3, Study #

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

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

Investigation #1	YES /___/	NO /_X__/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

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

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

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

Investigation #1 YES /___/ NO /X___/

Investigation #2 YES /___/ NO /_X__/

Investigation #3 YES /___/ NO /_X__/

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

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

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

Investigation #1_, Study # _96042A

Investigation #_2_, Study # 96043A

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the

conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

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

Investigation #1

IND # 51,188 YES /_X__/ ! NO /___/ Explain:

Investigation #2

IND # 51,188 YES /_X__/ ! 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 /_x__/

If yes, explain: _____

_____

_____

_____
Kassandra Sherrod, R.Ph. Date 11/19/03

Title: Regulatory Project Manager

Signature of Office or Division Director Date

cc:
Archival NDA 21-258
HFD-580/Division File
HFD-580/Kassandra Sherrod
HFD-610/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

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

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

/s/

Daniel A. Shames
11/19/03 04:01:41 PM

Request for Three Years Marketing Exclusivity

Pursuant to 21 U.S.C. 355(j)(4)(D)(iii) and 21 U.S.C. 355(c)(3)(D)(iii), and with reference to 21 CFR 314.50(j)(1) and to 21 CFR 314.108(b)(4)(iv), Berlex Laboratories, Inc. hereby requests a period of 3 years marketing exclusivity for ClimaraPro™ [Estradiol/Levonorgestrel Transdermal System], the subject of NDA 21-258. This request for a three-year exclusivity period is based upon the following criteria:

1. The Estradiol/Levonorgestrel Transdermal System that is the subject of NDA 21-258 has not been previously approved by the Food and Drug Administration.

2. The results of the two new clinical investigations included in NDA 21-258 that support a finding of substantial evidence of effectiveness of the Estradiol/Levonorgestrel Transdermal System for the treatment of moderate to severe vasomotor symptoms associated with menopause.

   A. Report B528 for Study 96042: A Multicenter, Double-Blind, Placebo-Controlled, Randomized Study to Determine Efficacy in the Relief of Hot Flushes in Women Receiving Transdermal Estradiol, can be found in NDA 21-258 in Item 8, Volume 32, beginning on Page 1.

   B. Report B529 for Study 96043: A Multicenter, Double-Blind, Randomized Study of Continuous Transdermal Estradiol-Levonorgestrel Combinations, Compared to Continuous Transdermal Estradiol, to Examine the Safety and Effect on the Endometrium, Symptoms and Bleeding Patterns in Postmenopausal Women, can be found in NDA 21-258 in Item 8, Volume 36, beginning on Page 1.

3. A determination that the two aforementioned clinical investigations are essential to the approval of the Estradiol/Levonorgestrel Transdermal System, the subject of NDA 21-258, for the treatment of moderate to severe vasomotor symptoms associated with menopause. Berlex Laboratories, Inc. certifies that there are not sufficient published studies or publicly available reports of clinical investigations to support the approval of NDA 21-258, other than those clinical investigations sponsored by Berlex Laboratories, Inc. under IND 51,188.

4. Berlex Laboratories, Inc. submitted IND 51,188 for Estradiol/Levonorgestrel Transdermal System to the Food and Drug Administration on July 24, 1996 for Review by the Division of Reproductive and Urologic Drug Products, HFD-580.

Certification Statement
as requested by the
Generic Drug Enforcement Act of 1992

— hereby certifies that it did not and will not use, in any capacity, the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with NDA 21-258 for Estradiol/Levonorgestrel Transdermal Delivery System.

22 June 2000
Date

Sr. Director, Regulatory Compliance and Quality Systems

16. Debarment Certification

Certification Under Section 306(k)(1) of the FD & C Act

Berlex Laboratories, Inc., hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal, Food, Drug and Cosmetic Act in connection with NDA 21-258 for Estradiol/Levonorgestrel Transdermal Delivery System.

BERLEX LABORATORIES, INC.

Joan Mutascio
Regulatory Submissions &
Information Associate

June 7, 2000
Date

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 21-258 Supplement Type (e.g. SE5): N/A Supplement Number: N/A

Stamp Date: June 29, 2000 Action Date: November 21, 2003

HFD 580 Trade and generic names/dosage form: Climara Pro™(estrradiol/levonrogestrel)

Applicant: Berlex Laboratories, Inc. Therapeutic Class: hormone therapy

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Treatment of moderate to severe vasomotor symptoms associated with menopause

Is there a full waiver for this indication (check one)?

×Yes: Please proceed to Section A.

☐ No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
×Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Other:_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for partial waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Adult studies ready for approval
☐ Formulation needed

☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA 21-258
HFD-950/ Terrie Crescenzi
HFD-960/ Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

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

/s/

Kassandra C. Sherrod
11/18/03 02:35:41 PM

MEMORANDUM

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

Date: May 31, 2001

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

Subject: Review of Financial Disclosure documents

To: NDA 21-258

I have reviewed the financial disclosure information submitted by Berlex Laboratories, Inc. in support of their NDA 21-258 for Climarapro™ (estradiol (EE)/levonorgestrel (LNG) transdermal system).

Two pivotal studies were conducted to assess the safety and efficacy of Climarapro™ (estradiol (EE)/levonorgestrel (LNG) transdermal system). This product is proposed as a transdermal drug delivery system for hormone replacement therapy. The study numbers and the results of the review of financial disclosure documents are summarized below:

Study Number/Title	**Study Status**	**Financial Disclosure Review**
Study 96042 / "A Multi-Center, Double-Blind, Placebo-Controlled, Randomized Study to Determine Efficacy in the Relief of Hot Flushes in Women Receiving Transdermal Estradiol."	Ongoing as of 2/2/99	Appropriate documentation received, no financial disclosure submitted.
Study 96043 / "A Multi-Center, Double-Blind, Randomized Study of Continuous Transdermal Estradiol-Levonorgestrel Combinations, Compared to Continuous Transdermal Estradiol, to Examine the Safety and Effect on the Endometrium, Symptoms and Bleeding Patterns in Postmenapausal Women.	Ongoing as of 2/2/99	Appropriate documentation received, no financial disclosure submitted.

Documents Reviewed:

- financial certification Information submitted June 29, 2000
- response to request for additional Financial Disclosure Information submitted May 30, 2001

The following information requested on May 2, 2001 included:

- a table including the following information:
  - study number
  - study site
  - number of patients enrolled at each site
  - names of investigators (principal and subinvestigators) at each site
  - financial disclosure information received for each investigator
  - disclosable information for each investigator
- any additional efforts taken to obtain disclosure information from each site
- any updates from previously non-compliant investigators

Study 96042

There were 217 principal and subinvestigators (investigators) at 38 sites in this trial.

- Site 4 had 4 subinvestigators for whom financial disclosure information was not received; this site enrolled 1.0% of the patients in the study
- Site 7 had 1 subinvestigator for whom financial disclosure information was not received; this site enrolled 2.1% of the patients in the study
- Site 9 had 1 subinvestigator for whom financial disclosure information was not received; this site enrolled 2.1% of the patients in the study
- Site 14 had 1 subinvestigator for whom financial disclosure information was not received; this site enrolled 5.9% of the patients in the study
- Site 34 had 2 principal investigators and 7 subinvestigators; none of whom supplied financial disclosure information; this site enrolled 3.5% of the patients in the study
- Site 26 had 2 subinvestigators for whom financial disclosure information was not received; this site enrolled 1.7% of the patients in the study
- Site 32 had 3 subinvestigators for whom financial disclosure information was not received; this site enrolled 1.7% of the patients in the study
- Site 33 had 1 principal investigator and 3 subinvestigators; none of whom supplied financial disclosure information; this site enrolled 1.4% of the patients in the study
- Site 35 had 1 subinvestigator for whom financial disclosure information was not received; this site enrolled 2.4% of the patients in the study
- Site 10 had 1 subinvestigator for whom financial disclosure information was not received; this site enrolled 4.2% of the patients in the study
- Site 13 had 2 subinvestigators for whom financial disclosure information was not received; this site enrolled 3.5% of the patients in the study
- Site 16 had 3 subinvestigators for whom financial disclosure information was not received; this site enrolled 2.4% of the patients in the study
- Site 8 had 12 subinvestigators for whom financial disclosure information was not received; this site enrolled 3.5% of the patients in the study
- Site 23 had 4 subinvestigators for whom financial disclosure information was not received; this site enrolled 2.1% of the patients in the study
- Site 24 had 1 subinvestigator for whom financial disclosure information was not received; this site enrolled 4.9% of the patients in the study

- Site 31 had 1 subinvestigator for whom financial disclosure information was not received; this site enrolled 7.0% of the patients in the study

Of the remaining investigators, none had any disclosable information.

Study 96043

There were 524 principal and subinvestigators (investigators) at 75 sites in this trial.

- Site 1 had 4 subinvestigators for whom financial disclosure information was not received; this site enrolled 0.6% of the patients in the study
- Site 2 had 2 subinvestigators for whom financial disclosure information was not received; this site enrolled 1.3% of the patients in the study
- Site 4 had 1 subinvestigator for whom financial disclosure information was not received; this site enrolled 1.7% of the patients in the study
- Site 6 had 1 subinvestigator for whom financial disclosure information was not received; this site enrolled 0.7% of the patients in the study
- Site 7 had 1 subinvestigator for whom financial disclosure information was not received; this site enrolled 0.8% of the patients in the study
- Site 8 had 5 subinvestigators for whom financial disclosure information was not received; this site enrolled 3.4% of the patients in the study
- Site 9 had 1 subinvestigator for whom financial disclosure information was not received; this site enrolled 1.3% of the patients in the study
- Site 10 had 1 subinvestigator for whom financial disclosure information was not received; this site enrolled 0.6% of the patients in the study
- Site 13 had 2 subinvestigators for whom financial disclosure information was not received; this site enrolled 1.9% of the patients in the study
- Site 14 had 1 subinvestigator for whom financial disclosure information was not received; this site enrolled 2.8% of the patients in the study
- Site 16 had 2 subinvestigators for whom financial disclosure information was not received; this site enrolled 1.4% of the patients in the study
- Site 17 had 1 subinvestigator for whom financial disclosure information was not received; this site enrolled 0.5% of the patients in the study
- Site 19 had 2 subinvestigators for whom financial disclosure information was not received; this site enrolled 0.4% of the patients in the study
- Site 20 had 1 subinvestigator for whom financial disclosure information was not received; this site enrolled 0.6% of the patients in the study
- Site 23 had 4 subinvestigators for whom financial disclosure information was not received; this site enrolled 2.0% of the patients in the study
- Site 24 had 1 subinvestigator for whom financial disclosure information was not received; this site enrolled 0.7% of the patients in the study
- Site 26 had 4 subinvestigators for whom financial disclosure information was not received; this site enrolled 1.0% of the patients in the study
- Site 27 had 10 subinvestigator for whom financial disclosure information was not received; this site enrolled 1.0% of the patients in the study
- Site 29 had 1 principal investigator and 2 subinvestigators for whom financial disclosure information was not received; this site enrolled 0.4% of the patients in the study
- Site 30 had 1 subinvestigator for whom financial disclosure information was not received; this site enrolled 1.7% of the patients in the study
- Site 32 had 3 subinvestigators for whom financial disclosure information was not received; this site enrolled 2.3% of the patients in the study

- Site 34 had 1 principal investigator and 8 subinvestigators for whom financial disclosure information was not received; this site enrolled 1.0% of the patients in the study
- Site 35 had 1 subinvestigator for whom financial disclosure information was not received; this site enrolled 0.5% of the patients in the study
- Site 39 had 1 subinvestigator for whom financial disclosure information was not received; this site enrolled 2.9% of the patients in the study
- Site 40 had 1 subinvestigator for whom financial disclosure information was not received; this site enrolled 1.2% of the patients in the study
- Site 43 had 2 subinvestigators for whom financial disclosure information was not received; this site enrolled 2.0% of the patients in the study
- Site 44 had 5 subinvestigators for whom financial disclosure information was not received; this site enrolled 1.2% of the patients in the study
- Site 46 had 2 subinvestigators for whom financial disclosure information was not received; this site enrolled 1.2% of the patients in the study
- Site 47 had 1 subinvestigator for whom financial disclosure information was not received; this site enrolled 2.6% of the patients in the study
- Site 49 had 1 principal investigator and 6 subinvestigators for whom financial disclosure information was not received; this site enrolled 1.1% of the patients in the study
- Site 50 had 1 subinvestigator for whom financial disclosure information was not received; this site enrolled 2.2% of the patients in the study
- Site 51 had 1 subinvestigator for whom financial disclosure information was not received; this site enrolled 2.0% of the patients in the study
- Site 52 had 5 subinvestigators for whom financial disclosure information was not received; this site enrolled 1.0% of the patients in the study
- Site 53 had 2 subinvestigators for whom financial disclosure information was not received; this site enrolled 0.8% of the patients in the study
- Site 54 had 1 subinvestigator for whom financial disclosure information was not received; this site enrolled 1.0% of the patients in the study
- Site 56 had 1 subinvestigator for whom financial disclosure information was not received; this site enrolled 1.2% of the patients in the study
- Site 57 had 2 subinvestigators for whom financial disclosure information was not received; this site enrolled 0.5% of the patients in the study
- Site 60 had 1 subinvestigator for whom financial disclosure information was not received; this site enrolled 1.8% of the patients in the study
- Site 61 had 1 principal investigator and 12 subinvestigators for whom financial disclosure information was not received; this site enrolled 0.2% of the patients in the study
- Site 62 had 5 subinvestigators for whom financial disclosure information was not received; this site enrolled 2.0% of the patients in the study
- Site 65 had 1 subinvestigator for whom financial disclosure information was not received; this site enrolled 3.4% of the patients in the study
- Site 67 had 3 subinvestigators for whom financial disclosure information was not received; this site enrolled 0.1% of the patients in the study
- Site 69 had 4 subinvestigators for whom financial disclosure information was not received; this site enrolled 0.8% of the patients in the study
- Site 70 had 2 subinvestigators for whom financial disclosure information was not received; this site enrolled 0.2% of the patients in the study
- Site 71 had 2 subinvestigators for whom financial disclosure information was not received; this site enrolled 0.2% of the patients in the study

- Site 72 had 5 subinvestigators for whom financial disclosure information was not received; this site enrolled 0.7% of the patients in the study
- Site 73 had 1 principal investigator for whom financial disclosure information was not received; this site enrolled 1.7% of the patients in the study
- Site 75 had 3 subinvestigators for whom financial disclosure information was not received; this site enrolled 2.3% of the patients in the study
- Site 76 had 1 subinvestigator for whom financial disclosure information was not received; this site enrolled 1.0% of the patients in the study
- Site 77 had 4 subinvestigators for whom financial disclosure information was not received; this site enrolled 0.5% of the patients in the study
- Site 78 had 1 principal investigator and 6 subinvestigators for whom financial disclosure information was not received; this site enrolled 0.4% of the patients in the study

Of the remaining investigators, none had any disclosable information.

The sponsor employed the following mechanisms in an attempt to obtain Financial Disclosure forms from investigators:

- a request was made during the course of the trial
- a follow-up phone call was made to the site if financial disclosure information was not received
- a certified letter was mailed to the site with the financial disclosure form enclosed

The sponsor states that the principal reason financial disclosure information could not be obtained from individuals was that they had left the practice and could not be contacted.

Conclusion:
Adequate documentation was submitted to comply with 21 CFR 54. While the sponsor could have used other means to obtain documentation from non-compliant investigators, the rate of return is acceptable; no individual site, for which documentation was not obtained, enrolled a significant amount of the study patients. There was no disclosure of financial interests that could bias the outcome of the trials.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

OCT 30 2003

Dear Mr —

Between April 17 and 23, 2003, Ms. Jean Kelahan, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review the Interactive Voice Response System (IVRS) associated with Berlex protocol # 96042, entitled "A Multicenter, Double-Blind, Placebo-Controlled, Randomized Study to Determine Efficacy in the Relief of Hot Flushes in Women Receiving Transdermal Estradiol". This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

We have evaluated the establishment inspection report and the documents submitted with that report, and your May 1, 2003, draft action plan. The determination of the accuracy and reliability of study subject recollection of clinical experiences and subsequent input of this data using your computerized system was not covered during this inspection. The computer system, as inspected and used in the collection of data for this protocol by your firm, adheres to the requirements of computer systems as outlined in 21 CFR Part 11.

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

Sincerely,

Khin Maung U, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

FEI:

Field Classification: Referred to Center

Headquarters Classification:
__x__1)NAI
_____2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

cc:
HFA-224
HFD-580/Doc.Rm. NDA# 21-258
HFD-580/Review Div. Dir./Shames
HFD-580/CSO/Lyght
HFD-580/MO/Price
HFD-46/47c/r/s/ GCP File #010522
HFD-46/Blay
HFR-CE350/Amador
HFR-CE3565/Isbill
HFR-MA350/Kelahan
GCF-1/Seth Ray

r/d: blay
reviewed:KMU:7/4/03:
reviewed:AEH:
f/t: /sg:7/14/03:10/23/03

O:/blay/ — 04.doc
C:/royblay/nai/ — 04.doc

Reviewer Note to Rev. Div. M.O.

The validation processes for the IVRS system as related to Berlex protocol # 96042 were reviewed. The investigation indicated that audit trails were maintained by having each diary entry date, time, and user stamped. Original data was maintained and coded to indicate whether an edit or a deletion of the data was made. Data entry was limited to the study subject through the use of a PIN number selected by the subject in conjunction with a valid site identification, protocol identification, and user access number. Subjects could modify diary entries retrospectively up to three days later. Such revisions are user, date, and time stamped. This inspection did not address the issue of whether the data inputted by study subjects were valid. A determination of the accuracy and reliability of study subject recollection of clinical experiences and the subsequent input of this data using the IVRS system was beyond the scope of this inspection. The final classification of this inspection is NAI (No Action Indicated).

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/s/

Khin U
11/10/03 02:58:45 PM

UPS OVERNIGHT

Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 487-2000

November 19, 2003

Daniel Shames, MD, Director
Division of Reproductive and Urologic Drug Products, HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857-1706

Dear Dr. Shames:

Re: NDA 21-258
Climara Pro™ (estradiol/levonorgestrel transdermal system)
Response to a Division Request

Reference is made to NDA 21-258 for Climara Pro™ and to our submission of September 19, 2003 (Complete Response to a Non-Approval Letter). Reference is also made to the Division's phone call of November 17, 2003 wherein your representatives, Ms. Kassandra Sherrod and Dr. Theresa Van Der Vlugt requested, and provided the wording for, a Phase IV commitment.

Berlex agrees to a commitment to design a Phase IV clinical study to find the lowest effective dose of Climara Pro. The timelines for the commitment are as follows:

- Protocol submission - within 6 months of receipt of the NDA approval letter
- Study start - within 6 months of the protocol agreement
- Final report - within 6 months of study completion

If you require any additional information please call me at (973) 487-2254.

Sincerely,

BERLEX LABORATORIES

Geoffrey Millington
Manager, Drug Regulatory Affairs
GPM/076

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/s/

Paul Seligman
11/19/03 07:05:01 AM

A

3 Page(s) Withheld

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

✓ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

Office Of Drug Safety

Memo

To: Daniel Shames, M.D.
Director, Division of Reproductive and Urologic Drug Products
HFD-580

From: Alina R. Mahmud, R.Ph.
Team Leader, Division of Medication Errors and Technical Support
Office of Drug Safety, HFD-420

Through: Carol Holquist, R.Ph.
Deputy Director, Division of Medication Errors and Technical Support
Office of Drug Safety, HFD-420

CC: Kassandra Sherrod
Project Manager
HFD-580

Date: November 14, 2003

Re: ODS Consult 00-0193-2; Climara Pro (Estradiol/Levonorgestrel Transdermal System) 0.045 mg/0.015 mg, 0.045 mg/0.030 mg, 0.045 mg/0.040 mg; NDA 21-258.

This memorandum is in response to an August 2, 2001 request from your Division to re-review the proposed proprietary name, Climara Pro. The labels and labeling were submitted for review and comment as well.

DMETS has not identified any additional proprietary or established names that have the potential for confusion with Climara Pro since we conducted our initial review on August 21, 2001 (ODS consult 00-0193-1) that would render the name objectionable. Therefore, we have no objections to the use of this proprietary name.

In reviewing the proposed labels and labeling for Climara Pro, DMETS has identified some areas of possible improvement in the interest of minimizing medication errors. DMETS offers the following comments:

A. GENERAL COMMENTS

1. Revise the statement "0.45/0.015 mg/day" appearing on all labels (including patch) and labeling to read "0.045 mg/0.015 mg/24 hr". This revision includes the addition of "mg" immediately following the number "0.45" and further clarifies the rate of drug release.

2. The foil labeling of the 0.45 mg/0.015 mg system utilizes a [redacted] Using different colors for the same strength may cause confusion. Please utilize the same color for labels and labeling of the same strength.

3. The labels and labeling for the [redacted]

B. FOIL POUCH LABELING (sample and stock supply)

1. See GENERAL COMMENTS above.

2. Include the route of administration on the primary display panel.

3. Delete the statement of strength located in the lower right corner of the labeling as it may cause confusion when it does not appear in conjunction with the proprietary and established names.

4. Revise the statements "-1 system" and "-Transdermal" located in lower right corner to read "-1 Transdermal system".

C. CARTON LABELING (sample supply)

1. See GENERAL COMMENTS and B.3.

2. Revise the statements "-4 system" and "-Transdermal" located in lower right corner to read "-4 Transdermal system".

3. Relocate the "For Transdermal Use Only" from the back panel to the primary display panel.

4. Delete the statement of strength appearing immediately to the right of the line located at the bottom right corner of the carton.

D. CARTON LABELING (stock supply)

1. See GENERAL COMMENTS and B.3.

2. Delete that statement — from the physician sample as it is misleading. The statement is sufficient.

E. PACKAGE INSERT (DOSAGE AND ADMINISTRATION)

Include the statement, which currently appears in the patient information leaflet "Do not apply the Climara Pro patch to your breasts" should also appear in the Application of the System section.

DMETS considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.

If you have any questions or need clarification, please contact Sammie Beam at 301-827-3242.

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/s/

Alina Mahmud
11/14/03 03:49:05 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
11/14/03 03:56:37 PM
DRUG SAFETY OFFICE REVIEWER

Internal Meeting Minutes

Date: November 14, 2003 Time: 3:00 - 4:00 PM Place: Parklawn; Room 17B-43

NDA: 21-258 Drug Name: Climara Pro™ (estradiol/levonorgestrel transdermal system)

Type of Meeting: Status Meeting

Indication: Treatment of moderate to severe vasomotor symptoms associated with the menopause

Sponsor: Berlex Laboratories, Inc.

FDA Lead: Dr. Theresa van der Vlugt, M.D., M.P.H.

Meeting Recorder: Kassandra Sherrod, R.Ph.

FDA Participants:
Daniel Shames, M.D., Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Theresa Van Der Vlugt, M.D., M.P.H., Acting Team Leader, Division of Reproductive and Urologic Drug Products DRUDP (HFD-580)
Phill Price, M.D., Medical Officer, DRUDP (HFD-580)
Kassandra Sherrod, R.Ph., Project Manager, (DRUDP; HFD-580)
Amit Mitra, Ph.D., Chemist, DNDC II @ DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D., Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)

Meeting Objective:
To discuss the status of the reviews for the sponsor's September 19, 2003, submission.

Background:
The original application for this product, Climara Pro, was submitted on June 29, 2000. The Division issued non-approval letters on June 27, 2001 and October 8, 2002. The 2-month User Fee Goal date is November 22, 2003.

Discussion:

Chemistry

- Dr. Mitra is in the process of finalizing his review. The project manager will continue to be responsible for sending the consults to DMETS and DDMAC and share them with the clinical team once they are completed. The chemists will not have to consult on the tradename, only the established name.

Clinical

- The label has been received with revisions from Berlex.
- A phase IV commitment will need to be agreed upon with Berlex prior to approval.

- Consistent nomenclature should be used in all reviews.

Action items:

- Drs. Van Der Vlugt and Price will review the revisions to the label received from Berlex on November 11, 2003.
- Dr. Shames will write a summary review of the resubmission of NDA 21-258.
- Drs. Price and Van Der Vlugt will do a label review and make reference to the division director's summary review of the resubmission of NDA 21-258. Also, in the medical officer's review a link to the dose being accepted based on bioequivalence should be made.
- Drs. Price and Van Der Vlugt and Ms. Sherrod will call the sponsor tomorrow and discuss labeling changes.

_____ _____

Signature, minutes preparer Signature, Chair

HFD-580:NDA 21-258
Drafted: KS/11.14.03
Finalized: Sherrod, 11.20.03
Concurrence/Comments: Price, 11.17.03/Mitra, 11.18.03/Shames, 11.19.03/Van Der Vlugt, 11.20.03

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/s/

Theresa Van Der Vlugt
11/20/03 09:16:46 AM
I concur with the meeting minutes.

Internal Meeting Minutes

Date: November 3, 2003 1:00 - 2:00 PM Place: Parklawn; Room 17B-43

NDA: 21-258 Drug Name: Climara Pro™ (estradiol/levonorgestrel transdermal system)

Type of Meeting: 2 Month Status Meeting

Indication: Treatment of moderate to severe vasomotor symptoms associated with the menopause

Sponsor: Berlex Laboratories, Inc.

FDA Lead: Dr. Theresa van der Vlugt, M.D., M.P.H.

Meeting Recorder: Kassandra Sherrod, R.Ph.

FDA Participants:
Theresa Van Der Vlugt, M.D., M.P.H., Acting Team Leader, Division of Reproductive and Urologic Drug Products DRUDP (HFD-580)
Phill Price, M.D., Medical Officer, DRUDP (HFD-580)
Kassandra Sherrod, R.Ph., Project Manager, (DRUDP; HFD-580)
Amit Mitra, Ph.D., Chemist, DNDC II @ DRUDP (HFD-580)
Ameeta Parekh, Ph.D., Pharmacokinetics Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)

Meeting Objective:
To discuss the status of the reviews for the sponsor's September 19, 2003, submission.

Background:
The original application for this product, Climara Pro, was submitted on June 29, 2000. The Division has issued a non-approval letter on June 27, 2001 and October 8, 2002. The 2-month User Fee Goal date is November 22, 2003, if this submission is a complete response.

Discussion:

Clinical Pharmacology

- Dr. Parekh will review of this latest submission and enter her review into DFS where Dr. Kavanaugh's review of the original submission is currently.
- Dr. Parekh will verify the pk numbers in table 1 of the label that were sent in by the sponsor.

Chemistry

- Dr. Mitra reviewed the DMF and now another amendment has been submitted after the review was completed. The amendment may need a review.
- The appropriateness of the storage conditions in the Patient Information [redacted] will be confirmed via review of the available stability data.

Clinical

- Dr. Van Der Vlugt and Dr. Price will finish working on the label with input from the biopharm reviewer.

Action items:

- Dr. Price and Ms. Sherrod will call the sponsor at 2:00 for clarification on data for the
- Dr. Mitra will finalize the chemistry NDA review.
- We will send the sponsor the label on Thursday, November 6, 2003.

Signature, minutes preparer

Signature, Chair

HFD-580:NDA 21-258
Drafted: KS/11.6.03
Finalized: Sherrod, 11.13.03
Concurrence/Comments: Mitra, Price, 11.6.03/Parekh/van der Vlugt, 11.12.03

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/s/

Theresa Van Der Vlugt
11/14/03 05:03:00 PM
I concur.

Internal Meeting Minutes

Date: October 6, 2003 Time: 12:00 - 1:00 PM Place: Parklawn; Room 17B-43

NDA: 21-258 Drug Name: Climara Pro™ (estradiol/levonorgestrel transdermal system)

Type of Meeting: Complete Response Meeting

Indication: Treatment of moderate to severe vasomotor symptoms associated with the menopause

Sponsor: Berlex Laboratories, Inc.

FDA Lead: Dr. Theresa van der Vlugt, M.D., M.P.H.

Meeting Recorder: Kassandra Sherrod, R.Ph.

FDA Participants:
Theresa Van Der Vlugt, M.D., M.P.H., Acting Team Leader, Division of Reproductive and Urologic Drug Products DRUDP (HFD-580)
Phill Price, M.D., Medical Officer, DRUDP (HFD-580)
Kassandra Sherrod, R.Ph., Project Manager, (DRUDP; HFD-580)
Amit Mitra, Ph.D., Chemist, DNDC II @ DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D., Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Suzanne Thornton, Ph.D., Acting Supervisory Pharmacologist, DRUDP (HFD-580)

Meeting Objective:
To discuss the acceptance of the sponsor's September 19, 2003, response to our Non-Approval letter dated October 8, 2002 as a complete response.

Background:
The original application for this product, Climara Pro, was submitted on June 29, 2000. The Division has issued a non-approval letter on June 27, 2001 and October 8, 2002. The 2-month User Fee Goal date is November 22, 2003, if this submission is a complete response.

Discussion:

Clinical

- The sponsor has submitted a response to a teleconference they held with Dr. Shames and Ms. Kober on September 8, 2003.
- The reviewers do not consider this submission a complete response to the non-approval letter issued to the sponsor on October 8, 2002.
- The label needs to be modified.
- Dr. Van Der Vlugt and Dr. Price will work on the label with input from the biopharm reviewer.

Chemistry

- It is a complete response to the chemistry issues.
- DMF information was submitted on Oct. 3, 2002, but the review was deferred.
- Microbiology review was included in chemistry.

Pharmtox

- There are no pharmtox issues.

Action items:

- Dr. Van Der Vlugt will discuss teleconference issues with Dr. Shames for determination of a complete response.
- Dr. Mitra will finalize the chemistry NDA review.
- PM will put the label on the "N" drive.

_____ _____

Signature, minutes preparer Signature, Chair

HFD-580:NDA 21-258
Drafted: KS/10.22.03
Finalized: Sherrod, 11.6.03
Concurrence: van der Vlugt, 11.6.03
Thornton, Price/10.22.03
Mitra, Rhee

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/s/

Theresa Van Der Vlugt
11/6/03 12:14:03 PM
I concur with the meeting minutes.

BERLEX
Laboratories

Facsimile
Transmittal Sheet

FROM: Geoffrey Millington	TELEPHONE: (973) 487-2254
ADDRESS: ✉ 340 Changebridge Road, P. O. Box 1000, Montville, NJ 07045-1000	
FAX NUMBER: ✉ Drug Regulatory Affairs (973) 487-2016	
TO: : **Dornette Spell-Lesane**, Project Manager Division of Reproductive and Urologic Drug Products	TELEPHONE: 301-827-7514
SUBJECT: NDA 21-258 –Climara Pro™	FAX NUMBER: 301-827-4267
	DATE: October 17, 2002
	TOTAL NUMBER OF PAGES (INCLUDING COVER SHEET): 2

Dear Ms. Spell-Lesane:

The attached letter is notification of our intent to amend NDA 21-258 and our request that the application not be withdrawn.

Please call me at 973-487-2254 if you have any questions regarding this subission.

Sincerely,

Geoffrey Millington
Manager, Drug Regulatory Affairs
BERLEX LABORATORIES

GPM/057

BERLEX

UPS OVERNIGHT
TELEFAX

Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 487-2000

October 17, 2002

Daniel Shames, M.D., Director
Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane, HFD-580, Room 17B-45
Rockville, Maryland 20857-1706

Dear Dr. Shames:

Re: NDA 21-258 Climara Pro™
Estradiol/Levonorgestrel Transdermal System

Reference is made to NDA 21-258 submitted on June 29, 2000 for Climara Pro™ (Estradiol/Levonorgestrel Transdermal System), to your June 27, 2001 action letter, to our March 26, 2002 resubmission (considered a complete class 2 response), and to your October 8, 2002 not approvable letter.

The purpose of this letter is to notify the Division that Berlex currently intends to submit an amendment to include various options. However, this letter is being sent with the understanding that Berlex will be requesting an informal meeting with the Division in accordance with 21 CFR 314.102(d) as stated in your October 8, 2002 letter. The outcome of this meeting may impact our decision to amend the application.

Berlex does not wish to have the application withdrawn, and may choose another option as provided for under 21 CFR 314.120 after the meeting takes place.

Please contact the undersigned at (973) 487-2254 if you have any questions regarding this submission.

Sincerely,

BERLEX LABORATORIES, INC.

Geoffrey Millington
Manager, Drug Regulatory Affairs

GPM/055

cc: Ms. Dornette Spell-Lesane (telefax)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-258

Berlex Laboratories, Inc.
Attention: Geoffrey Millington
Manager, Drug Regulatory Affairs
340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000

Dear Mr. Millington:

Please refer to your new drug application (NDA) dated April 8, 2002, received April 9, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Climara Pro™ (estradiol/levonorgestrel) 0.045/0.015, 0.045/0.030, 0.045/0.040 mg/day transdermal system.

We acknowledge receipt of your submission dated June 5, and 19, 2001, September 25 and 26, 2002.

The April 8, 2002, submission constituted a complete response to our June 27, 2001, action letter.

On February 22, 2002, Dr. Florence Houn, Director of the Office of Drug Evaluation III, sent a letter to you offering 3 options to address data validation issues in order to obtain approval of NDA 21-258. These options were:

1. Submit a new clinical study as requested in the June 27, 2001, letter.
2. Submit information that demonstrates that prior to study initiation, subjects were able to use the IVRS successfully to report the frequency and severity of their vasomotor symptoms and that the system accurately captured the data. An example of demonstrating patient success with using the system could be a test procedure used to show that instructions for using the system were understood and that the subject entered data correctly. Validation of the IVRS would include information showing that the system could record data accurately, maintain study blinding, and preclude errors in data creation, modification, maintenance, archiving, retrieval, or transmission. (Refer to the Guidance for Industry: Computerized Systems Used in Clinical Trials).
3. Conduct and submit an analysis showing that the data recorded on the available worksheets verifies the data in the Interactive Voice Response System (IVRS). The analysis should include the history behind the worksheets (e.g. what was done to locate them, verify their authenticity, maintain their control, etc.) and how the analysis was conducted.

We have completed our review and find the information presented is inadequate. Therefore, the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies are summarized as follows:

Clinical:

1. Insufficient information was submitted to demonstrate that prior to study initiation, subjects were able to use the IVRS to accurately record the data specifically related to the frequency and severity of their vasomotor symptoms. You provided evidence that your investigational staff was trained to instruct subjects on the use of the IVRS. You also provided evidence to support that prior to study initiation, subjects were able to use the IVRS system to successfully create a personal identification number. However, this does not provide

evidence that prior to starting the baseline recording period, subjects were able to accurately record and report vasomotor symptoms. Therefore, submitted evidence does not support the IVRS system as a validated tool for capturing data for moderate-to-severe vasomotor symptoms.

2. The analyses of the available study worksheets (subject diaries) do not verify the data in the IVRS. The analyses from the Phase 3 clinical trial (Study 096042) submitted to verify the IVRS data was based on only 9 worksheets from 3 subjects out of 293 subjects in the Intent-to-Treat population. No data was presented on protocol-specified worksheets for the baseline period. The only baseline data submitted comes from one subject who composed her own diary.

To address the above deficiencies, the following is required:

An additional 12-week clinical study with two dosages of the estradiol/levonorgestrel transdermal system must be conducted to support — treatment of moderate-to-severe vasomotor symptoms — . The study should include the 4.4 mg E2/LNG 1.39 mg dose because that dose appears to be the lowest effective dose for reducing the incidence of endometrial hyperplasia.

Chemistry:

The DMF — is not adequate to support the NDA.

To address the above deficiencies, the following is required.

All deficiencies in DMF — must be corrected prior to approval of this application.

Please note the trademark Climara Pro™ as two words is acceptable. Labeling comments are reserved until the requested additional clinical study data are submitted.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   a. Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.

   b. Present tabulations of the new safety data combined with the original NDA data.

   c. Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.

   d. For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with this Division to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact Dornette Spell-LeSane, NP-C, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Dan Shames, M.D.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Shelley Slaughter
10/8/02 04:16:25 PM
Shelley R. Slaughter acting Division Director for Daniel Shames
Division Director

B

4 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

FACSIMILE TRANSMISSION RECORD

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Reproductive and Urologic Drug Products (HFD-580)
Parklawn Building, Room 17B-45
5600 Fishers Lane, Rockville, Maryland 20857

__Number of Pages (including cover sheet) **Date**: September 25, 2002

To: Geoffrey Millingon, Manager, Drug Regulatory Affairs

Fax Number: 973-487-2016 **Voice Number**: 973-487--2254

From: Dornette Spell-LeSane
Project Manager

Fax Number: 301-827-4267 **Voice Number**: 301-827-7514

Message:
IR Letter

NOTE: If you do not receive a legible document, or do not receive all of the pages, please telephone us immediately at the voice number above.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-258

INFORMATION REQUEST LETTER

Berlex Laboratories, Inc.
Attention: Geoffrey Millington
Manager, Drug Regulatory Affairs
340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000

Dear Mr. Millington:

Please refer to your April 8, 2002, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Climara Pro™ (estradiol/levonorgestrel) transdermal system.

We are reviewing the Clinical, Statistical, and Chemistry, Manufacturing and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. You submitted worksheets for only three of the patients from Study 96042A (nine sheets out of a possible 594 worksheets were submitted). Please confirm that the nine sheets submitted are the only available worksheets from that study.

2. You submitted datasheets, although not on the official worksheet form, on a single patient that included baseline data. Please confirm that this patient was a study participant and that the data was included in the study results.

3. Study worksheets and corresponding IVRS information for data entry prior to initiation of study was not provided. This information would be helpful in the validation of the IVRS. Please confirm that this information is not available.

4. Please provide the status of any ongoing or completed clinical studies that have not been submitted to the NDA, for the vasomotor symptom indication.

5. DMF — is deficient; a letter will be forwarded to the DMF holder.

If you have any questions, call Dornette Spell-LeSane, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph.
Chief, Project Management Staff
Division of Reproductive and Urologic
Drug Products, HFD-580
Center for Drug Evaluation and Research

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/s/

Margaret Kober
9/25/02 10:46:00 AM
Chief, Project Management Staff

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/s/

Margaret Kober
9/25/02 10:46:00 AM
Chief, Project Management Staff

INTERNAL MEETING MINUTES

MEETING DATE: September 18, 2002

TIME: 9:30 a.m. – 10:30 a.m.

LOCATION: Parklawn; 17B-43

APPLICATION: NDA 21-258

SPONSOR: BERLEX

DRUG Climara Pro

TYPE OF MEETING: 5-month status meeting

MEETING CHAIR: Phill Price, M.D.

MEETING RECORDER: Dornette Spell-LeSane, NP-C

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

Name of FDA Attendee	Title	Division Name & HFD#
1.Florence Houn, M.D.	Office Director	Office of Drug Evaluation III, Office of New Drugs (HFD-103)
2.Phill Price, M.D.	Medical Officer	Division of Reproductive and Urologic Drug Products DRUDP (HFD-580)
3.Amit Mitra, Ph.D.,	Chemist	Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
4.Kate Meaker, M.S.	Statistician	Division of Biometrics II (DBII) @ DRUDP (HFD-580)
5.Bronwyn Collier, BSN	Associate Director for Regulatory Affairs	Office of Drug Evaluation III, (ODE III; HFD-103)
6.Dornette Spell-LeSane, NP-C	Regulatory Project Manger	DRUDP (HFD-580)

BACKGROUND:
The original application for this product, Climara Pro, was submitted on June 29, 2000. The Division issued a non-approval letter on June 27, 2001. The Division accepted the sponsors April 8, 2002, submission as a complete response to the June 27, 2001, action letter. The Goal date for this submission is October 8, 2002.

MEETING OBJECTIVES:
To discuss the status of the reviews for this application.

DISCUSSION:

Chemistry

- DMF — is deficient
- an information request letter is being crafted to be sent to the DMF holder
- chemistry recommends approvable pending satisfactory response to DMF deficiencies

Clinical

- the sponsor provided responses to options 2 and 3 of the dispute resolution letter which state:
    1) Submit a new clinical study as requested in the June 27, 2001, letter.
    2) Submit information that demonstrates that, prior to study initiation, subjects were able to use the IVRS successfully to report the frequency and severity of their vasomotor symptoms and that the system accurately captured the data; an example of demonstrating patient success with using the system could be a test procedure used to show that instructions for using the system were understood and that the subject entered data correctly. Validation of the IVRS would include information showing that the system could record data accurately, maintain study blinding, and preclude errors in data creation, modification, maintenance, archiving, retrieval, or transmission. (Refer to the *Guidance for Industry: Computerized Systems Used in Clinical Trials*)
    3) Conduct and submit an analysis showing that the data recorded on the available worksheets verifies the data in the IVRS. The analysis should include the history behind the worksheets (e.g., what was done to locate them, verify their authenticity, maintain their control, etc.) and how the analysis was conducted.
- the sponsor started the study with worksheets, these worksheets were not stored as required; therefore, we are unable to determine if the baseline data were consistent with submitted data
- data on 3 patients were submitted for the pivotal study; 9 worksheets were submitted for those three patients; no baseline data was submitted; generally each patient would have 13 worksheets each, if the protocol was followed; each sheet would contain 3 weeks of data; patient #1 had 3 sheets; no baseline; no symptoms at wk-4; patient #2; 2 sheets; no baseline; patients did not meet entrance criteria; patient 3 2weeks baseline;3 sheets ;however data was not documented on sponsor's worksheet
- corresponding IVRS information was not sufficient to support data
- Clinical recommends non-approval; the sponsor should conduct a clinical trial to demonstrate efficacy

Statistics:

- inadequate information was provided to support a conclusion that the IVRS was validated prior to study starting
- patients were instructed as to selecting PIN numbers, not tested for instructions on use of the IVRS to collect vasomotor symptom information
- baseline study entrance data was not provided
- statistics recommends non-approval

Tradename:

- the tradename review was outstanding at the time of the not-approvable letter and listed as a deficiency
- OPDRA has since approved "Climara Pro" in place of "Climarapro"

DECISIONS REACHED:

- DRUDP recommends a not approvable action for this application for this second review cycle

ACTION ITEMS:

- PM to send an information request letter to the sponsor conveying the Divisions concerns; including comment regarding the deficient DMF
- PM to send a information request letter to the DMF holder

Minutes Preparer: _____
SIGNERS NAME & TITLE

Chair Concurrence: _____
SIGNERS NAME & TITLE

cc: Original
HFD-580/Div. Files
HFD-580/Spell-LeSane
HFD-580/Price, Slaughter, Mitra, Houn, Collier

Drafted by: DS-L, 9.28.02
Initialed by: Collier, Houn, Mitra, Meaker, 10. 4.02/, Price, 10.7.02
final: Spell-LeSane, 10.8.02

MEETING MINUTES

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/s/

Phill H. Price
10/8/02 02:47:22 PM

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

REQUEST FOR CONSULTATION

TO: **Office of New Drug Chemistry (HFD 160)**
Attention: Peter Cooney, Microbiology Team Leader,
Room # 18B08.

FROM: HFD-580 (Division of Reproductive and Urologic Drug Products) Dornette Spell-LeSane, Regulatory Project Manager

DATE:	IND NO.:	NDA NO.:	TYPE OF DOCUMENT:	DATE OF DOCUMENT:
August 20, 2002		21-258 DMF —	Response to information request dated June 14, 2001	**June 22, 2001**

NAME OF DRUG:	PRIORITY CONSIDERATION:	CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE:
Estradiol/levonorgesterel	**standard**		**September 15, 2002**

NAME OF FIRM: —

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

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

III. BIOPHARMACEUTICS

Γ DISSOLUTION
Γ BIOAVAILABILTY STUDIES
Γ PHASE IV STUDIES
Γ DEFICIENCY LETTER RESPONSE
Γ PROTOCOL-BIOPHARMACEUTICS
Γ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

Γ CLINICAL
Γ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: See follow-up information attached.
cc: Original NDA 21-258
HFD-580/Div. Files
HFD-580/Spell-LeSane/ Mitra/Rhee/Bennett/Slaughter/Kober/Olmstead

SIGNATURE OF REQUESTER:	METHOD OF DELIVERY (Check one): Γ MAIL ☐ HAND
SIGNATURE OF RECEIVER:	SIGNATURE OF DELIVERER:

INTERNAL MEETING MINUTES

MEETING DATE: April 22, 2002

TIME: 12:00 p.m. – 1:00 p.m.

LOCATION: Parklawn; 17B-43

APPLICATION: NDA 21-258

SPONSOR: BERLEX

DRUG Climara Pro

TYPE OF MEETING: filing meeting (resubmission)

MEETING CHAIR: Shelley Slaughter, M.D., Ph.D.

MEETING RECORDER: Dornette Spell-LeSane, NP-C

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

Name of FDA Attendee	Title	Division Name & HFD#
1.Shelley Slaughter, M.D., Ph.D.	Medical Team Leader	Division of Reproductive and Urologic Drug Products, DRUDP (HFD-580)
2.Phill Price, M.D.	Medical Officer	DRUDP (HFD-580)
3.Amit Mitra, Ph.D.,	Chemist	Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
4.Margaret Kober, R.Ph.	Chief, Project Management Staff	DRUDP (HFD-580)
5.Dornette Spell-LeSane, NP-C	Regulatory Project Manger	DRUDP (HFD-580)
6.Kassandra Sherrod, R.Ph.	Regulatory Project Manger	DRUDP (HFD-580)

BACKGROUND:
This application was originally submitted on June 29, 2000. The Division issued a not-approvable letter on June 27, 2001. On February 22, 2002, in response to a Formal Dispute Resolution, the sponsor received from the Agency alternative responses for a resubmission. This submission dated April 8, 2002, is a response to the not-approvable deficiencies.

MEETING OBJECTIVES:
To qualify this submission as a complete response to the non-approvable action letter, assign a resubmission classification and a PDUFA goal date

DISCUSSION:
Chemistry:

- the submission dated June 5, 2001, referenced for this resubmission, and not reviewed during the first review cycle, qualifies as a complete response to the chemistry approvable issues
- additional request for information may be required

Clinical:

- the sponsor provided responses to options 2 and 3 of the dispute resolution letter which state:
  1) Submit a new clinical study as requested in the June 27, 2001, letter.
  2) Submit information that demonstrates that, prior to study initiation, subjects were able to use the IVRS successfully to report the frequency and severity of their vasomotor symptoms and that the system accurately captured the data; an example of demonstrating patient success with using the system could be a test procedure used to show that instructions for using the system were understood and that the subject entered data correctly. Validation of the IVRS would include information showing that the system could record data accurately, maintain study blinding, and preclude errors in data creation, modification, maintenance, archiving, retrieval, or transmission. (Refer to the *Guidance for Industry: Computerized Systems Used in Clinical Trials*)
  3) Conduct and submit an analysis showing that the data recorded on the available worksheets verifies the data in the IVRS. The analysis should include the history behind the worksheets (e.g., what was done to locate them, verify their authenticity, maintain their control, etc.) and how the analysis was conducted.
- clinical supports this submission as a complete response to the alternative resolution of the non-approvable deficiencies

DECISIONS REACHED:

- DRUDP will accept submission as a complete response
- the application qualifies as a Class 2 resubmission (the data submitted is new data, not considered minor, and not reviewed during cycle 1)
- the review period will be 6 months; The goal date will be October 8, 2002

ACTION ITEMS:
PM to schedule status meetings appropriate for review cycle

Minutes Preparer: _____
SIGNERS NAME & TITLE

Chair Concurrence: _____
SIGNERS NAME & TITLE

cc: Original
HFD-580/Div. Files
HFD-580/Spell-LeSane
HFD-580/Price, Slaughter, Mitra,

Drafted by:
Initialed by: Mitra, Sherrod, 10.4.02/Price, Kober, 10.7.02
Final: Spell-LeSane, 10.8.02

MEETING MINUTES

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/s/

Shelley Slaughter
10/8/02 04:07:57 PM
I concur.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-258

Berlex Laboratories, Inc.
c/o Hyman, Phelps & McNamara, P.C.
Attention: Roger C. Thies
700 Thirteenth Street, N.W.
Washington, D.C. 20005-5929

Dear Mr. Thies:

We refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ClimaraPro® (estradiol/levonorgestrel transdermal system). The application proposed use of ClimaraPro® for — treatment of moderate to severe vasomotor symptoms associated with the menopause in women with an intact uterus —

Your January 24, 2002, request for dispute resolution, received on January 24, 2002, concerned the Division of Reproductive and Urologic Drug Products' (DRUDP) decision not to accept Study 96042A in support of approval of ClimaraPro® because source documentation for the study could not be verified. Data for Study 96042A were collected using paper worksheets and an electronic data capture system (IVRS). Study 96043A also relied, in part, on collection of data with worksheets and the IVRS, and DRUDP noted the same validation issue. However, Study 96043A is not part of your appeal since a repeat of this study was not required to resolve the deficiencies precluding approval of NDA 21-258. Your appeal was considered under our formal dispute resolution process.

You asserted that the worksheets were an aid for study subjects to assist them in entering data into the IVRS and should not be considered source documents. You stated that the protocol for the study, conduct of the study, as well as analysis of the data, all support this position. Conduct of a study is based on the conditions and procedures specified in the study protocol. Communications and instructions to study investigators relating to changes in the protocol and/or changes in conduct of the trial that were not submitted to or reviewed by FDA cannot be assumed to be acceptable. In consideration of your appeal, we reviewed the protocol for Study 96042A that was submitted and on file at FDA.

In the protocol for Study 96042A, procedures for the "run-in" phase and cycle 1 (from Visit 2 to Visit 3) of the treatment phase of the study indicate that worksheets were to be used by patients to record hot flushes and urogenital symptoms as well as entry of data into the IVRS. For the balance of the study, the protocol discusses data collection only by IVRS, although presumably, some patients found it useful to continue using the worksheets. The following are statements in the protocol regarding the worksheets and IVRS:

1. (protocol section 5.1; Study Design) "These subjects will then enter the run-in period for up to 4 weeks. They will be given a worksheet to record weekly observations of urogenital symptoms. They will be instructed in the use of the Interactive Voice Response System (IVRS) to record the daily number and severity of hot flushes and weekly presence and severity of urogenital symptoms. ... Hot flush frequency and severity will be entered daily by each subject via IVRS. Presence and severity of urogenital symptoms will be entered weekly by IVRS."
2. (protocol section 5.5.2; Run-In Period) "After the entry criteria have been satisfied to determine eligibility for the study, subjects will be supplied with a worksheet for recording hot flushes and urogenital symptoms

for up to 4 weeks. ...Subjects will be instructed in the use of the IVRS to record hot flush severity and frequency daily and urogenital symptoms weekly."

3. (protocol section 5.5.3; Visit 2 (Baseline/Randomization)) "Subjects will be reminded to continue to record their hot flushes daily and urogenital symptoms weekly on the worksheet provided. Subjects will be reminded to continue to use the IVR system to record their symptoms."
4. (protocol section 5.5.4; Visit 3 (After Cycle 1)) "Subjects are reminded to continue to record symptoms via the IVRS."

Although Study 96043A is not specifically part of the appeal, the same worksheets and IVRS were used by a portion of the study population to record symptoms of hot flushes and urogenital symptoms. The procedures detailed in the protocol for this study are ambiguous as to whether worksheets were to be used by the symptomatic population subset throughout the study in addition to the IVRS. Thus, information from this protocol is not helpful in interpreting the procedures for Study 96042A. The following are statements in the protocol for Study 96043A regarding worksheets and the IVRS for recording hot flushes and urogenital symptoms:

1. (protocol section 5.1; Study Design) "All subjects will be given a worksheet to record their symptoms and bleeding patterns throughout the study. At Visit 2 (which will be performed within 4 weeks of Visit 1) the Investigator will determine the subjects eligibility for study participation. ... Women who qualify and have symptoms between Visits 1 and 2 will be asked to record the frequency and severity of hot flushes by Interactive Voice Response System (IVRS) for the next 2 weeks."
2. (protocol section 5.5.3; Symptoms) Subjects who qualify for the symptom substudy will be supplied with worksheets for recording the number and severity of daily hot flushes for 12 weeks and urogenital symptoms weekly for the duration of the study. ...Urogenital symptoms include... These data will then be entered by the subject via an Interactive Voice Response System (IVRS).

Additional statements in the protocol for Study 96042A indicated that the IVRS might be a more efficient data-collection tool (protocol section 6.4.1; Dropouts and Missing Data: "Due to the method of hot flush data collection by the [IVRS], it is anticipated that there will be little if any missing data.") and that statistical analyses would work with the data entered into the IVRS (protocol section 6.7; Statistical Analysis of Efficacy: "Hot flushes and their severity will be recorded using the IVR System in a daily diary throughout the study."). However, the source documents for verification of data were not specifically designated in any section of the protocol. Source documents are original documents and records and must be preserved.[1] Based on the protocol, original documentation for the run-in phase and the first cycle of the treatment phase of Study 96042A was the subject worksheets. Since the protocol did not discuss use of the worksheets after Visit 3 of the treatment phase, we agree that source documentation for the balance of the study could be interpreted to mean the IVRS. FDA's acceptance of data from clinical trials intended to support drug efficacy depend, in part, on verification of the quality and integrity of such data through reconstruction and evaluation of the trial against source documents. The unavailability of the worksheets that were specified to be used through cycle 1 of the trial precluded verification of the data collected during that segment of the study and rendered the data collected during the balance of the study subject to question.

Electronic and/or paper methods of capturing data from study subjects are both acceptable provided the systems ensure that data are attributable, original, accurate, contemporaneous, and legible.[2] Your appeal indicated that since your receipt of the June 27, 2001, not approvable letter for the ClimaraPro® application, your continued efforts to locate any existing subject worksheets has turned up 90-100 of them. This new information was not considered in this dispute resolution process. However, given this situation, there are three options that may be able to address the data validation issue:

---

[1] Center for Drug Evaluation and Research Guidance for Industry: Computerized Systems Used in Clinical Trials. April 1999.

[2] ibd.

1. Submit a new clinical study as requested in the June 27, 2001, letter.
2. Submit information that demonstrates that, prior to study initiation, subjects were able to use the IVRS successfully to report the frequency and severity of their vasomotor symptoms and that the system accurately captured the data. An example of demonstrating patient success with using the system could be a test procedure used to show that instructions for using the system were understood and that the subject entered data correctly. Validation of the IVRS would include information showing that the system could record data accurately, maintain study blinding, and preclude errors in data creation, modification, maintenance, archiving, retrieval, or transmission. (Refer to the *Guidance for Industry: Computerized Systems Used in Clinical Trials*)
3. Conduct and submit an analysis showing that the data recorded on the available worksheets verifies the data in the IVRS. The analysis should include the history behind the worksheets (e.g., what was done to locate them, verify their authenticity, maintain their control, etc.) and how the analysis was conducted.

We recommend that you consult with the Division of Reproductive and Urologic Drug Products to further discuss the option you wish to pursue. The division looks forward to working with you on resolving this issue and continuing its review of the data to determine approvability of the ClimaraPro ® application.

If you wish to appeal this decision to the next level, your appeal should be directed to John Jenkins, M.D., Director, Office of New Drugs, Center for Drug Evaluation and Research. The appeal should be sent through the Center's Dispute Resolution Project Manager, Ms. Kim Colangelo at (301) 594-5413.

Sincerely,

{See appended electronic signature page}

Florence Houn, M.D., M.P.H.
Office of Drug Evaluation III
Office of New Drugs
Center for Drug Evaluation and Research

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/s/

Florence Houn
2/22/02 08:56:27 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-258

Berlex Laboratories, Inc.
C/o Hyman, Phelps & McNamara, P.C.
Attention: Mr. Roger C. Thies
700 Thirteenth Street N.W.
Suite 1200
Washington, D.C. 20005-5929

Dear Mr. Thies:

We refer to Berlex Laboratories' New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Climara Pro® (estradiol/levonorgestrel transdermal system).

We acknowledge receipt on January 24, 2002, of your January 24, 2002, request for informal dispute resolution concerning the Division of Reproductive and Urologic Drug Products' decision not to accept data from Studies 96042A or 96043A due to an inability to verify the data. Thus, the studies were not accepted in support of efficacy for Climara Pro® for the treatment of moderate-to-severe vasomotor symptoms associated with the menopause in women with an intact uterus. We do not have a process for informal dispute resolution. Since you have already met with the Division of Reproductive and Urologic Drug Products, obtained assistance from the Center for Drug Evaluation and Research's Ombudsman, and since your current request meets all the requirements for an appeal for formal dispute resolution, we are reviewing your request under the formal process.

Pursuant to the CDER/CBER draft Guidance to Industry "Formal Dispute Resolution: Appeals Above the Division Level," we have thirty (30) calendar days from the receipt date of your request to respond to your appeal. Therefore, we will forward our response on or before February 23, 2002.

Your appeal was forwarded for review to Dr. Florence Houn, Director, Office of Drug Evaluation III, Center for Drug Evaluation and Research. Review of the appeal will be conducted in consultation with the Office of Medical Policy. We will contact you if we have any questions or require additional information.

If you have any questions, please call me at (301) 594-5413.

Sincerely,

{See appended electronic signature page}

Kim Colangelo
Formal Dispute Resolution Project Manager
Center for Drug Evaluation and Research

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/s/

Kim Colangelo
1/25/02 05:39:48 PM

Meeting Minutes

Date: August 23, 2001 **Time:** 12:00 - 1:30 PM **Place:** Parklawn; Conf. Room "K"

IND: 51,188 **Drug Name:** Climara Pro (estradiol/levonorgestrel transdermal delivery system) 0.045/0.015, 0.045/0.030 and 0.045/0.040 mg per day

Indications: Treatment of moderate-to-severe vasomotor symptoms associated with menopause

Type of Meeting: Industry Type-A meeting post NDA non-approval action

External Constituent: Berlex Laboratories, Inc.

FDA Lead: Dr. Susan Allen **External Constituent Lead:** Ms. June Bray

Meeting Recorder: Ms. Diane Moore

FDA Participants:
Susan Allen, M.D., M.P.H. – Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Daniel Shames, M.D. – Deputy Director, DRUDP (HFD-580)
Shelley Slaughter, M.D., Ph.D. – Team Leader, DRUDP (HFD-580)
Phill Price, M.D., – Medical Officer, DRUDP (HFD-580)
Diane Moore - Regulatory Project Manager, DRUDP (HFD-580)
Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Venkateswar R. Jarugula, Ph.D. - Pharmacokinetic Reviewer, OCPB @ DRUDP (HFD-580)
Kate Meaker, M.S. - Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
John Martin, M.D. - Division of Scientific Investigations, Branch Chief, Good Clinical Practices Branch I (CIB; HFD-46)
Constance Lewin, M.D. -Senior Regulatory Review Officer, DSI, GCP Branch I (CIB; HFD-46)

External Participants:
Ms. June Bray, Vice President, Drug Regulatory Affairs, Berlex
Ms. Sharon Brown, Director, Drug Regulatory Affairs, Berlex
Dr. Wolfgang Eder, Project Manager, Berlex
Dr. Marie Foegh, Medical Director, Female Health Care, Berlex
Dr. Adel Karara, Associate Director, Clinical Pharmacology, Berlex
Mr. Geoffrey Millington, Manager, Drug Regulatory Affairs, Berlex
Dr. Minoo Niknian, Associate Director, Statistics, Berlex
Dr. Harji Patel, Senior Statistical Consultant, Berlex
Dr. Vladimir Yankov, Director, Female Health Care, Berlex

Dr. Lester Harrison, Section Head, Clinical Pharmacokinetics – 3 M Pharmaceuticals
Mr. Michael Rowe, Business Director, Berlex

Meeting Objective: To discuss the questions raised in the pre-meeting package from Berlex dated August 7, 2001, regarding the resubmission of their Climara Pro NDA.

Background: The Agency sent Berlex a non-approval letter for their Climarapro NDA on June 27, 2001. The sponsor requested a meeting to discuss their development plan in light of the Agency decision.

Discussion Items: (See overheads, attached)

- a response to the NDA chemistry and manufacturing deficiencies has been submitted to the DMF; these will not be discussed at the industry meeting; upon review, the chemistry reviewer will discuss any outstanding issues with the DMF holder

Decisions:

- **Question 1:** Does the Division concur that Climara Pro is an efficacious product for the treatment of VMS based on:
  - a) serum estradiol levels obtained from pharmacokinetic studies with Climara Pro?
    - **response**:
    - the sponsor suggested that one possible way to establish efficacy of Climara Pro for relief of post-menopausal symptoms was to use the therapeutic range of estradiol serum levels to demonstrate efficacy based on bioequivalence to approved Climara® NDA (see attached overheads)
    - the Division stated that it has not used serum estradiol levels as primary efficacy endpoints for a "relief of vasomotor symptoms" (VMS) indication for a new product (such as Climara Pro); the Division noted that serum estradiol levels have been used as secondary endpoints to provide supportive information for demonstration of VMS relief as the primary endpoint
    - the Division also noted that the sponsor's arguments about the Agency's previous acceptance of bioequivalence (BE) data for other HRT products do not apply to the current situation with Climara Pro
    - the Division clarified that it has allowed use of BE studies to support (1) a change in manufacturing site for an approved product, (2) a proposed change in application site for a previously approved transdermal product containing the same active ingredient, and (3) the approval of bracketed doses of a product
    - the Agency acknowledged that it might be possible for the sponsor to conduct a BE study with the approved Climara® to obtain an indication for Climara Pro; however, the specifics of the study are as follows:
      - the bioavailability study sited in the pre-meeting package which compared Climara® with Climara Pro utilized an oral progesterone dosage form with the Climara® system which is not the same as giving the Climara® transdermal system alone; due to the effects of progesterone on SHBG, Climara Pro must be compared to Climara® alone
      - the effects of levonorgestrel on SHBG levels and clearance of estradiol must be taken into consideration; the sponsor should assess the effects of SHBG steady state levels on estradiol clearance
      - both C_{max} and AUC must meet the BE criteria in the comparison between Climara® and Climara Pro; in addition to estradiol, the pharmacokinetics of estrone and metabolites should be addressed

- the study must adhere to strict BE criteria including Climara® at steady state levels and Climara Pro at steady state levels due to effects on SHBG which stabilize in about three weeks
- the sponsor asked if they could dose-adjust for different strengths
  - the Division clarified that dosage adjustment is not acceptable in BE studies, especially when the potential for interaction is being examined, as in this case
- the Division explained the relevance for the bioequivalence studies for the change in manufacturing site, change in application site (— and bracketed doses (— — in the examples raised in the sponsor's meeting package; these examples are different issues and are not applicable with Climara Pro
- if the sponsor seeks to pursue the performance of a bioequivalence study between Climara® and Climara Pro instead of a clinical trial, the Division will review protocol submissions and respond with appropriate recommendations

- b) Statistical analysis of the pivotal study results in comparison to similar studies conducted with approved HRT transdermal system, Climara®?
- **response:**
  - the Division appreciates the intent of the sponsor's reanalysis (to demonstrate that the blinded study could not have been fraudulently created); however, the audit of the data determined that the data could not be verified; therefore, the Agency could not rely on the given data-set to support efficacy and safety of the product; the statistical results of the reanalysis do not address the issue of the inability to verify the Interactive Voice Response System (IVRS) data upon audit
  - the Division of Scientific Investigations representatives reiterated to the sponsor that during the clinical audit of the study sites for Studies 96042 and 96043, protocol-specified patient worksheets, which were to capture safety and efficacy data (including the primary efficacy endpoint data for study 96042), were not found at any of the three inspected sites
  - the first place information is recorded is considered to be the source documents; because these protocol-specified worksheets were to be the initial recording of subject-reported data, these worksheets are regarded by DSI as the source documents; as such, they should have been available at the study sites; in their absence, the data which were to be collected on these worksheets could not be audited
  - without amending the protocol or otherwise obtaining FDA's agreement, the sponsor or monitor advised clinical investigators that these protocol-specified worksheets were not to be considered source documents
  - the protocol did not specify that worksheets would not be used during the study; the protocol was not followed in regard to the IVRS system
  - DSI expressed concern that the self-reported data to be captured in these studies was of sufficient amount and complexity that the subjects' memories might have been insufficient to permit IVRS alone, without worksheets, to provide reliable data
  - the sponsor indicated that the IVRS captured the data consistently throughout the study; however, the original protocol specified the data worksheet
  - the Division reiterated comments made to the sponsor in a teleconference held on June 27, 2001, in which the following was explained:
    - in Section 5.5.2 and 5.5.3 of the Protocol, subjects were supplied with up to four weeks of worksheets to collect data on VMS and urogenital symptoms during the study run-in period; the subjects were reminded to record the data on the worksheets provided

- data also collected in the IVRS system was not stated as primary source documentation; it is difficult to consider the baseline data as valid in light of the DSI inspection findings and the wording in the protocol
- the Division stated that copies of documents provided by the sponsor during the review cycle did not support the sponsor's position that appropriate notification, that patient worksheets were no longer to be considered source documents, had been provided to either the principal investigators or to the Agency
  - specifically, a July 22, 1998, letter to a principal investigator, referencing a coversheet for shipment of study supplies, did not appear to have, as its primary purpose, notification that the patient worksheets were no longer considered source documents
  - in addition, a May 11, 1998, letter from — to the principal investigators of the study did not constitute a formal protocol amendment, nor was the Division notified that patient worksheets would no longer be considered source documents
- had the Division received this request for a change in protocol, the Division most likely would have regarded the protocol-specified worksheets as source documents that were necessary for capturing endpoint data; the Agency was not notified of the change in study plan prior to its implementation
- it was acknowledged that the sponsor could follow the appeal process outlined in the guidance entitled, "Formal Dispute Resolution: Appeals Above the Division Level"

- **Question 2:** In the event that the Division does not concur with question 1, does the proposed vasomotor symptom study design satisfy the Division requirements?
  - **response:**
    - the Division clarified to the sponsor that they could not submit an additional vasomotor study as a Phase-4 study for the Climara Pro NDA
    - although the outline of the proposed clinical study presented in the pre-meeting package appeared to address a standard VMS study, the Division did not comment on this outline because it did not contain the appropriate detail; if the sponsor seeks to perform an additional VMS study, a complete protocol that includes a statistical analysis proposal should be submitted for review and comment
    - it was noted, however, that the Division would entertain further discussion of proposed entry criteria for the study with the sponsor upon submission of a more detailed study protocol
    - if an IVRS system is to be used in a study, the baseline data should also be collected via IVRS; all source documents should be available for audit
    - an 8-week washout period for women on oral hormone replacement therapy cannot be reduced
    - the Agency noted that because both the 1.39 mg dose and the 2.75 mg dose of levonorgestrel (LNG) demonstrated no hyperplasia when administered with estradiol in Study 96043, the lowest effective dose of LNG that protects the endometrium from hyperplasia for the prospective dose of estradiol is unknown; the sponsor noted that the 2.75 mg dose of LNG is the medium dose being marketed worldwide
    - the sponsor should describe the reason why the dose of LNG was chosen when the protocol is submitted; a complete statistical analysis plan should be included; a 45-day special protocol review could be requested based on this being a Phase-3 pivotal study (refer to the guidance entitled, "Special Protocol Assessment")
    - a computer input system can be developed, but it needs to be discussed with the Agency prior to initiation of the study

- the sponsor should refer to the guidance entitled, "Regulatory Submissions in Electronic Format: New Drug Applications" for future NDA and SNDA submissions (a copy was provided to the sponsor)

- **Question 3:** Is the tradename, "Climara Pro" acceptable?
  - **response:**
    - the Office of Drug Risk Assessment (OPDRA) has reviewed the study data submitted by the sponsor and has reconsidered their position on the acceptability of Climara Pro; with the caveat that the tradename is two separate words "Climara®" and "Pro", the tradename is acceptable
    - the Division noted that during the review of the NDA, the tradename must be submitted to OPDRA twice, so that it is possible that the decision to allow the Climara Pro tradename could be reversed upon findings of conflict with another look-alike or sound-alike name as far as the day of the NDA approval action

Action Items

• **Item**	**Responsible Person:**	**Due Date:**
• send Telecon minutes to sponsor	DRUDP	September 23, 2001
• submit revised protocol	Berlex	prior to initiation of study

{See appended electronic signature page}

Note to sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

drafted: dm/8.2901/I51188MM82301.doc

Concurrence:
T.Rumble, P.Price 9.6.01/K.Meaker 9.7.01/J.Martin 9.10.01/S.Slaughter 9.13.01
A.Parekh, V.Jarugula 9.18.01/S.Allen 9.19.01/D.Shames 9.20.01

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/s/

Diane V. Moore
9/24/01 06:40:08 PM

Susan Allen
9/25/01 03:46:05 PM

Office of Post-Marketing Drug Risk Assessment

Memo

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

From: Alina R. Mahmud, R.Ph.
Safety Evaluator, Office of Post-Marketing Drug Risk Assessment
HFD-400

Through: Jerry Phillips, R.Ph.
Associate Director, Office of Post-Marketing Drug Risk Assessment
HFD-400

CC: Diane Moore
Project Manager
HFD-580

Date: August 21, 2001

Re: OPDRA Consult 00-0193-1; Climara Pro (estradiol/levonorgestrel transdermal system) 0.045 mg /0.015 mg, 0.045 mg/0.030 mg, 0.045 mg/0.040 mg; NDA 21-258

This memorandum is in response to an August 2, 2001 request from your Division to review the sponsor's response to OPDRA's recommendation regarding their proposed proprietary name, Climara Pro.

Upon a re-review of the proprietary name Climara Pro, OPDRA was informed by the Project Manager that the sponsor intends to market the drug name as two separate words (e.g., Climara Pro and not Climarapro, as initially reviewed). Often practitioners do not clearly script the last few letters of the drug name, therefore adding confusion as one drug name is mistaken for another because the full name is not legible. However, the use of a modifier assists in distinguishing the proposed name "Climara Pro" from the approved product name "Climara" as two separate words must be scripted.

Furthermore, differences in strength will assist in distinguishing "Climara Pro" from "Climara" (products vary in estrogen value) since physicians will have to write for a strength with each name and those strengths do not overlap with each other. Therefore, based on the aforementioned differences, OPDRA does not object to the use of the proprietary name "Climara Pro". OPDRA has also reviewed [redacted] study submitted by the applicant and agree with the sponsor that the likelihood of confusion between Climara and Climara Pro is negligible.

OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.

If you have any questions or need clarification, please contact Alina Mahmud at 301-827-0916.

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/s/

Alina Mahmud
8/22/01 11:25:57 AM
PHARMACIST

Jerry Phillips
8/22/01 11:31:12 AM
DIRECTOR

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-258

Berlex Laboratories, Inc.
Attention: Geoffrey Millington
Manager, Drug Regulatory Affairs
340 Changebridge Road
P.O. Box 1000
Montville, NJ 07450-1000

Dear Mr. Millington:

Please refer to your new drug application (NDA) dated June 29, 2000, received June 29, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Climarpro™ estradiol (E_2)/levonorgestrel (LNG) transdermal system.

We acknowledge receipt of your submissions dated July 31, August 8 and 9 (telefacsimile), October 17, and December 22, 2000; January 3, 5 and 12, February 7, March 16, 23 and 30, April 6, May 9 and 30, and June 13 and 20, 2001.

We also refer to your submissions dated June 5 and 19, 2001. These submissions have not been reviewed in the current review cycle. You may incorporate these submissions by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review and find the information presented is inadequate, and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies may be summarized as follows:

Clinical:

Efficacy of the estradiol and levonorgestrel transdermal system for the —— ("treatment of moderate-to-severe vasomotor symptoms associated with the menopause in women with an intact uterus" ——
—— was not demonstrated in study 96042A or 96043A. Source documentation for these studies could not be verified, thereby precluding acceptance of the data from these studies in support of approval for these indications.

To address the above deficiency, the following is required:

An additional 12-week clinical study with two dosages of the estradiol/levonorgestrel transdermal system must be conducted to support the —— —— indications noted above. The study should include the 4.4 mg E_2/LNG 1.39 mg dose since that dose appears to be the lowest effective dose for reducing the incidence of endometrial hyperplasia.

Chemistry:

The DMF — is not adequate to support the NDA.

To address the above deficiencies, the following is required:

All deficiencies in DMF — must be corrected prior to approval of this application.

Labeling comments are reserved until the requested additional clinical study data are submitted.

Please be advised that the tradename, "Climarapro" for this product was found unacceptable by OPDRA because it could be confused with the tradename "Climara."

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. The safety update should include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.

   - Present tabulations of the new safety data combined with the original NDA data.

   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.

   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but

less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action, FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

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

Sincerely,

(See appended electronic signature page)

Susan Allen, M.D.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Name	Title	Signature	Date
Susan Allen, M.D., M.P.H.	Division Director		
Dan Shames, M.D.	Deputy Division Director		10/7/02
Shelley Slaughter, M.D., Ph.D.	Medical Team Leader		6/26/01
Phill Price, M.D.	Medical Officer		6/14/01
Moo-Jhong Rhee, Ph.D.	Chemistry Team Leader		
Amit Mitra, Ph.D.	Chemistry Reviewer		6/15/01
Steve Langille	Microbiology Reviewer		6/15/01
Peter Cooney	Microbiology Team Leader		6/18/01
Alex Jordan, Ph.D.	Pharmacology Team Leader		6/18/01
Ameeta Parekh, Ph.D.	Clinical Pharmacology and Biopharmaceutics Team Leader		6/15/01
Kate Meaker	Biometrics Reviewer		6/15/01
Mike Welch, Ph.D.	Biometrics Team Leader		6/15/01
Terri Rumble	Chief, Project Management Staff		6/15/01
Diane Moore	Project Manager		6/25/01

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Susan Allen
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____ § 552(b)(5) Deliberative Process

____ § 552(b)(4) Draft Labeling

Minutes of Teleconference

Date: June 27, 2001 **Time:** 4:00 - 4:20 PM **Place:** Parklawn; Dr. Allen's Office

NDA: 21-258 **Drug Name:** Climarapro (estradiol/levonorgestrel transdermal delivery system) 0.045/0.015, 0.045/0.030 and 0.045/0.040 mg per day

Indications: Treatment of moderate-to-severe vasomotor symptoms (VMS) associated with menopause

Type of Meeting: Advice

External Constituent: Berlex Laboratories, Inc.

FDA Lead: Dr. Susan Allen **External Participant Lead:** Dr. June Bray

Meeting Recorder: Ms. Diane Moore

FDA Participants:
Susan Allen, M.D., M.P.H. – Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Daniel Shames, M.D. – Deputy Director, DRUDP (HFD-580)
Diane Moore - Regulatory Project Manager, DRUDP (HFD-580)

External Participants:
June Bray, Ph.D. – Vice President, Regulatory Affairs - Berlex Pharmaceuticals, Incorporated
Sharon Brown – Director Drug Regulatory Affairs - Berlex Pharmaceuticals, Incorporated
Geoffrey Millington – Regulatory Affairs - Berlex Pharmaceuticals, Incorporated
Marle Foegh, M.D. – Female Health Care, Berlex Pharmaceuticals, Incorporated
Vladimir Yankov, M.D. – Female Health Care, Berlex Pharmaceuticals, Incorporated

Meeting Objective: To convey comments regarding the status of the review for Climarpro (estradiol and levonorgestrel) transdermal system.

Background: March 26, 2001, teleconference and subsequent March 30, 2001, submission from Berlex Pharmaceuticals in response to the Agency's request for additional information to support the sponsor's position regarding the source documents for Studies 96042A and 96043A.

Discussion Items:
- Study 96043 supported the — however, the review of the entire NDA resulted in a nonapproval recommendation based on clinical and chemistry deficiencies
- the main clinical deficiency in the application was a lack of source documents (protocol-specified worksheets for daily recording of hot flushes and weekly recording of urogenital symptoms) in both Study 96042 and 96043 for the VMS — protocols for these studies specified that written worksheets would be used to collect data on these symptoms during the baseline/run-in period of the study while volunteers learned to use the Interactive Voice Response System (IVRS);

original source data should have included the participant-completed worksheets as well as entries into the IVRS

- the Division of Scientific Investigations (DSI) inspected three of seven investigator sites and determined that this source data was not available at any of the three sites and thus the data could not be used to support the NDA; this caused concern regarding the validity of the rest of all the study data
- the March 30, 2001, submission included a May 1998, memo from — to the study investigators that suggested that the worksheet given to the study subjects was not a source document; this memo had not previously been submitted to the associated IND for comment or concurrence by the Agency; this documentation was not included in the original study protocol, nor was it submitted in any subsequent protocol amendments; the Agency was not notified of this protocol change prior to the March 26, 2001, teleconference
- in Section 5.5.2 and 5.5.3 of the Protocol, subjects were supplied with up to four weeks of worksheets to collect data on VMS and urogenital symptoms during the study run-in period; the subjects were reminded to record the data on the worksheets provided; data also collected in the IVRS system was not stated as primary source documentation; it is difficult to consider the baseline data valid in light of the DSI inspection findings and the wording in the protocol
- the additional information submitted on April 6, 2001, was reviewed; the arguments made therein were assessed and it was determined that the arguments presented did not address the Agency's concerns regarding the lack of source data for Studies 96042 and 96043; the Agency did not have any subsequent information requests of the sponsor; the issues noted were also discussed; the issues were discussed with the Office prior to a decision being made on this application

Decisions:

- the sponsor should perform a 12-week VMS study that includes the lowest dose of product from Study 96043A (4.4 mg estradiol and 1.3 mg levonorgestrel); an additional study for endometrial protection is not needed; it is recommended that the protocol for the study be discussed with the Division prior to study initiation
- the Division does not object to the use of the IVRS system in an appropriately designed study; the problem for this application was the inability to validate the study data due to missing source documents; the source documentation for baseline VMS and urogenital symptoms is important for determining efficacy and safety of the reviewed product; any new study that incorporates the IVRS system should state the use of the IVRS system in the protocol; additional guidelines for a DSI audit of electronic data can be given when the protocol is submitted; the data should be auditable and verifiable
- the DMF — is not adequate to support approval of the NDA; the sponsor was referred to the DMF holder for details on specific deficiencies to be addressed; it was noted that any submissions received late in the review cycle may be held for review during the subsequent review cycle
- labeling comments regarding the Climarapro NDA are deferred to the next review cycle
- regarding the tradename, the Office of Drug Risk Assessment (OPDRA) does not find the proposed tradename (Climarapro) to be acceptable; review of the June 19, 2001, submission regarding the tradename is deferred to the next review cycle

Action Items

• **Item**	**Responsible Person:**	**Due Date:**
• send Telecon minutes to sponsor	DRUDP	July 15, 2001

{See appended electronic signature page}

Signature, minutes preparer

{See appended electronic signature page}

Signature, Chair

Note to sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

drafted: dm/7.5.01/N21258TC62701.doc
Concurrence:
T.Rumble 7.6.01/D.Shames 7.9.01/S.Allen 7.23.01

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/s/

Diane V. Moore
7/24/01 10:51:35 AM

Susan Allen
7/24/01 03:37:16 PM

Minutes of Teleconference

Date: June 15, 2001 **Time:** 11:00 - 11:15 AM **Place:** Parklawn; Ms. Moore's Office

NDA: 21-258 **Drug Name:** Climarapro (estradiol/levonorgestrel transdermal delivery system) 0.045/0.015, 0.045/0.030 and 0.045/0.040 mg per day

Indications: Treatment of moderate-to-severe vasomotor symptoms associated with menopause

Type of Meeting: Clinical Pharmacology and Biopharmaceutics

External Constituent: Berlex Laboratories, Inc.

FDA Lead: Diane Moore

Meeting Recorder: Ms. Diane Moore

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

External Participants:
Sharon Brown – Director Drug Regulatory Affairs - Berlex Pharmaceuticals, Incorporated

Meeting Objective: To convey clinical pharmacology and biopharmaceutics comments regarding the calculation of transdermal delivery rate (TDR).

Discussion Items:

- the following comments were conveyed to the sponsor:
  - The concentration at the end of the dosage interval is not always the same as the minimum concentration. When minimum concentration is appropriate to be reported (i.e., as for the formulation in this NDA) then the true minimum should be reported.
  - The calculation of transdermal delivery rate (TDR) should have been calculated based on system depletion. For estradiol, the accuracy and precision of the assay should be sufficient to obtain accurate depletions in spite of the fact that the amount depleted represents a small fraction of the total amount in the patch. A review of protocol 97067 and letter to the sponsor dated November 28, 1997, co-signed by Dr. Dorantes, recommended use of the system depletion method. This was the Agency's most recent communication regarding this issue and was received prior to beginning studies examining TDR in January 1999. Consequently, the sponsor should have used the system depletion method regardless of any prior communications.

Decisions:

- the calculations submitted to this NDA were considered to be adequate; no further action is needed regarding this issue for this NDA; however, the above comments should be considered for future applications

Action Items

• **Item**	**Responsible Person:**	**Due Date:**
• send Telecon minutes to sponsor	DRUDP	July 15, 2001

{See appended electronic signature page}

Signature, minutes preparer

Note to sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

drafted: dm/6.15.01/N21258TC61501.doc

Concurrence:
T.Rumble 6/15/01

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/s/

Diane V. Moore
6/15/01 12:07:36 PM

Meeting Minutes

Date: May 15, 2001 **Time:** 10:30 - 11:30 AM **Place:** Parklawn; Room 17B-45

NDA: 21-258 **Drug Name:** Climarapro (estradiol/levonorgestrel transdermal delivery system) 0.045/0.015, 0.045/0.030 and 0.045/0.040 mg per day

Indications: Treatment of moderate-to-severe vasomotor symptoms (VMS) associated with menopause

Type of Meeting: 10-Month Status/Labeling

Sponsor: Berlex Laboratories, Inc.

FDA Lead: Dr. Daniel Shames

Meeting Recorder: Ms. Diane Moore

FDA Participants:
Daniel Shames, M.D., – Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Shelley Slaughter, M.D., Ph.D. – Team Leader, DRUDP (HFD-580)
Phill Price, M.D. - Medical Officer, DRUDP (HFD-580)
Terri Rumble – Chief, Project Management Staff, DRUDP (HFD-580)
Diane Moore - Regulatory Project Manager, DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Amit Mitra, Ph.D. - Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580) @ DRUDP (HFD-580)
Ron Kavanagh, B.S. Pharm., Pharm.D., Ph.D. – Pharmacokinetics reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB)
Kate Meaker, M.S. - Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)

Meeting Objective: To discuss the status of reviews for NDA 21-258.

Background: The NDA was submitted on June 29, 2000. The 10-month goal date is April 29, 2001. The 12-month user fee date is June 29, 2001. This NDA will be reviewed on a 12-month clock (user fee date).

Decisions:
- Regulatory
  - the reviews should be completed by June 7, 2001 in order to give the Clinical Team Leader enough time to review the Action Package and complete the secondary review; the Action Package should be given to the Deputy Director by June 14, 2001
  - discussion of labeling will be deferred to the next review cycle
- Clinical
  - review pending

- safety update has been submitted for review
- the clinical data obtained from the IVRS system will not be accepted in support of the VMS indications as the protocol did not accurately reflect the procedure used by the investigators; worksheets containing baseline data are missing from the studies; reference for future trials can be made to the Guidance for Industry entitled, "Computerized Systems Used in Clinical Trials," dated April 1999, which outlines acceptable practices for electronic data collection
- the Medical Officer is currently reviewing patient data from the endometrial protection study to see if the study is acceptable

- DSI
  - review complete; recommend that the data in Study 96042A not be used to support approval
- Chemistry, Manufacturing and Quality Control
  - additional chemistry data was requested from the sponsor and DMF holder in two regulatory letters dated May 9, 2001; if the requested data is not received by the completion of the review, the deficiency comments will be ranked according to approvability; data received after completion of the chemistry review will be deferred to the next review cycle
  - chemistry reviewer does not agree with the comments in the review from OPDRA regarding the insert labeling; the suggestion tha
  - the method validation for related products was not performed according to ICH guidelines; a satisfactory response regarding the method validation must be received or this may be an approvability issue
  - Tradename
    - although there is precedence with adding the suffix "pro" to the end of a previously approved tradename to indicate the addition of a progestin, it was felt that if any signal exists for misinterpretation of a drug name, it would be better to address the concern at this stage than to address a change of tradename once a drug has been approved and marketed; the Division does not have a significant justification to override the OPDRA recommendation to not accept the tradename "Climarapro"; the sponsor will be notified of the tradename decision in the action letter
  - Microbiology
    - review complete, recommending approval
- Pharmacology
  - review complete, recommending approval
- Clinical Pharmacology and Biopharmaceutics
  - review complete, recommending approval; secondary review pending
  - the sponsor clarified that the placebo systems in the adhesion study are identical to the active transdermal systems
  - there are deficiencies with dissolution, *in vivo-in vitro* correlation, bioequivalence between strengths, and transdermal delivery rates
- Statistics
  - review pending

Action Items

• **Item:**	**Responsible Party:**	**Due Date:**
• inform DDMAC that no labeling review is needed for this first review cycle	Ms. Moore	1-week
• inform OPDRA that no safety meeting will be held for this application	Ms. Moore	1-week

Signature, minutes preparer

Signature, Chair

drafted: dm/5.17.01/N2125810MSM51501.doc

Concurrence:

T.Rumble 5.18.01/P.Price, D.Shames, K.Meaker 5.22.01/M.Rhee 5.23.01
S.Slaughter, A.Mitra 5.24.01/R.Kavanagh 6/1/01

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/s/

Diane V. Moore
6/4/01 02:09:25 PM

Daniel A. Shames
6/6/01 05:09:36 PM

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

____ § 552(b)(5) Deliberative Process

____ § 552(b)(4) Draft Labeling

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-258

DISCIPLINE REVIEW LETTER

Berlex Laboratories, Inc.
Attention: Geoffrey Millington
Manager, Drug Regulatory Affairs
340 Changebridge Road
P.O. Box 1000
Montville, NJ 07450-1000

Dear Mr. Millington:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for estradiol/levonorgestrel transdermal system, 0.045 mg/0.015 mg per day, 0.045 mg/0.030 mg per day, and 0.045 mg/0.040 mg per day.

We also refer to your submissions dated July 19 and August 8, 2000.

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

1. The DMF — is not adequate to support the NDA.

2. The storage condition in the pouch and carton labels should be revised to "Store at — 25°C (excursion permitted 15-30°C)." The inactive component should include polyethylene backing, and polyester release liner.

3. Please correct the error on the carton label as follows: "contains X mg estradiol USP and X levonorgestrel USP per day" to "contains X mg estradiol, USP and X mg levonorgestrel, USP per transdermal system"

4. The standard storage statement in the **HOW SUPPLIED** section should be revised to: "Store at — 25°C (77°F), excursions permitted to 15-30° C (59-86°F)."

5. Since the drug product when disposed would contain a large quantity of the residual drug, it may pose a hazard by accidental use. Please provide a disposal procedure for the transdermal patch in the **HOW SUPPLIED** section.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and

subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

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

Sincerely,

{See appended electronic signature page}

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

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/s/

Moo-Jhong Rhee
5/9/01 01:53:47 PM

F

5 Page(s) Withheld

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

1 § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

Meeting Minutes

Date: April 16, 2001 **Time:** 10:00 - 10:30 AM **Place:** Parklawn; Room 17B-45

NDA: 21-258 **Drug Name:** Climarapro (estradiol/levonorgestrel transdermal delivery system) 0.045/0.015, 0.045/0.030 and 0.045/0.040 mg per day

Indications: Treatment of moderate-to-severe vasomotor symptoms (VMS) associated with menopause

Type of Meeting: 9-Month Status

Sponsor: Berlex Laboratories, Inc.

FDA Lead: Dr. Daniel Shames

Meeting Recorder: Ms. Diane Moore

FDA Participants:
Daniel Shames, M.D., – Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Shelley Slaughter, M.D., Ph.D. – Team Leader, DRUDP (HFD-580)
Phill Price, M.D. - Medical Officer, DRUDP (HFD-580)
Terri Rumble – Chief, Project Management Staff, DRUDP (HFD-580)
Diane Moore - Regulatory Project Manager, DRUDP (HFD-580)
Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Lisa Stockbridge, Ph.D. - Regulatory Reviewer, Division of Drug Marketing, Advertising and Communications (DDMAC; HFD-42)

Meeting Objective: To discuss the status of reviews for NDA 21-258.

Background: The NDA was submitted on June 29, 2000. The 10-month goal date is April 29, 2001. The 12-month user fee date is June 29, 2001. This NDA will be reviewed on a 12-month clock (user fee date).

Decisions:
- Clinical
  - review pending
  - the data from the endometrial hyperplasia studies appears to be appropriate and can be reviewed in support of a there have not been any hyperplasias noted up to this point in the review
  - safety update should be submitted for review
  - the data from the study in support of the VMS trial (Study 96042A) are in question as source documents are not available for validation of these data; the VMS indication may not be supported

-

- DSI
  - review complete; recommend the data for vasomotor symptom trial not be relied upon in support of the VMS indication because no source documents were available to validate the data at the study centers that were inspected
- Regulatory
  - the safety data has been requested from the sponsor
- Chemistry, Manufacturing and Quality Control
  - additional chemistry data will be requested from the sponsor
- Pharmacology
  - both drugs in the application have been approved independently; a 28-day toxicology study review for qualification of degradation products is pending
- Clinical Pharmacology and Biopharmaceutics
  - review pending
  - the sponsor should clarify whether the placebo systems in the adhesion study are identical to the active transdermal systems
- Statistics
  - review pending

Action Items

• **Item:**	**Responsible Party:**	**Due Date:**
• check with Office on the acceptance of only electronic data collection for this NDA	Dr. Shames	1 month
• request clarification on identity of systems in the adhesion study	Ms. Moore	1-2 weeks
• contact sponsor for safety update submission	Ms. Moore	1-week
• request additional chemistry data from sponsor	Dr. Mitra	1-2 weeks

Signature, minutes preparer

Signature, Chair

drafted: dm/2.24.01/N21258SM21301.doc

Post Meeting Addendum: On April 16, 2001, the project manager requested clarification with the sponsor on whether the placebo system and active system used in the adhesion study were identical. The sponsor verified that the two systems were identical. The sponsor was also requested to provide the safety update for the NDA.

Concurrence:

T.Rumble 5.2.01/P.Price 5.3.01/S.Shames 5.11.01/S.Slaughter 5.17.01

No response was received from A.Parekh, L.Stockbridge

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/s/

Diane V. Moore
5/21/01 04:13:46 PM

Daniel A. Shames
5/24/01 04:37:05 PM

Division of Reproductive and Urologic Drug Products

ADMINISTRATIVE REVIEW OF APPLICATION

Application Number: **NDA 21-258**

Name of Drug: **Climarapro™ (estradiol/levonorgestrel transdermal system) 0.045/0.015, 0.045/0.030, and 0.045/0.040 mg/day**

Sponsor: **Berlex Laboratories, Inc.**

Material Reviewed: **NDA volumes**

Submission Date: **June 29, 2000**

Receipt Date: **June 29, 2000**

Filing Date: **August 28, 2000**

User-Fee Goal Date(s): **April 29, 2001, June 29, 2001**

Proposed Indication: **Treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause**

Other Background Information: Associated IND: IND 51,188
— Type II DMF —

Review

PART I: OVERALL FORMATTING[a]

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

	Y	N	COMMENTS (list volume & page numbers)
1. Cover Letter (original signature)	X		Vol. 1.1, Page 2
2. Form FDA 356h (original signature)	X		Vol. 1.1
a. Reference to DMF(s) & Other Applications	X		on FORM FDA 356h and June 16, 2000 letter in Vol. 1.1
3. Patent information & certification	X		Vol. 1.1, Page 2-3.
4. Debarment certification (note: must have a definitive statement)	X		Vol. 1.1, Page 5

5. Financial Disclosure	X		Vol. 1.1, Page 12-13
6. Comprehensive Index	X		Vol. 1.1, Page 14-22
7. Pagination	X		throughout
8. Summary Volume	X		Volume 1.2
9. Review Volumes	X		
10. Labeling (PI, container, & carton labels)	X		Vol. 1, Page 23-57
a. unannotated PI	X		Vol. 1.1, Page 23-48
b. annotated PI	X		Vol. 1.2, Page 6-25
c. immediate container	X		Vol. 1, Page 50-51, 53-54 and 56-57
d. carton	X		Vol. 1, page 49, 52 and 55
e. foreign labeling (English translation)		X	Not applicable, no foreign marketing for this product
11. Foreign Marketing History		X	no foreign marketing of this product (Vol. 1.2, page 27)
12. Case Report Tabulations (CRT) (paper or electronic) (by individual patient data listing or demographic)	X		electronic CRT
13. Case Report Forms (paper or electronic) (for death & dropouts due to adverse events)	X		electronic CRT

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

PART II: SUMMARY[b]

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

	Y	N	COMMENTS (list volume & page numbers)
1. Pharmacologic Class, Scientific Rationale, Intended Use, & Potential Clinical Benefits	X		Vol. 1.1, Page 26
2. Summary of Each Technical Section			
a. Chemistry, Manufacturing, & Controls (CMC)	X		Vol. 1.2, Page 28
b. Nonclinical Pharmacology/Toxicology	X		Vol. 1.2, page 29-37
c. Human Pharmacokinetic & Bioavailability	X		vol. 1.2, page 39-56
d. Microbiology		X	N/A, Vol. 1.2, Page 57
e. Clinical Data & Results of Statistical Analysis	X		Vol. 1.2, Page 58
3. Discussion of Benefit/Risk Relationship & Proposed Postmarketing Studies	X		Vol. 1.2, Page 174 – 180
4. Summary of Safety	X		Vol. 1.2, Page 162
5. Summary of Efficacy	X		Vol. 1.2, Page 174

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

PART III: CLINICAL/STATISTICAL SECTIONS[c]

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

	Y	N	COMMENTS (list volume & page numbers)
1. List of Investigators	X		Vol. 1.2, Page 22-52
2. Controlled Clinical Studies	X		Volume 3.2, pages 01A, 01B
a. Table of all studies	X		Vol. 1.2, Page 3-21
b. Synopsis, protocol, related publications, list of investigators, & integrated clinical & statistical report for each study (including completed, ongoing, & incomplete studies)			Vol. 4.2 Vol. 3.2, Page 01B
c. Optional overall summary & evaluation of data from controlled clinical studies	X		Vol. 1.2, Pages 58-80
3. Integrated Summary of Efficacy (ISE)	X		Vol. 4.3- 5.8, Page 1
4. Integrated Summary of Safety (ISS)	X		Vol. 5.9-6.7, Page 1
5. Drug Abuse & Overdosage Information	X		Vol. 6.8, Page 375
6. Integrated Summary of Benefits & Risks of the Drug	X		Vol. 6.8, Page 377
7. Gender/Race/Age Safety & Efficacy Analysis Studies	X		Vol. 1.47

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

PART IV: MISCELLANEOUS

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

	Y	N	COMMENTS (list volume & page numbers)
1. Written Documentation Regarding Drug Use in the Pediatric Population		X	Waiver requested in July 31, 2001, submission.
2. Diskettes	X		
a. Proposed unannotated labeling in MS WORD 8.0	X		electronic file
b. Stability data in SAS data set format		X	
c. Efficacy data in SAS data set format		X	
d. Biopharmacological information & study summaries in MS WORD 8.0		X	(paper in Vol. 1.2 page 362-429)
e. Animal tumorigenicity study data in SAS data set format		X	
3. User-fee payment receipt	X		Vol. 1, Page 11

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

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

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

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

Additional Comments:
Compliance of Good Clinical Practices Vol. 1.2, Page 54 and Vol. 29, Page 54
Helsinki agreement, Vol. 1.2, page 55

Conclusions: Fileable from a regulatory perspective.

_____
Regulatory Health Project Manager

_____
Concurrence

cc:
Original NDA 21-258
HFD-580/Div. Files
HFD-580/PM/DMoore/TRumble
HFD-580/Allen/Shames
HFD-580/Reviewers
draft: dm/July 17, 2000
final: May 15, 2001

ADMINISTRATIVE REVIEW

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/s/

Diane V. Moore
5/15/01 05:17:44 PM
CSO

Terri F. Rumble
5/16/01 10:23:11 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Moore

Food and Drug Administration
Rockville MD 20857

APR - 5 - ..

Susan Savage, M.D.
7720 South Broadway, Suite 330
Littleton, Colorado 80122

Dear Dr. Savage:

Between November 14 and December 14, 2000, Ms. Kelly Moore, representing the Food and Drug Administration (FDA), met with you to review your conduct of clinical studies (Protocol 96042A, A Multicenter, Double-Blind, Placebo-Controlled, Randomized Study to Determine Efficacy in the Relief of Hot Flushes in Women Receiving Transdermal Estradiol-Levonorgestrel Combinations, and Protocol 96043A, A Multicenter, Double-Blind, Randomized Study of Continuous Transdermal Estradiol-Levonorgestrel Combinations Compared to Continuous Transdermal Estradiol, to Examine the the Safety and Effect of the Endometrium, Symptoms and Bleeding Patterns in Postmenopausal Women) of the investigational drug, Climarapro™ (17β-estradiol-levonorgestrel combination transdermal system), performed for Berlex Laboratories. 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 our evaluation of the inspection report and the documents submitted with that report, we conclude that there were deviations from pertinent Federal regulations and/or good clinical investigational practices governing the conduct of clinical investigations and the protection of human subjects. We note that at the conclusion of the inspection, Ms. Moore presented and discussed with you the items listed on Form FDA 483, Inspectional Observations. We recognize that you were the principal investigator for only a portion of this study. We wish to emphasize the following:

In violation of 21 CFR 312.62(b), you failed to maintain adequate and accurate records. For both protocols, you failed to maintain protocol-specified worksheets which were required to document the number and severity of hot flushes (the primary efficacy endpoint for Study 96042A) and the occurrence of urogenital symptoms.

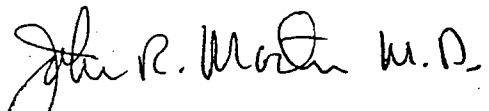
You did not report a diagnosis of simple endometrial hyperplasia made on July 21, 1999, for subject #8010 as an adverse event on the case report form (CRF) for the fifth visit. Also, subject # 8018 experienced bleeding, cramps, and breast tenderness and reported these adverse events via telephone on — these were not listed on the CRF for the fifth visit dated August 9, 1999.

Also, the endometrial biopsy for subject # 8017, which, according to the diagnostic report, was performed on — was reported on the CRF as having been performed on —

You are responsible for conducting clinical studies in compliance with applicable protocols and regulations as you have agreed by signing the Form FDA 1572. Because of the nature of the violations of FDA regulations discussed above, we request that you inform this office, in writing, of the actions you have taken or plan to take to assure that the findings noted above are not repeated in any ongoing or future studies and to bring your procedures into compliance with FDA regulations.

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

Sincerely yours,



John R. Martin, M.D.
Branch Chief
Good Clinical Practice I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Suite 103
Rockville, MD 20855

cc:
HFA-224
HFD-510/Doc. Rm.: NDA 21-258
HFD-580/Moore
HFD-580/Price
HFD-45/Reading File
HFD-46/Chron File
HFD-46/GCP file #10292
HFD-46/Blay
HFD-46/Martin
HFR-SW250/Singleton
HFR-SW250/Sherer
HFR-SW250/Moore

Field Classification: VAI
Headquarters Classification:

_____1)NAI
_____2)VAI (no response required)
__x__3)VAI-R (response requested)
_____4)VAI-RR (adequate response received)
_____5)OAI-WL

Deficiencies noted:

____inadequate consent form
____inadequate drug accountability
____deviation from protocol
__x__inadequate records
____failure to report ADRs
____failure to obtain IRB approval
____failure to personally conduct or supervise study
____other

O:/blay/moore.rab
r/d: drafted/rab/3.6.01
reviewed:jrm:4/2/01
final type:jau:4/4/01

Note to Review Division:

Based on our review of the information provided to us regarding the inspection of this clinical investigator, DSI recommends that data at this site which was to be collected on worksheets not be accepted for use in support of the NDA submission. These protocol-specified worksheets which were required to document the number and severity of hot flushes (including the primary efficacy endpoint for Study 96042A) and the occurrence of urogenital symptoms were unavailable for review.

Our final classification of this inspection is Voluntary Action Indicated-Response Requested (VAI-R).

Minutes of Teleconference

Date: April 2, 2001 **Time:** 3:00 - 3:15 PM **Place:** Parklawn; Room 17B-45

NDA: 21-258 **Drug Name:** Climarapro (estradiol/levonorgestrel transdermal delivery system) 0.045/0.015, 0.045/0.030 and 0.045/0.040 mg per day

Indications: Treatment of moderate-to-severe vasomotor symptoms associated with menopause

Type of Meeting: Clinical Guidance

External Constituent: Berlex Laboratories, Inc.

FDA Lead: Dr. Daniel Shames

Meeting Recorder: Ms. Diane Moore

FDA Participants:
Daniel Shames, M.D., – Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Kim Colangelo – Senior Regulatory Associate, DRUDP (HFD-580)
Diane Moore - Regulatory Project Manager, DRUDP (HFD-580)

External Participants:
Geoffrey Millington – Regulatory Affairs - Berlex Pharmaceuticals, Incorporated

Meeting Objective: To discuss the IVRS system used in capturing the data for NDA 21-258.

Background: On March 30, 2001, Berlex Pharmaceuticals sent via telefacsimile, a response to the Division's March 23, 2001, request for additional data to clarify the use of the IVRS system. The sponsor provided an information packet describing the IVRS system and procedures, a memo to the investigators, a sample subject worksheet and a sample study initiation visit report.

Discussion Items:
- Berlex referred to a meeting with the Division on October 24, 1997, where Protocol 97036, to study PMS, was discussed under IND 53,905; the protocol procedure was described using a Calendar of Premenstrual Experiences (COPE) scale and the IVRS system; the data that is entered into the computer via telephone each day needs to be clarified
- the system identifies the study subjects using a pin number that has 6 digits assigned by the center and 4 digits chosen by the patient which are unknown by the center
- the type of security system that is in place should be described
- it was noted by the sponsor that the number of events decreased as time went on during the study

Decisions:
- additional information is needed regarding the audit trail to track all changes in the database

- the volume of changes made to the database should be characterized
- the manner in which the data is audited or verified should be explained
- the sponsor will respond with additional data to clarify the use of the IVRS system by the end of the week

Action Items

• Item	Responsible Person:	Due Date:
• submit further explanation of IVRS system	Berlex Laboratories, Inc	April 6, 2001
• send Telecon minutes to letter to sponsor	DRUDP	May 2, 2001

Signature, minutes preparer

Signature, Chair

Post Meeting Addendum: On April 6, 2001, Berlex Laboratories, Inc. submitted additional information regarding the IVRS system for studies 96042A and 96043A for review.

drafted: dm/4.6.01/N21258TC4201.doc

Concurrence:
J.Best 4.9.01/K.Colangelo 4.10.01/D.Shames 4.19.01

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/s/

Diane V. Moore
4/19/01 05:01:10 PM

Daniel A. Shames
4/20/01 10:51:12 AM

Minutes of Teleconference

Date: March 26, 2001 **Time:** 11:00 - 11:30 AM **Place:** Parklawn; Room 17B-45

NDA: 21-258 **Drug Name:** Climarapro (estradiol/levonorgestrel transdermal delivery system) 0.045/0.015, 0.045/0.030 and 0.045/0.040 mg per day

Indications: Treatment of moderate-to-severe vasomotor symptoms associated with menopause

Type of Meeting: Clinical Guidance

External Constituent: Berlex Laboratories, Inc.

FDA Lead: Dr. Daniel Shames

Meeting Recorder: Ms. Diane Moore

FDA Participants:
Daniel Shames, M.D., – Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Phill Price, M.D. - Medical Officer, DRUDP (HFD-580)
Kim Colangelo – Senior Regulatory Associate, DRUDP (HFD-580)
Jeanine Best, MSN, RN – Project Manager, DRUDP (HFD-580)
Diane Moore - Regulatory Project Manager, DRUDP (HFD-580)
Kate Meaker, M.S. - Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
John Martin, M.D. - Division of Scientific Investigations, Branch Chief, Good Clinical Practices Branch I (CIB; HFD-46)
Roy A. Blay, Ph.D.- Senior Regulatory Review Officer, DSI, GCP Branch I (CIB; HFD-46)

External Participants:
Berlex Pharmaceuticals, Incorporated
Anthony Badalamenti- Biostatistics
Sharon Brown – Regulatory Affairs
Wolfgang Eder – Project Management
Marle Foegh – Female Health Care
Geoffrey Millington – Regulatory Affairs
Vladimir Yankov – Female Health Care

Meeting Objective: To discuss the status of reviews for NDA 21-258.

Background: On March 21, 2001, the Division of Reproductive and Urologic Drug Products requested a teleconference with representatives from Berlex Laboratories, Inc. and — to discuss the collection of the study data for the pivotal study for NDA 21-258.

Discussion Items:

- the Division of Scientific Investigations (DSI) inspected three sites from the pivotal studies for the NDA; during those inspections, it was noted that protocol-specified (Protocol 96042, sections 5.5.2, 5.5.3) Worksheets used by the study subjects for the pivotal studies (note: also specified in Protocol 96043) were not available at any of the three study sites; therefore, the data from these Worksheet source documents, entered into the database via the telephone could not be validated
- the sponsor noted that the patients were instructed to input the data daily into the IVRS telephone system and that the Worksheets were not supposed to be source documents; the Worksheets were intended to be merely an aid for the study participants, but their use was not required; the IVRS data was intended to be the primary data; the subjects used a password when they called the IVRS system to input the data
- the Division noted that the protocols included statements that paper listings and computer files will be generated (see Protocol 96042, Data Handling, Section 5.2.6.2)
- the sponsor noted that the Worksheets were used as a screening document for use as an enrollment log to keep track of which patients were entered into the study; they maintained that a Worksheet is different from an enrollment log
- the Division further noted that the protocol states that all data accumulated would be maintained
- the sponsor acknowledged that there are places in the protocol that implies the Worksheet would be a source document, however, that was changed over time; a letter dated July 22, 1998, that was sent to the investigator site informed the investigator(s) that the Worksheet was not considered to be a source document (see telefacsimilie dated March 23, 2001)
- the sponsor acknowledged that neither a copy of the letter to the investigators, nor clarification regarding the status of the Worksheet was submitted to the Agency in a protocol amendment
- the Division noted that the letter included in the March 23, 2001, telefacsimilie does not instruct the investigators to tell study subjects that the Worksheet is not needed
- according to the list of items included on the Worksheet (see March 23, 2001 telefacsimilie), the patients were expected to recall the number of hot flushes they had during the day and whether their hot flushes were mild, or moderate, or severe along with other symptomatology at the end of the day when they called the IVRS system
- the sponsor said that the Worksheets were not collected from the patients by the investigation site or inspected by — the information packet was silent on what to do with the Worksheets

Decisions:

- written data on a daily basis for a study is a source document
- the sponsor will respond with additional data to clarify the use of the IVRS system by the end of the week

Action Items

• Item	Responsible Person:	Due Date:
• submit further explanation of IVRS system	Berlex Laboratories, Inc	March 30, 2001
• send Telecon minutes to letter to sponsor	DRUDP	April 26, 2001

Signature, minutes preparer

Signature, Chair

drafted: dm/3.31.01/N21258TC32601.doc

Concurrence:

J.Best, K.Meaker, R.Blay, D.Shames, J.Martin 04.02.01/K.Colangelo 4.5.01/P.Price 4.19.01

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/s/

Diane V. Moore
4/19/01 01:45:34 PM

Daniel A. Shames
4/20/01 10:42:12 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MAR - 7 2001

Enrique deCastro, M.D.
Northwest Women's Clinic
2222 N.W. Lovejoy, Suite 619
Portland, Oregon 97210

Dear Dr. deCastro :

Between November 27 and December 5, 2000, Mr. James Henry, representing the Food and Drug Administration (FDA), met with you to review your conduct of clinical studies (Protocol 96042A, A Multicenter, Double-Blind, Placebo-Controlled, Randomized Study to Determine Efficacy in the Relief of Hot Flushes in Women Receiving Transdermal Estradiol-Levonorgestrel Combinations, and Protocol 96043A, A Multicenter, Double-Blind, Randomized Study of Continuous Transdermal Estradiol-Levonorgestrel Combinations Compared to Continuous Transdermal Estradiol, to Examine the the Safety and Effect of the Endometrium, Symptoms and Bleeding Patterns in Postmenopausal Women) of the investigational drug, Climarapro™ (17β-estradiol-levonorgestrel combination transdermal system), performed for Berlex Laboratories. 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 our evaluation of the inspection report and the documents submitted with that report, we conclude that there were deviations from pertinent Federal regulations and/or good clinical investigational practices governing the conduct of clinical investigations and the protection of human subjects. We note that at the conclusion of the inspection, Mr. Henry presented and discussed with you the item listed on Form FDA 483, Inspectional Observations. We wish to emphasize the following:

In violation of 21 CFR 312.62(b), you failed to maintain adequate and accurate records. For both protocols, you failed to maintain protocol-specified worksheets which were required to document the number and severity of hot flushes (the primary efficacy endpoint for Study 96042A) and the occurrence of urogenital symptoms.

You are responsible for conducting clinical studies in compliance with applicable protocols and regulations as you have agreed by signing the Form FDA 1572. Because of the nature of the violation of FDA regulations discussed above, we request that you inform this office, in writing, of the actions you have taken or plan to take to assure that this finding noted above is not repeated in any ongoing or future studies and to bring your procedures into compliance with FDA regulations.

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

Sincerely yours,

John R. Martin, M.D.
Branch Chief
Good Clinical Practice I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Suite 103
Rockville, Maryland 20855

cc:
HFA-224
HFD-510/Doc. Rm.: NDA 21-258
HFD-580/Moore
HFD-580/Price
HFD-45/Reading File
HFD-46/Chron File
HFD-46/GCP file #10274
HFD-46/Blay
HFD-46/Martin
HFR-PA350/Corcoran
HFR-PA3540/Mattson
HFR-PA3515/Henry

Field Classification: VAI
Headquarters Classification:

_____1)NAI
_____2)VAI (no response required)
__x__3)VAI-R (response requested)
_____4)VAI-RR (adequate response received)
_____5)OAI-WL

The record-keeping deficiency is substantial; therefore, a response is requested from the clinical investigator on how this deficiency will be avoided in future studies.

Deficiencies noted:

_____inadequate consent form
_____inadequate drug accountability
_____deviation from protocol
__x__inadequate records
_____failure to report ADRs
_____failure to obtain IRB approval
_____failure to personally conduct or supervise study
_____other

O:/blay/decastro.rab
r/d: drafted/rab/3.5.01
reviewed:jrm:3/6/01
final type:jau:3/6/01

Note to Review Division:

Based on our review of the information provided to us regarding the inspection of this clinical investigator, DSI recommends that the data at this site which was to be collected on worksheets not be accepted for use in support of the NDA submission. These protocol-specified worksheets which were required to document the number and severity of hot flushes (the primary efficacy endpoint for Study 96042A) and the occurrence of urogenital symptoms were unavailable for review.

Our final classification of this inspection is Voluntary Action Indicated-Response Requested (VAI-R).

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MAR - 7 2001

Julian L. Peskin, M.D.
29001 Cedar Road
Lyndhurst, Ohio 44124

Dear Dr. Peskin:

Between December 1 and December 8, 2000, Mr. Stephen Kilker, representing the Food and Drug Administration (FDA), met with you to review your conduct of clinical studies (Protocol 96042A, A Multicenter, Double-Blind, Placebo-Controlled, Randomized Study to Determine Efficacy in the Relief of Hot Flushes in Women Receiving Transdermal Estradiol-Levonorgestrel Combinations, and Protocol 96043A, A Multicenter, Double-Blind, Randomized Study of Continuous Transdermal Estradiol-Levonorgestrel Combinations Compared to Continuous Transdermal Estradiol, to Examine the the Safety and Effect of the Endometrium, Symptoms and Bleeding Patterns in Postmenopausal Women) of the investigational drug, Climarapro™ (17β-estradiol-levonorgestrel combination transdermal system), performed for Berlex Laboratories. 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 our evaluation of the inspection report and the documents submitted with that report, we conclude that there were deviations from pertinent Federal regulations and/or good clinical investigational practices governing the conduct of clinical investigations and the protection of human subjects. We note that at the conclusion of the inspection, Mr. Kilker presented and discussed with you the item listed on Form FDA 483, Inspectional Observations. We wish to emphasize the following:

In violation of 21 CFR 312.62(b), you failed to maintain adequate and accurate records. For both protocols, you failed to maintain protocol-specified worksheets which were required to document the number and severity of hot flushes (the primary efficacy endpoint for Study 96042A) and the occurrence of urogenital symptoms.

You are responsible for conducting clinical studies in compliance with applicable protocols and regulations as you have agreed by signing the Form FDA 1572. Because of the nature of the violation of FDA regulations discussed above, we request that you inform this office, in writing, of the actions you have taken or plan to take to assure that this finding noted above is not repeated in any ongoing or future studies and to bring your procedures into compliance with FDA regulations.

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

Sincerely yours,

John R. Martin, M.D.
Branch Chief
Good Clinical Practice I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Suite 103
Rockville, Maryland 20855

cc:
HFA-224
HFD-510/Doc. Rm.: NDA 21-258
HFD-580/Moore
HFD-580/Price
HFD-45/Reading File
HFD-46/Chron File
HFD-46/GCP file #10262
HFD-46/Blay
HFD-46/Martin
HFR-CE450/Heppe
HFR-CE450/Eastham
HFR-CE4525/Kilker

Field Classification: Referred to Center
Headquarters Classification:

_____1)NAI
_____2)VAI (no response required)
__x__3)VAI-R (response requested)
_____4)VAI-RR (adequate response received)
_____5)OAI-WL

Deficiencies noted:

____inadequate consent form
____inadequate drug accountability
____deviation from protocol
__x__inadequate records
____failure to report ADRs
____failure to obtain IRB approval
____failure to personally conduct or supervise study
____other

O:/blay/peskin.rab
r/d: drafted/rab/3.5.01
reviewed:jrm:3/6/01
final type:jau:3/6/01

Note to Review Division:

Based on our review of the information provided to us regarding the inspection of this clinical investigator, DSI recommends that data at this site which was to be collected on worksheets not be accepted for use in support of the NDA submission. These protocol-specified worksheets which were required to document the number and severity of hot flushes (including the primary efficacy endpoint for Study 96042A) and the occurrence of urogenital symptoms were unavailable for review.

Our final classification of this inspection is Voluntary Action Indicated-Response Requested (VAI-R).

Meeting Minutes

Date: February 6, 2001 **Time:** 11:00 - 11:30 AM **Place:** Parklawn; Room 17B-45

NDA: 21-258 **Drug Name:** Climarapro (estradiol/levonorgestrel transdermal delivery system) 0.045/0.015, 0.045/0.030 and 0.045/0.040 mg per day

Indications: Treatment of moderate-to-severe vasomotor symptoms associated with menopause

Type of Meeting: 7-Month Status

Sponsor: Berlex Laboratories, Inc.

FDA Lead: Dr. Daniel Shames

Meeting Recorder: Ms. Diane Moore

FDA Participants:
Daniel Shames, M.D., – Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Shelley Slaughter, M.D., Ph.D. – Team Leader, DRUDP (HFD-580)
Phill Price, M.D. - Medical Officer, DRUDP (HFD-580)
Diane Moore - Regulatory Project Manager, DRUDP (HFD-580)
Amit Mitra, Ph.D. - Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Ron Kavanagh, B.S. Pharm., Pharm.D., Ph.D. – Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)
Kate Meaker, M.S. - Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)

Meeting Objective: To discuss the status of reviews for NDA 21-258.

Background: The NDA was submitted on June 29, 2000. The 10-month goal date is April 29, 2001. The 12-month user fee date is June 29, 2001. This NDA will be reviewed on a 12-month clock (user fee date).

Decisions:
- Clinical
  - review pending
  - there was a high dropout rate at the end of Year 1 (47%) in the endometrial protection study; the sponsor should submit a further breakdown for the reasons for not having biopsies on study subjects who dropped out of the study between 6 months and 12 months into the study (late dropouts); it should be determined how diligently the sponsor attempted to obtain end of study biopsies from these subjects
  - additional inspections may be warranted depending on the DSI report

- DSI
  - problems verifying the data in the automated system have been identified; in two centers, the data suggests that two out of three vasomotor study investigators did not perform the study according to protocol with regard to maintaining the data; source data was been destroyed after the studies were completed
- Regulatory
  - the designation of the NDA is 4S, however, this application will be signed at the Division level
- Chemistry, Manufacturing and Quality Control
  - a drug master file (DMF) is needed for the : — or chemistry and manufacturing information should be submitted on the — iiner
  - although OPDRA has objections to the trademark "Climarapro", the Division finds the name acceptable
  - an information request letter will be sent to the sponsor
- Pharmacology
  - both drugs in the application have been approved independently; a 28-day toxicology study review for qualification of degradation products is pending
- Clinical Pharmacology and Biopharmaceutics
  - review pending
  - additional pharmacokinetic parameters for the final study were requested
  - additional comments will be added to the information request letter to be sent to the sponsor
  - the sponsor should submit data to identify the transdermal deliver rate of the transdermal system
- Statistics
  - review pending

Action Items

- send IR letter to sponsor

Signature, minutes preparer

Signature, Chair

drafted: dm/2.24.01/N21258SM21301.doc

Concurrence:

T.Rumble 2.28.01/P.Price 3.1.01

S.Slaughter, K,Meaker, A. Mitra, R.Kavanagh, D.Shames 3.5.01

Response not received from A.Parekh

/s/

Diane V. Moore
3/19/01 12:52:16 PM

Daniel A. Shames
3/19/01 12:59:02 PM

Roy Blay
DSI

facsimile transmittal

To:	Diane Moore/Dr. Price	Fax:	827-4267
From:	Roy Blay/DSI	Date:	01/11/01
Re:	NDA 21-258	Pages:	2 (inc. cover)
CC:			

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

Attached is a copy of the worksheet that was used at the site of Dr. Julian Peskin in Ohio. It appears that this paper document was disposed of once the subjects inputted their data into the telephone. It remains unclear from the language in the inspection report whether this form, or a similar form, was used at other clinical sites, and whether the form was retained or tossed out. Other possibilities are that the CRAs in place at other sites generated their own versions of this form, or, even, that no form was used at all and information was inputted directly through the telephone.

In any event, it remains unclear what procedures were implemented for data capture at each of the sites. I am awaiting two more inspection reports that may shed more light on these questions. Please call me if you would like to discuss this further.

Thanks,

Roy

Subject Worksheet Protocol 96042

Subject No. _____

	1st Week							2nd Week							3rd Week							4th Week						
Day of Cycle	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Patch A Worn*																												
Patch B Worn*																												
Bleeding Pattern (check one) None																												
Light																												
Moderate																												
Heavy																												
Sanitary Protection needed? 1=no 2=yes																												
Number of Hot Flushes Daily (per 24 hours)If none enter 0 Mild																												
Moderate																												
Severe																												
UROGENITAL SYMPTOMS																												
Vaginal Dryness	No ☐ Yes ☐							No ☐ Yes ☐							No ☐ Yes ☐							No ☐ Yes ☐						
Pain during intercourse	No ☐ Yes ☐ N/A ☐							No ☐ Yes ☐ N/A ☐							No ☐ Yes ☐ N/A ☐							No ☐ Yes ☐ N/A ☐						
Frequent Urination	No ☐ Yes ☐							No ☐ Yes ☐							No ☐ Yes ☐							No ☐ Yes ☐						
Difficulty or pain during urination	No ☐ Yes ☐							No ☐ Yes ☐							No ☐ Yes ☐							No ☐ Yes ☐						
Involuntary urination when laughing or coughing	No ☐ Yes ☐							No ☐ Yes ☐							No ☐ Yes ☐							No ☐ Yes ☐						
Urination at night	No ☐ Yes ☐ If yes, note # ☐ 1 ☐ 2-4 ☐ more than 4							No ☐ Yes ☐ If yes, note # ☐ 1 ☐ 2-4 ☐ more than 4							No ☐ Yes ☐ If yes, note # ☐ 1 ☐ 2-4 ☐ more than 4							No ☐ Yes ☐ If yes, note # ☐ 1 ☐ 2-4 ☐ more than 4						

Degree of Bleeding defined as:

None: no vaginal bleeding
Light: Less than associated with normal menstruation relative to the subject's experience
Moderate: Like normal menstruation relative to the subject's experience
Heavy: More than normal menstruation relative to the subject's experience.

The severity of Hot Flushes defined as:

mild: Sensation of heat without perspiration.
moderate: Sensation of heat with perspiration, able to continue activity.
severe: Sensation of heat with sweating, causing the subject to stop activity.

N/A=Not Applicable

*Please note if extra patch used during cycle.

Meeting Minutes

Date: January 8, 2001 **Time:** 10:45 - 11:00 AM **Place:** Parklawn; Room 17B-45

NDA: 21-258 **Drug Name:** Climarapro (estradiol/levonorgestrel transdermal delivery system) 0.045/0.015, 0.045/0.030 and 0.045/0.040 mg per day

Indications: Treatment of moderate-to-severe vasomotor symptoms associated with menopause

Type of Meeting: 6-month status

Sponsor: Berlex Laboratories, Inc.

FDA Lead: Dr. Dan Shames

Meeting Recorder: Ms. Diane Moore

FDA Participants:
Daniel Shames, M.D. – Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Phill Price, M.D., – Medical Officer, DRUDP (HFD-580)
Diane Moore - Regulatory Project Manager, DRUDP (HFD-580)
Amit Mitra, Ph.D. - Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Ron Kavanagh, B.S. Pharm., Pharm.D., Ph.D. – Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)
Kate Meaker, M.S. - Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)

Meeting Objective: To discuss the status of the reviews for NDA 21-258.

Background: The NDA was submitted on June 29, 2000. The primary goal date is April 29, 2001. The secondary goal date is June 29, 2001.

Decisions:
- Pharmacology
  - review pending
- Clinical
  - review pending
  - although no hyperplasia cases were seen by the sponsor, the data needs closer investigation to determine if there is actually a less than 4% hyperplasia rate in the study
  - the data for the VMS indication needs to be validated; the data collection procedure in the US study is unclear
- DSI
  - three clinical sites have been requested for DSI audit; upon inspection, DSI indicated that the way in which the data was obtained (via telephone surveys at a central location, not at the immediate study site) could be problematic; the data needs to be verified

- Regulatory
  - the designation of the NDA is 4S (new drug combination), however, this application action letter may be signed at the Division level
  - the goal date for all reviews to be completed, including Team Leader sign-off is March 22, 2001
- Chemistry, Manufacturing and Quality Control
  - the sponsor has requested a categorical exclusion for environmental assessment
  - an information request letter will be sent to the sponsor delineating chemistry and manufacturing deficiencies
  - sponsor maintains tha[redacted] the information will be reviewed for appropriateness
  - the manufacturing sites have been inspected; report is satisfactory
- Clinical Pharmacology and Biopharmaceutics
  - review pending with a targeted completion date in early February 2001
  - requested assay validation reports were submitted
  - the requested pharmacokinetic report from the multiple-dose study is still pending; the sponsor has until January 15, 2001 to submit the data; this is an approvability issue for the lowest strength E_2/LVG (4.4/1.39) transdermal system
- Statistics
  - review pending

Action Items

• **Item**	**Responsible Person:**	**Due Date:**
• determine validity of study data	Dr. Price	February 1, 2001

Signature, minutes preparer

Signature, Chair

drafted: dm/1.9.01/N21258SM1801.doc

final:

Concurrence:
T.Rumble, KMeaker, R.Kavanagh 1.10.01/AMitra 1.16.01/DShames 1.1.01/PPrice 1.29.01

cc:
Archival: NDA 21-258
HFD-580/Div File
HFD-580/DMoore/TRumble
HFD-580/SAllen/DShames/SSlaughter/PPrice/AParekh/RKavanagh/MRhee/AMitra
HFD-580/AJordan

/s/

Diane V. Moore
1/29/01 01:07:00 PM

Daniel A. Shames
1/30/01 11:03:51 AM

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

DATE RECEIVED: 7/18/2000	DUE DATE:11/29/2000	OPDRA CONSULT #: 00-0193

TO:

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

THROUGH:

Diane Moore
Project Manager
HFD-580

PRODUCT NAME: Climarapro (Estradiol/Levonorgestrel transdermal system) **NDA #: 21-258**	**MANUFACTURER:** Berlex Laboratories, Inc.

SAFETY EVALUATOR: Peter Tam, R.Ph.

OPDRA RECOMMENDATION:

OPDRA does not recommend the use of the proprietary name, Climarapro.

Jerry Phillips 11/22/00

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

Martin H Himmel 11/22/00

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

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: 11/7/2000

NDA#: 21-258

NAME OF DRUG: Climarapro
(Estradiol/Levonorgestrel transdermal system)

NDA HOLDER: Berlex Laboratories, Inc.

I. INTRODUCTION:

This consult is written in response to a request from the Division of Reproductive and Urologic Drug Products, (HFD-580) received on 7/18/2000 to review the proposed proprietary name, Climarapro, in regard to potential names conflict with existing proprietary/generic drug names.

PRODUCT INFORMATION

Climarapro (estradiol/levonorgestrel transdermal system) is an adhesive-based matrix transdermal patch designed to release both estradiol and levonorgestrel, a progestational agent, continuously upon application to intact skin. Three systems are available in two sizes, 22 cm^2 and 30 cm^2. The 22 cm^2 has two nominal delivery rate of 0.045 mg estradiol/0.015 mg levonorgestrel per day and 0.045 mg estradiol/0.030 mg levonorgestrel per day. The 30 cm^2 has a nominal delivery rate of 0.045 mg estradiol/0.040 mg levonorgestrel per day.

Climarapro is indicated for the treatment of moderate-to-severe vasomotor symptoms associated with menopause —

Climarapro administered to postmenopausal women produces mean maximum estradiol concentration in serum in about 2 to 2.5 days. Estradiol concentrations equivalent to the normal ranges observed at the early follicular phase in premenopausal women are achieved within 12-24 hours after the first application. Levonorgestrel concentrations are maximum in about 2.5 days and gradually decrease to day 7. Each transermal delivery system lasts for 7 days.

Climarapro transdermal delivery system will be available in — with 4 systems per carton.

II. RISK ASSESSMENT:

The medication errors staff of OPDRA conducted a search of several standard published drug product reference texts[1,2,3] as well as several FDA databases[4] for existing drug names which sound alike or look alike to Climarapro to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[5]. An expert panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel Discussion was held by OPDRA to gather professional opinions on the safety of the proprietary name, Climarapro. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of OPDRA's Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

The following product was identified that have some sound-alike and look-alike properties, relative to Climarapro :

Product Name	Dosage form(s), Generic name	Usual Dose	Observation
Climarapro	Transdermal delivery system: 22 cm^2 (0.045 estradiol /0.015 levonorgestrel mg/day), 22 cm^2 (0.045 estradiol /0.030 levonorgestrel mg/day), 30 cm^2 (0.045 estradiol /0.040 levonorgestrel mg/day), Estradiol/Levonorgestrel Transdermal System	1 Transdermal system weekly/ 28-day cycle	
Climara	Transdermal system: 12.5 cm^2 (estradiol 3.9 mg/day), Estradiol Transdermal System	1 Transdermal system weekly/28 day cycle	*SA/LA

*SA = Sound-alike
*LA = Look-alike

The expert panel was concerned that the modifier "pro" conveys suggestion of progesterone. In addition, the existing product, Climara sounds like and looks like the proposed name, Climarapro. The potential risk for name confusion between Climara and Climarpro appears likely.

---

[1] MICROMEDEX Healthcare Intranet Series, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Emergindex, Reprodisk, Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc).

[2] American Drug Index, online version, Facts and Comparisons, St. Louis, MO.

[3] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[4] Drug Product Reference File [DPR], the Established Evaluation System [EES], the AMF Decision Support System [DSS], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, and the electronic online version of the FDA Orange Book.

[5] WWW location http://www.uspto.gov/tmdb/index.html.

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Studies were conducted by OPDRA and involved 90 health professionals comprised of pharmacists, physicians, and nurses within FDA to determine the degree of confusion of Climarapro with other drug names due to the similarity in handwriting and verbal pronunciation of the name. Inpatient and outpatient prescriptions were written, each consisting of known drug products and a prescription for Climarapro (see below). These prescriptions were scanned into a computer and were then delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

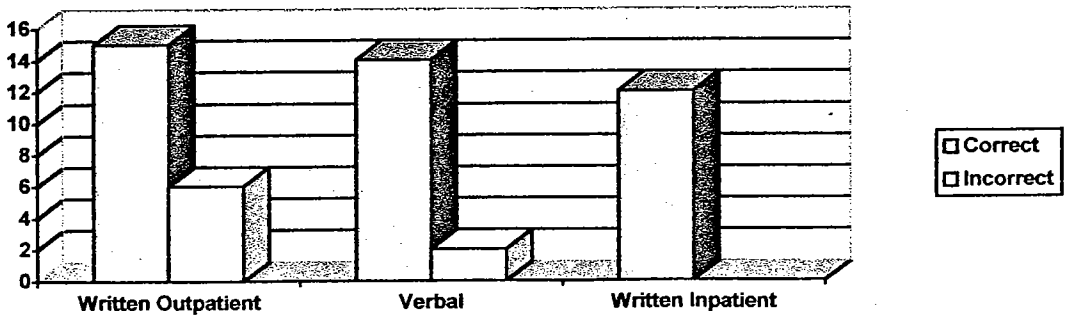
HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: Climarapro #6 Sig: Apply one per week	Outpatient Rx: Climarapro #6 Sig: Apply one per week
Inpatient RX: Discharge medication Climarapro apply 1/wk	

2. Results:

The results are summarized in Table I.

Table I

Study	# of Participants	# of Responses (%)	Correctly Interpreted	Incorrectly Interpreted
Written Outpatient	30	21(70%)	15	6
Verbal	31	16(52%)	14	2
Written Inpatient	29	16(55%)	12	4
Total	90	53(59%)	41(77%)	12(23%)



Twenty-three per cent of participants responded with the incorrect name. The incorrect written and verbal responses are summarized in Table II.

Table II

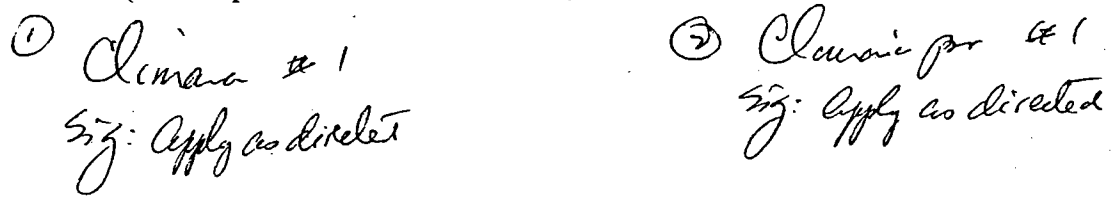
	Incorrectly Interpreted
Written Outpatient	*Climara (4)
	Climenapro
	*Clinara
Verbal	Climera-Pro
	Climara Probe
Written Inpatient	Clinarapro
	Climanapro
	Clonapro
	*Climara Patch

* Existing approved product, one spelled as Clinara presumably Climara.

C. SAFETY EVALUATOR RISK ASSESSMENT

The results of the verbal prescription study indicated that two out of sixteen respondents interpreted Climarapro incorrectly. In the first written outpatient study, six out of twenty-one respondents interpreted the name incorrectly. In the inpatient written study, four out of sixteen respondents interpreted the name incorrectly. There were incorrect responses that were misspelled/phonetic variations of the drug name. The incorrect interpretations in all three studies of the proposed name did overlap with one existing approved product, Climara. Six respondents interpreted Climarapro as Climara.

A positive finding in a study with a small sample size may indicate a high risk and potential for medication errors. Climara poses a significant risk in name confusion with Climaraparo. Both Climara and Climarapro are available in transdermal delivery systems and have overlapping dosing schedule (see sample hand written Rx below).



When examining the clinical consequences of an error between Climara and Climarapro, two possibilities exist if the modifier "pro" is misinterpreted as "prn":

1. A prescription for Climara if misinterpreted and Climarapro dispensed could have a serious outcome in an adult female patient. Postmenopausal women who have had hysterectomies should receive estrogen alone, since there is currently no definite role for progestins other than the prevention of endometrial hyperplasia. Progestins should be used with caution in patients with cardiovascular, hepatic impairment, diabetes mellitus and other conditions which may be aggravated by fluid retention. Progestin may also exacerbate the manifestation of mental depression.

2. A prescription for Climarapro if misinterpreted and Climara dispensed could put patients at risk for endometrial hyperplasia and adverse lipid profile.

We consider our study significant when extrapolated to the general population. Past experience has shown that products that have similar names and overlapping properties such as similar dosage forms and dosing intervals increase the potential risk for medication errors.

In addition, the expert panel considered the modifier "pro" promotional in tone. The modifier could be interpreted as suggestive of progesterone in association with the proposed proprietary name. However, many trade names have been approved with the same modifier "pro". Examples are 1) Cipro, 2) Akpro, 3) Avapro, 4) Daypro, 5) Compro and 6) Prempro. Prempro is a very similar product compared to Climarapro. Both formulations consist of a combination of estrogen and progesterone. Prempro is a tablet while Climarapro is a transdermal delivery system. Therefore, the expert panel's concern about the modifier "pro" being suggestive of progesterone is unfounded.

Based on our prescription studies, there is evidence that Climara could be confused with Climarapro. We, therefore, do not recommend the proposed proprietary name, Climarapro.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container, carton and insert labeling of Climarapro, OPDRA has attempted to focus on safety issues relating to possible medication errors. OPDRA has reviewed the current insert labeling and has identified several areas of possible improvement, which might minimize potential user error.

A. CONTAINER LABEL

Not submitted for review.

B. CARTON LABELING

Not submitted for review.

C. INSERT LABELING

1.

2. The — is misleading. It is unclear whether the table relates to the active ingredient or placebo.

3. On page 41, third paragraph under Application of the System, the term ' — is confusing.

RECOMMENDATIONS:

1. OPDRA does not recommend the use of the proprietary name, Climarapro.

2. OPDRA recommends the above insert labeling revisions that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the insert labeling from the manufacturer.

OPDRA would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Peter Tam at 301-827-3241.

11/14/00

Peter Tam, R.Ph.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

11/22/00

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

CC:

NDA – 21-258
HFD-# 580; DivFiles; Diane Moore, Project Manager
HFD-# 580; Susan Allen, M.D., Acting Division Director
HFD-400; Jerry Phillips, Associate Director, OPDRA
HFD-400; Peter Tam, Safety Evaluator, OPDRA

Electronic only cc:

HFD-400; Sammie Beam, Project Manager, OPDRA
HFD-042; Patricia Staub, Regulatory Review Officer, DDMAC
HFD-#440; Mary Dempsey, DDREII, OPDRA
HFD-002; Heidi M. Jolson, M.D., Acting Deputy Center Director for Review Management
HFD-400; Peter Honig, Director, OPDRA

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6

4 Page(s) Withheld

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

✓ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

Meeting Minutes

Date: August 15, 2000 **Time:** 1:00 - 1:14 PM **Place:** Parklawn; Room 17B-45

NDA: 21-258 **Drug Name:** Climarapro (estradiol/levonorgestrel transdermal delivery system) 0.045/0.015, 0.045/0.030 and 0.045/0.040 mg per day

Indications: Treatment of moderate-to-severe vasomotor symptoms associated with menopause

Type of Meeting: Filing

Sponsor: Berlex Laboratories, Inc.

FDA Lead: Dr. Susan Allen

Meeting Recorder: Ms. Diane Moore

FDA Participants:
Susan Allen, M.D., M.P.H. – Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Shelley Slaughter, M.D., Ph.D. – Team Leader, DRUDP (HFD-580)
Diane Moore - Regulatory Project Manager, DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Amit Mitra, Ph.D. - Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Ron Kavanagh, B.S. Pharm., Pharm.D., Ph.D. – Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)
Lisa Kammerman, Ph.D. - Team Leader, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
Roy A. Blay, Ph.D.- Senior Regulatory Review Officer, Division of Scientific Investigations, Good Clinical Practices Branch I (HFD-46)

Meeting Objective: To discuss the fileability of NDA 21-258.

Background: The NDA was submitted on June 29, 2000. The primary goal date is April 29, 2001. The secondary goal date is June 29, 2001.

Decisions:
- Pharmacology
  - NDA is fileable per pharmacology reviewer
- Clinical
  - fileable
  - two studies were submitted; Study 96042 for VMS and 96043 for protection of the endometrium
  - Comments sent from Medical Officer:

- the sponsor presents two multi-center studies to determine the safety and efficacy of ClimaraPro; this will be the first submitted HRT regimen using levonorgestrel as the progestin
- Study 96042 is a 12-week placebo controlled study which appears to show efficacy; the sponsor's label needs revisions; the — is unacceptable; —
- Study 96043 is a 52-week randomized trial comparing three dosages of E_2/levonorgestrel against estradiol alone; although there were significant dropouts during the study, it was adequately powered to sustain a dropout rate of 42% at one year; no hyperplasia cases were reported, this will be a review issue

- DSI
  - the clinical sites for audit need to be determined and forwarded to Dr. Blay
- Regulatory
  - additional financial disclosure information has been requested from the sponsor; sponsor sent information on July 20, 2000
  - the designation of the NDA is 4S, however, this application may be signed at the Division level
- Chemistry, Manufacturing and Quality Control
  - Environmental Assessment (EA)
    - the sponsor has requested a categorical exclusion; EA is a review issue
  - an issue regarding the clarification of the manufacturing facility has been resolved
  - measurements should be a test attribute on release and stability of the drug product
  - release test method to be evaluated during review
  - the sponsor has requested a — shelf life based on submitted — data for two formulations and — data for one formulation; additional — stability data updates are to be submitted; this is a review issue
- Clinical Pharmacology and Biopharmaceutics
  - fileable
  - the clinical formulation is the same as the to-be-marketed formulation; a bridging study is not needed
  - a bridging study with Climara is not needed
- Statistics
  - fileable

Action Items

- none

Signature, minutes preparer

Signature, Chair

drafted: dm/8.16.00/N21258FM81500.doc

Concurrence:

LKammerman, RBlay, SAllen 8.21.00/SSlaughter 8.23.00/AMitra, RKavanagh 9.7.00
MRhee 9.18.00/TRumble 9.19.00

Response not received from AParekh

cc:
Archival: NDA 21-258
HFD-580/Div File
HFD-580/DMoore/TRumble
HFD-580/SAllen/DShames/SSlaughter/PPrice/AParekh/RKavanagh/MRhee/AMitra
HFD-580/AJordan

Electronic Mail Message

Date: 8/10/00 6:14:26 PM
From: Phil Price (PRICEP)
Subject: ClimaraPro NDA 21-258

Shelley,
Sorry I'm missing this meeting, but the NMA PROGRAM is excellent on Tuesday.

As I know you are aware, the NDA for ClimarPro is fileable. The sponsor presents two multicenter studies to determine the safety and efficacy of ClimarPro. This will be the first submitted HRT regimen using levonorgestrel as the progestin.

Study 96042 is a 12-week placebo controlled study which appears to show efficacy. The sponsor's Label needs work since there is a — — which I doubt will fly. — /

Study 96043 is a 52-week randomized trial comparing three dosages of E/levonorgestrel against estradiol alone. Although there were significant dropouts during the study it was powered enough to substain a dropout rate of 42% at one year. No hyperplasia were reported, this will be a review issue.

You will find the Jacket for ClimaraPro on the front of my desk. See you Thursday afternoon.
Phill

Room

NDA 21-258

JUL 5 2000

Berlex Laboratories, Inc.
Attention: Geoffrey Millington
Manager, Drug Regulatory Affairs
340 Changebridge Road
P.O. Box 1000
Montville, NJ 07450-1000

Dear Mr. Millington:

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:	Climarapro™ (estradiol/levonorgestrel transdermal system)
Therapeutic Classification:	Standard (S)
Date of Application:	June 29, 2000
Date of Receipt:	June 29, 2000
Our Reference Number:	NDA 21-258

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 August 28, 2000 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be April 29, 2001, and the secondary user fee goal date will be June 29, 2001.

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

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

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

Please cite the 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, call Diane Moore, BS, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

6/30/00

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

cc:
Archival NDA 21-258
HFD-580/Div. Files
HFD-580/D.Moore
HFD-580/SAllen/MMann/DShames/SSlaughter/PPrice
HFD-580/MRhee/AMitra/AJordan/KRaheja/LKammerman
HFD-580/AParekh/RKavanagh
DISTRICT OFFICE

Drafted by: dm/June 30, 2000
Initialed by: TRumble 6.30.00
final: June 30, 2000
filename: N21258AK.DOC

ACKNOWLEDGEMENT (AC)

Diane Morse 6/30/00

BERLEX

HAND DELIVERED

Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 276-2000

June 29, 2000

Susan Allen, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room (Room 17B20)
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Allen:

RE: NDA 21-258 - CLIMARAPRO™
(Estradiol/Levonorgestrel Transdermal System)
ORIGINAL NEW DRUG APPLICATION

Pursuant to Section 505 (b) of the Federal Food, Drug and Cosmetic Act and to 21 CFR §314.50, Berlex Laboratories, Inc. is submitting herewith a New Drug Application for CLIMARAPRO™[1] [Estradiol (E2)/Levonorgestrel (LNG) Transdermal System], a transdermal drug delivery system for hormone replacement therapy.

The development program was discussed in a Pre-IND meeting between representatives of Berlex/3M and the Division of Reproductive and Urologic Drug Products on March 6, 1996. A Pre-NDA meeting was held with the Division on February 8, 2000. The Division minutes for the Pre-NDA meeting are provided immediately following this cover letter.

Safety and efficacy data in this NDA were obtained from two pivotal studies:

- Report B528 (Study No. 96042) - A Multicenter, Double-Blind, Placebo-Controlled, Randomized Study to Determine Efficacy in the Relief of Hot Flushes in Women Receiving Transdermal Estradiol.

- Report B529 (Study No. 96043) - A Multicenter, Double-Blind, Randomized Study of Continuous Transdermal Estradiol-Levonorgestrel Combinations, Compared to Continuous Transdermal Estradiol, to Examine the Safety and Effect on the Endometrium, Symptoms and Bleeding Patterns in Postmenopausal Women.

[1] The Division informed Berlex in the Pre-NDA meeting held on February 8, 2000 that the proposed tradename ,CLIMARAPRO, has been submitted to the Labeling and Nomenclature Committee for consideration.

The two pivotal studies, in addition to the supportive studies provided in this NDA, confirm that CLIMARAPRO™ appears to be well tolerated, safe and effective HRT.

This NDA is comprised of 283 volumes that include five technical sections. The structure and pagination for this application are as follows:

- Volume 1 contains Items 13-19, Items 1 (Index) and 2 (Labeling) and is paginated consecutively from page "1" through page "n" in the lower right hand corner.
- Volume 2 contains Item 3 (Summary) and is paginated consecutively from page "1" through page "n" in the lower right hand corner.
- Items 4, 5 and 6 are paginated per Item (Item number followed by a five-place page number) in the lower right hand corner.
- Items 8, 10, 11 and 12 are paginated per volume consecutively from page "1" through page "n" in the lower right hand corner.

The application provides for the CLIMARAPRO™ commercial product in three patch strengths as follows (patch size followed by E2/LNG content):

- 22 square cm, 4.4 / 1.39 mg
- 22 square cm, 4.4 / 2.75 mg
- 30 square cm, 4.5 / 3.75 mg

To date, the estradiol/levonorgestrel transdermal system has not been marketed anywhere in the world.

3M Pharmaceuticals is the manufacturer of the combination hormone replacement patch containing estradiol and levonorgestrel for Berlex Laboratories, Inc. During the Pre-NDA Meeting of February 8, 2000, the Division Representatives agreed that 3M Pharmaceuticals will submit all Chemistry, Manufacturing, and Controls information for the estradiol/levonorgestrel transdermal delivery system ——

Included in this submission is a CD-ROM copy of the SAS datasets for the reviewing statistician (located in the first volume of Item 10). Included on the CD-ROM is documentation which explains the content of the SAS datasets and instructions for use.

Please contact the undersigned at (973) 276-2254 with any questions regarding this submission.

Sincerely,

BERLEX LABORATORIES, INC.

Geoffrey Millington
Manager, Drug Regulatory Affairs

GPM/064

Meeting Minutes

Date: February 8, 2000 **Time:** 1:00 - 3:30 PM **Place:** Parklawn; Potomac Room

IND: 51,188 **Drug Name:** levonorgestrel and estradiol hemihydrate

Indications: Reduction of postmenopausal vasomotor symptoms,

Type of Meeting: pre-NDA meeting

External Constituent: Berlex Laboratories, Inc.

FDA Lead: Dr. Susan Allen

FDA Participants:
Susan Allen, M.D., M.P.H. - Acting Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Marianne Mann, M.D. - Deputy, DRUDP (HFD-580)
Shelley Slaughter, M.D. - Medical Officer, DRUDP (HFD-580)
Phill Price - Medical Officer, DRUDP (HFD-580)
Terri Rumble – Chief, Project Management Staff, DRUDP (HFD-580)
Diane Moore - Regulatory Project Manager, DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
David Lin, Ph.D. - Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Lisa Kammerman, Ph.D. - Team Leader, Division of Biometrics II (DBII) @ DRUDP (HFD-580)

External Participants:
Nancy Bower, M.S., L.A.T.G. – Research Toxicologist, Preclinical Development, Berlex
Armen P. Melikian, Ph.D. – Associate Director, Clinical Pharmacology, Berlex
Geoffrey P. Millington – Manager, Drug Regulatory Affairs, Berlex
Harji Patel, Ph.D. – Associate Director, Biostatistics, Berlex
Herman Ellman, M.D. – Director, Medical Science Liaison, Female Health Care, Berlex
Marie Foegh, M.D. - Medical Director, Clinical R&D, Female Health Care, Berlex

Lester I. Harrison, Ph.D. – Section Head, Clinical Pharmacokinetics, 3M
Mary L. Mathisen – Regulatory Affairs, 3M
Thomas S. Robison – Research Specialist, Analytical Research and Development, 3M

Meeting Objective: To discuss the general format of the proposed NDA and provide comments regarding the proposed NDA submission.

Background:
Berlex submitted a pre-meeting package on January 11, 2000, which contained a draft NDA index, sample draft labeling, and summary of the Clinical, Chemistry, Preclinical, Statistical and Clinical Pharmaceutical information and case report forms.

Discussion Items:
- the target date for the NDA submission is June 2000

Decisions:
- **ITEM 1: DRAFT INDEX**
  - **Question:** Does the Division have any comments regarding the DRAFT NDA Index?
  - **Answer:**
    - the proposed draft index appears to acceptably follow general index guidelines; additional information may be requested after NDA submission

- **ITEM 2: DRAFT LABELING:** The draft package insert was prepared using the approved labeling for CombiPatch™ (estradiol/norethindrone acetate).
  - **Question 1:** Does the DRAFT labeling meet the requirements of the Division?
  - **Answer:**
    - organizationally, the proposed labeling is acceptable
    - adhesion data must be included for the to-be-marketed product
    - pharmacokinetic (PK) profiles at Week 1 and Week 4 differed; these differences should be presented in the labeling
    - **Question 2:** Is the proposed tradename, Climara™Pro, acceptable?
  - **Answer:**
    - a tradename should be submitted for review by the Office of Post-Marketing Drug Risk Assessment (OPDRA)
    - the established name presented by the sponsor (17β-estradiol) is incorrect; the established name should be estradiol; the labeling should state in the DESCRIPTION section that levonorgestrel is a . . . after USP
    - a storage statement should be inserted in the **HOW SUPPLIED** section

- **ITEM 4: CHEMISTRY, MANUFACTURING AND CONTROLS**
  - **Question:** Does the Division agree that the CMC information submission plan is adequate?
  - **Answer:**
    - — Type 2 DMF that refers to items in the overheads which is similar to the one for Climara; the DMF is acceptable
    - although the sponsor claims that the excipient — , used in the formulation to — an explanation should be provided in the CMC section of the NDA
    - regarding the — estradiol drug substance — if the impurity profiles differ for — the sponsor will need stability data for the product from three batches each for — drug substances
    - in the stability protocol, the sponsor should perform impurity testing during stability on impurities and degradation products
    -

proposal should be sent to the Project Manager prior to NDA submission for review by the chemist
- a stability commitment can be provided by the sponsor as outlined in Attachment 1 (see attachment)
- the tradename and delivery strength must be imprinted on the patch backing

- **ITEM 5: NONCLINICAL PHARMACOLOGY AND TOXICOLOGY**
  - **Question:** Does the Division concur that the type, duration and overall design of the nonclinical studies conducted are sufficient to assess the safety of the E2/LNG transdermal system?
  - **Answer:**
    - the proposed studies appear to be acceptable; however, a drug master file (DMF) for the adhesive should be referenced in the NDA

- **ITEM 6: HUMAN PHARMACOKINETICS AND BIOAVAILABILITY**
  - **Issue 1**: The performance characteristics of these patches are understood. The average daily delivery of estradiol for 2 strengths was obtained from a single dose study. For labeling purposes, both patch strengths deliver a nominal 50 μg estradiol per day. Levonorgestrel average daily delivery will also be determined from this study.
  - **Question 1:** Does the Division concur with our labeling approach for these 2 patches?
  - **Answer:**
    - labeling is a review issue; it is inappropriate to comment specifically on the content of the labeling at this time because the labeling reflects the data provided; labeling format, however, should be consistent with other approved HRT products
    - adhesion data should be included in the labeling and should be from the to-be-marketed product (not data from the clinical batches from the wear study)
    - the PK profiles after single and multiple doses should be described in the NDA, as well as the label; literature references for the absorption, distribution, metabolism, and excretion subsections should be provided for levonorgestrel as there is no first pass hepatic effect
    - any available information regarding any first pass effect for skin should be provided for review in the NDA

  - **Issue 2**: From a multiple dose study no accumulation of levonorgestrel or estradiol was observed after 4 weeks of application. The estradiol levels were lowered, indicating a possible interaction.
  - **Question 2:** Does the Division concur that the multiple dose pharmacokinetics is adequately characterized?
  - **Answer:**
    - there could be interactions with estradiol and levonorgestrel and sex hormone binding globulin (SHBG)
    - the sponsor claims that SHBG interactions cause estradiol levels to drop during the first 2-3 weeks of use and then the estradiol levels stabilize to a steady-state level by the end of 3-4 weeks; this data should be provided in the NDA to assure that efficacy will be maintained over time

  - **Issue 3:** A single dose study will determine the average daily delivery of levonorgestrel and estradiol. There is no need for a further multiple dose study for this strength because accumulation was not seen with higher strength patches.
  - **Question**: Does the Division concur with this approach to characterize the lowest strength patch?

- **Answer:**
  - the sponsor has three estradiol/levonorgestrel combination transdermal systems (4.4/3.75; 4.4/2.75; and 4.4/1.39); the proposed clinical trials to study vasomotor symptoms utilize the 4.4/3.75 and 4.4/2.75 systems
  - because the estradiol component of all three systems is identical, the sponsor proposes to — from the two strengths tested for the 4.4/1.39 system
  - the underlying assumption for the sponsor's proposal is that a single dose study demonstrates similar estradiol levels in all three systems
  - the profile for the three strengths may not be linear; in order to establish efficacy for the lowest dose, a multiple dose proportionality study may be necessary; bioequivalence calculations should be made at steady-state considering interactions between estradiol and levonorgestrel and sex hormone binding globulin (SHBG)
  - given that SHBG interactions occur with these products, and that stabilization takes about 3-6 weeks, a bioequivalence (BE) study comparing the estradiol from the 4.4/1.39 (lowest dose) system should be conducted where this system is compared to the other systems in a cross-over design study using single treatment groups and multiple applications; this study should be a 3-4 week study (until SHBG and estradiol levels stabilize)
  - the protocol should be submitted to the IND prior to study initiation; if the proposal is submitted after NDA submission, the proposal for submission time should be included

- **ITEM 8: CLINICAL DATA**
  - Of the clinical studies that will be included in this NDA, 3 are Phase 1 studies that were conducted by 3M to investigate the sensitization and irritation potential adhesion characteristics of the product. The other studies are Phase 2 and 3 studies which are part of the development program for this product in the US and Europe. Pivotal studies 96042 (efficacy in postmenopausal symptoms) and 96043 (efficacy and safety postmenopausal symptoms and endometrial protection) are ongoing.
  - **Question:** Is the Clinical program adequate to support the filing of the NDA?
  - **Answer:**
    - yes, however, in addition to frequency, severity should also be measured in the VMS trials

    - the clinical data should support the efficacy and safety of each dose
    - full analysis of biopsy data is needed rather than just the presence or absence of endometrial hyperplasia
    - the sponsor proposed to perform an analysis on a subset of patients in the endometrial hyperplasia study who used the lowest dose system for VMS; unless the HRT guidance recommendations for limiting enrollment to those patients with moderate-to-severe VMS were followed, the information obtained from the proposed subset analysis may not be sufficient to demonstrate VMS efficacy for the lowest dose system

- **ITEM 10: STATISTICS**
- **Question 1:** Do the format, content and plan for data analysis for the pivotal studies meet the requirements of the Division?—

- **Answer:**
  - the primary efficacy variables for the VMS indication should be the change from baseline in the number and severity of moderate-to-severe hot flushes at Weeks 4, 8 and 12; this is similar to item 2 under "secondary endpoints" in the pre-meeting package
  - results should report only moderate-to-severe data for frequency and severity
  - most women with mild symptoms received the lowest dose system; the numbers of subjects from the study with moderate-to-severe hot flushes at baseline may not be large enough to demonstrate efficacy for the lowest dose transdermal system
  - the NDA should discuss why ANOVA on the ranks, instead of the actual observed values, was used
  - an argument for using the last observation carried forward should be included in the NDA; the impact of missing data on the interpretation of data should be discussed
  - subgroup analyses should be included for age and ethnicity
  - for Study 43 (Prevention of Endometrial Hyperplasia Trial), the NDA should include an additional analysis limited to women with biopsies performed between six months and twelve months
  - comment should be provided on dropout rates in the analyses submitted to the NDA
  - Kaplan Meier plots of time to discontinuation, by treatment arm, should be included in the NDA
  - confidence intervals should be used to indicate that results among treatment groups are similar (p-value is not significant and is not acceptable)

- **Question 2:** Do the methods for summarizing the overall results for the NDA (e.g. ISE, ISS) meet the requirements of the Division?
- **Answer:**
  - the format is acceptable

- **ITEM 11: CASE REPORET TABULATIONS**
- **Question:** Will subject listings satisfy the requirements of the Division?
  - the proposal appears to be appropriate

• **Action Items**	**Responsible Person:**	**Due Date:**
• submit BE protocol for lowest dose	Berlex	prior to study initiation
• provide stability commitment	Berlex	one week after receipt of Feb 8, 2000, meeting minutes
• provide minutes to sponsor	DRUDP	one month

Diane Moore 2/24/00
Signature, minutes preparer

Susan Allen, MD 2/25/00
Signature, Chair

Note to sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

drafted: dm/2.10.00I51188pm2200.doc

Concurrence:
TRumble 2.14.00/SAllen, PPrice 2.15.00/MMann, DLin, AParekh, LKammerman 2.16.00
MRhee 2.18.00/SSlaughter 2.22.00

cc:
Archival
HFD-580/Div File
HFD-580/DMoore/TRumble
HFD-580/SAllen/MMann/SSlaughterPPrice/LMeaker/LKammerman/AParekh/DLin/MRhee
HFD-580/AJordan/KRaheja/KBonson

Attachment 1

1. Conduct and/or complete the necessary studies on the first three production batches and annual batches thereafter of each drug product, container, and closure according to the approved stability protocol through the expiration dating period.

2. Submit stability study results at the time intervals and in the format specified by the FDA, including the annual batches.

3. Withdraw from the market any batches found to fall outside the approved specifications for the drug product. If the applicant has evidence that the deviation is a single occurrence that does not affect the safety and efficacy of the drug product, the applicant should immediately discuss it with the appropriate chemistry team and provide justification for the continued distribution of that batch. The change or deterioration in the distributed drug or biological product must be reported under 21 CFR 314.81 (b)(1)(ii) or 21 CFR 601.14, respectively.

H

16 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

Meeting Minutes

Date: February 2, 2000 **Time:** 3:00 - 3:55 PM **Place:** Parklawn; Room 17B-43

IND: 51,188 **Drug Name:** levonorgestrel and estradiol hemihydrate

Indications: — postmenopausal vasomotor symptoms (VMS), —

Type of Meeting: Internal meeting prior to industry pre-NDA meeting

Sponsors: Berlex Laboratories, Inc. and 3M

FDA Lead: Dr. Susan Allen

FDA Participants:
Susan Allen, M.D., M.P.H. - Acting Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Marianne Mann, M.D. - Deputy, DRUDP (HFD-580)
Shelley Slaughter, M.D. - Medical Officer, DRUDP (HFD-580)
Phill Price - Medical Officer, DRUDP (HFD-580)
Lesley Furlong, M.D. - Medical Officer, DRUDP (HFD-580)
Terri Rumble – Chief, Project Management Staff, DRUDP (HFD-580)
Diane Moore - Regulatory Project Manager, DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
David Lin, Ph.D. - Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Lisa Kammerman, Ph.D. - Team Leader, Division of Biometrics II (DBII) @ DRUDP (HFD-580)

Meeting Objective: To discuss the general format of the proposed NDA and any outstanding issues regarding the NDA submission.

Background:
Berlex submitted a pre-meeting package on January 11, 2000, which contained a draft NDA index, sample draft labeling, and summary Clinical, Chemistry, Preclinical, Statistical and Clinical Pharmaceutical information and case report forms.

Decisions:

- **ITEM 1: DRAFT INDEX**
  - **Question:** Does the Division have any comments regarding the DRAFT NDA Index?
  - **Answer:**
    - the proposed draft index appears to follow general index guidelines

- **ITEM 2: DRAFT LABELING**: The draft package insert was prepared using the approved labeling for CombiPatch™ (estradiol/norethindrone acetate).
  - **Question 1:** Does the DRAFT labeling meet the requirements of the Division?
  - **Answer:**
    - organizationally, the proposed labeling is acceptable
  - **Question 2:** Is the proposed tradename, Climara™Pro , acceptable?
  - **Answer:**
    - a tradename should be submitted for review by the Office of Post-Marketing Drug Risk Assessment (OPDRA)

Note: No ITEM 3 was listed in the sponsor's questions

- **ITEM 4: CHEMISTRY, MANUFACTURING AND CONTROLS**
  - **Question**: Does the Division agree that the CMC information submission plan is adequate?
  - **Answer:**
    - pertinent data was omitted from the **DESCRIPTION** section of the draft labeling submitted
    - the established name presented by the sponsor, "17B-estradiol" is incorrect; the established name should be "estradiol"
    - the excipient used in the formulation should be monitored during stability and release;
    - the sponsor should clarify what is being studied in the stability protocol regarding monitoring of purity (degredants, potency, etc.); an improved stability commitment is needed
    - the product should be packaged in the to-be-marketed material on stability
    - the sponsor has for the estradiol drug substance; if the impurity profiles differ for the , the sponsor will need stability data for the product using drug substances
    - additional information will be required in the product labeling
    - the tradename and delivery strength must be imprinted on the backing of the patch
    - it would be acceptable to submit the information on the drug product in a drug master file (DMF)

- **ITEM 5: NONCLINICAL PHARMACOLOGY AND TOXICOLOGY**
  - **Question:** Does the Division concur that the type, duration and overall design of the nonclinical studies conducted are sufficient to assess the safety of the E_2/LNG transdermal system?
  - **Answer:**
    - literature reference is acceptable for estradiol and levonorgestrel, however, a DMF for the adhesive is needed for a safety analyses, especially for the monomers
    - the appropriate toxicology studies have been performed

- **ITEM 6: HUMAN PHARMACOKINETICS AND BIOAVAILABILITY**
  - **Issue 1**: The performance characteristics of these patches are understood. The average daily delivery of estradiol for 2 strengths was obtained from a single dose study. For labeling purposes, deliver a nominal estradiol per day. Levonorgestrel average daily delivery will also be determined from this study.
  - **Question 1:** Does the Division concur with our labeling approach for patches?
  - **Answer:**

- the sponsor has characterized the release rates
- the labeling will reflect the data provided; previous issues have been addressed
- adhesion data should be included in the labeling and should be from the to-be-marketed product (not data from the clinical batches from the wear study)

- **Issue 2:** From a multiple dose study no accumulation of levonorgestrel or estradiol was observed after 4 weeks of application. The estradiol levels were lowered, indicating a possible interaction.
- **Question 2:** Does the Division concur that the multiple dose pharmacokinetics is adequately characterized?
- **Answer:**
  - the pharmacokinetic (PK) information included in the package is from one table showing steady-state levels, but the steady-state levels from the levonorgestrel are not shown; there could be interactions with estradiol and levonorgestrel and sex hormone binding globulin (SHBG); the labeling will be modified based on interactions and data
  - interactions with estradiol and levonorgestrel will be included in the labeling; the sponsor has one short-term study comparing this transdermal system to Climara showing that SHBG stabilizes by four weeks, therefore, four weeks is adequate

- **Issue 3:** A single dose study will determine the average daily delivery of levonorgestrel and estradiol. There is no need for a further multiple dose study for this strength because accumulation was not seen with higher strength patches.
- **Question**: Does the Division concur with this approach to characterize the lowest strength patch?
- **Answer:**
  - a multiple-dose study for the lowest strength is not necessary, if the doses can be bracketed with the 22 and 30 cm^2 systems; a need for a waiver should be justified

- **Additional Comment:**
  - the adhesive was changed between Phase 1 and Phase 2; a separate wear study is being performed; if a different adhesive was used for the to-be-marketed product, a linking study can be incorporated

Note: No ITEM 7 was listed in the sponsor's questions

- **ITEM 8: CLINICAL DATA**
  - Of the clinical studies that will be included in this NDA, 3 are Phase 1 studies that were conducted by 3M to investigate the sensitization and irritation potential adhesion characteristics of the product. The other studies are Phase 2 and 3 studies which are part of the development program for this product in the US and Europe. Pivotal studies 96042 (efficacy in postmenopausal symptoms) and 96043 (efficacy and safety postmenopausal symptoms and endometrial protection) are ongoing.
  - **Question:** Is the Clinical program adequate to support the filing of the NDA?
  - **Answers:**
    - although the 12-week VMS trial (96042) has been completed, it is unclear whether all clinical studies have been completed; all pivotal studies should be completed before NDA submission
    - adhesion and irritation studies should be included in the submission
    - the drop in estradiol and levonorgestrel depicted in the PK level figure may pose a possible concern regarding efficacy

- the sponsor will need to clarify whether the VMS trial followed the HRT guidance document and enrolled only women with moderate-to-severe vasomotor symptoms
- transvaginal ultrasound readings are proposed at seven months; if the ultrasound is greater or equal to 5 mm, a biopsy is performed; the cut off for the endometrial thickness should be 4 mm instead of 5 mm
- the text proposed related to cumulative amenorrhea rate increases will not be allowed in the labeling; only a cumulative amenorrhea rate figure would be acceptable as in other approved labels
-
- clinical and statistical significance in endpoints should be shown for the lowest dose transdermal system; pharmacodynamics studies could be performed to alleviate concern that the transdermal system efficacy may decrease at 4 months; also pharmacokinetics data should be obtained at 4 to 12 weeks
-
- data from the endometrial protection study can not be used to support efficacy of the lowest dose strength system for relief of vasomotor symptoms because patients were enrolled with mild-to-moderate (not moderate-to-severe) VMS at baseline

Note: No ITEM 9 was listed in the sponsor's questions

- **ITEM 10: STATISTICS**
- **Question 1:** Do the format, content and plan for data analysis for the pivotal studies meet the requirements of the Division?
- **Answer:**
  - the primary efficacy variables for the VMS indication should be assessed at Weeks 4, 8 and 12 only; a subgroup analysis could be performed for patients who have satisfied FDA entry criteria for the first 12 weeks in the 1-year study; this should be clarified
  - the sponsor proposes the primary efficacy variable in Study 96042 as "The change from baseline in the mean weekly number of hot flushes"; this proposed statistical analysis plan is not appropriate; the appropriate primary efficacy variable should be "The change from baseline in the number of hot flushes by day at Week 4 of Cycles 1, 2, and 3 (at 4, 8 and 12 weeks of treatment). (Only for ISE)" (as proposed in the sponsor's second secondary efficacy variable)
  - the intent-to-treat (ITT) population should be clarified as the population for primary analysis
  - the sponsor should clarify why it is proposing to use ranks in the format plan
- **Question 2:** Do the methods for summarizing the overall results for the NDA (e.g. ISE, ISS) meet the requirements of the Division?
- **Answer:**
  - this question was not addressed during the internal meeting

- **ITEM 11: CASE REPORT TABULATIONS**
- **Question:** Will subject listings satisfy the requirements of the Division?
- **Answer:**
  - the listings appear to be adequate

Action Items: none

Diane Moore 2/25/00
Signature, minutes preparer

Susan Alli, MD 2/28/00
Signature, Chair

drafted: dm/2.10.00I51188pm2200.doc

Concurrence:
TRumble, DLin 2.17.00/MMann, MRhee 2.18.00/SSlaughter, LFurlong 2.22.00/SAllen 2.24.00
AParekh 2.25.00
Concurrence not received from PPrice, LKammerman

cc:
Archival
HFD-580/Div File
HFD-580/DMoore/TRumble
HFD-580/SAllen/MMann/SSlaughterPPrice/LMeaker/LKammerman/AParekh/DLin/MRhee
HFD-580/AJordan/KRaheja/KBonson

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-375

Berlex Laboratories, Inc.
Attention: Mr. Geoffrey Millington
340 Changebridge Road
Montville, NJ 07045-1000

Dear Mr. Millington:

Thank you for your letter dated November 7, 2003, in which you requested, under 21 CFR 314.90(a), a waiver from the requirement under 21 CFR 314.80 to submit to the Food and Drug Administration (FDA), as part of your post-marketing periodic safety reporting responsibilities, FDA form 3500A for each adverse experience that is determined to be both nonserious and labeled. This waiver applies to specific approved new drug application (NDA) listed below.

I note the written commitment in your letter: (1) to hold in your corporate drug product safety files the individual case reports of adverse experiences that are nonserious and labeled; (2) to submit these individual case reports to FDA within five (5) calendar days after receipt of a request by FDA to do so; and (3) to continue to include the nonserious, labeled adverse experiences in each periodic adverse drug experience report you submit to FDA for this NDA, in the section that includes a summary tabulation by body system of all adverse experience terms and counts of occurrences submitted during the reporting period.

Provided you continue to abide by the commitments in paragraph two of this letter, your requested waiver is hereby granted and will remain in effect until further notice.

As requested, this waiver applies to the following approved NDA:

NDA 20-375 Climara (estradiol transdermal system)

If you have any questions about this waiver, please do not hesitate to contact me at (301) 827-3219.

Sincerely,

{See appended electronic signature page}

Paul J. Seligman, M.D., M.P.H.
Acting Director
Office of Drug Safety
Director
Office of Pharmacoepidemiology and Statistical Science
Center for Drug Evaluation and Research

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA #21-258 Supplement # N/A SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8

Trade Name: Climara Pro™
Generic Name: estradiol/levonorgestrel
Strengths: 0.045/0.015 mg/day transdermal system

Applicant: Berlex Laboratories

Date of Application: June 29, 2000
Date of Receipt: June 29, 2000
Date clock started after UN:
Date of Filing Meeting: August 15, 2000
Filing Date: August 15, 2000
Action Goal Date (optional): November 21, 2003 User Fee Goal Date: November 22, 2003

Indication requested: Treatment of moderate to severe vasomotor symptoms associated with menopause

Type of Original NDA: (b)(1) ___×_____ (b)(2) _____
OR
Type of Supplement: (b)(1) _____ (b)(2) _____
NOTE: A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2) application, complete the (b)(2) section at the end of this review.

Therapeutic Classification: S ___×_____ P _____
Resubmission after withdrawal? _____ Resubmission after refuse to file? _____
Chemical Classification: (1,2,3 etc.) __4S_____
Other (orphan, OTC, etc.) _____

User Fee Status: Paid __×_____ Exempt (orphan, government) _____
Waived (e.g., small business, public health) _____

Form 3397 (User Fee Cover Sheet) submitted: YES NO
User Fee ID # 3926
Clinical data? YES ___×_____ NO, Referenced to NDA # _____

Is there any 5-year or 3-year exclusivity on this active moiety in either a (b)(1) or a (b)(2) application? It has been requested by the applicant.

YES NO

If yes, explain:

Does another drug have orphan drug exclusivity for the same indication? YES NO

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

YES NO

Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain.

If yes, has OC/DMPQ been notified of the submission? YES NO

- Does the submission contain an accurate comprehensive index? YES NO
- Was form 356h included with an authorized signature? YES NO
  If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES NO
  If no, explain:
- If an electronic NDA, does it follow the Guidance? N/A YES NO
  If an electronic NDA, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments:
- If in Common Technical Document format, does it follow the guidance? N/A YES NO
- Is it an electronic CTD? N/A YES NO
  If an electronic CTD, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments:
- Patent information submitted on form FDA 3542a? YES NO
- Exclusivity requested? YES, 3 years NO
  Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
- Correctly worded Debarment Certification included with authorized signature? YES NO
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., *"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application."* Applicant may not use wording such as "To the best of my knowledge. . . ."

- Financial Disclosure forms included with authorized signature? YES NO
  (Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)

- Field Copy Certification (that it is a true copy of the CMC technical section)? YES NO

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? YES NO
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.

- List referenced IND numbers: 51,188

- End-of-Phase 2 Meeting(s)? Date(s) _____ NO
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date 2/8/00
  NO
  If yes, distribute minutes before filing meeting.

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
  YES NO

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? YES NO

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A YES NO

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS?
  N/A YES NO

- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO

If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to Nancy Sager (HFD-357)? YES NO

- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO

- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES NO

If 505(b)(2) application, complete the following section:

- Name of listed drug(s) and NDA/ANDA #:

- Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs.)

  YES NO

- Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 314.101(d)(9).

  YES NO

- Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? (See 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9).

  YES NO

- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

  ____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

  ____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

  ____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

  ____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

  IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

  ____ 21 CFR 314.50(i)(1)(ii): No relevant patents.

  ____ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications

that are covered by the use patent. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.

Formatted: Bullets and Numbering

____ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above.)
____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

- Did the applicant:
  - Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

    YES NO
  - Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

    YES NO
  - Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

    N/A YES NO
  - Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

    N/A YES NO
- If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):
  - Certification that each of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

    YES NO
  - A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

    YES NO
  - EITHER
    The number of the applicant's IND under which the studies essential to approval were conducted.

    IND # _____ NO

    OR

    A certification that it provided substantial support of the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

    N/A YES NO
- Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

  YES NO

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

ATTACHMENT

MEMO OF FILING MEETING

Meeting Minutes

Date: August 15, 2000 Time: 1:00 - 1:14 PM Place: Parklawn; Room 17B-45

NDA: 21-258 Drug Name: Climarapro (estradiol/levonorgestrel transdermal delivery system) 0.045/0.015, 0.045/0.030 and 0.045/0.040 mg per day

Indications: Treatment of moderate-to-severe vasomotor symptoms associated with menopause

Type of Meeting: Filing

Sponsor: Berlex Laboratories, Inc.

FDA Lead: Dr. Susan Allen

Meeting Recorder: Ms. Diane Moore

FDA Participants:
Susan Allen, M.D., M.P.H. – Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Shelley Slaughter, M.D., Ph.D. – Team Leader, DRUDP (HFD-580)
Diane Moore - Regulatory Project Manager, DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Amit Mitra, Ph.D. - Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Ron Kavanagh, B.S. Pharm., Pharm.D., Ph.D. – Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)
Lisa Kammerman, Ph.D. - Team Leader, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
Roy A. Blay, Ph.D.- Senior Regulatory Review Officer, Division of Scientific Investigations, Good Clinical Practices Branch I (HFD-46)

Meeting Objective: To discuss the fileability of NDA 21-258.

Background: The NDA was submitted on June 29, 2000. The primary goal date is April 29, 2001. The secondary goal date is June 29, 2001.

Decisions:

· Pharmacology
· NDA is fileable per pharmacology reviewer

· Clinical
· fileable
· two studies were submitted; Study 96042 for VMS and 96043 for protection of the endometrium
· Comments sent from Medical Officer:
· the sponsor presents two multi-center studies to determine the safety and efficacy of ClimaraPro; this will be the first submitted HRT regimen using levonorgestrel as the progestin
· Study 96042 is a 12-week placebo controlled study which appears to show efficacy; the sponsor's label needs revisions; the table for — is unacceptable; —

· Study 96043 is a 52-week randomized trial comparing three dosages of E2/levonorgestrel against estradiol alone; although there were significant dropouts during the study, it was adequately powered to sustain a dropout rate of 42% at one year; no hyperplasia cases were reported, this will be a review issue

· DSI
· the clinical sites for audit need to be determined and forwarded to Dr. Blay

· Regulatory
additional financial disclosure information has been requested from the sponsor; sponsor sent information on July 20, 2000
· the designation of the NDA is 4S, however, this application may be signed at the Division level

· Chemistry, Manufacturing and Quality Control
· Environmental Assessment (EA)
· the sponsor has requested a categorical exclusion; EA is a review issue
· an issue regarding the clarification of the manufacturing facility has been resolved
— should be a test attribute on release and stability of the drug product
· release test method to be evaluated during review
· the sponsor has requested a — shelf life based on submitted — data for two formulations and — data for one formulation; additional — month stability data updates are to be submitted; this is a review issue

· Clinical Pharmacology and Biopharmaceutics
· fileable
· the clinical formulation is the same as the to-be-marketed formulation; a bridging study is not needed
· a bridging study with Climara is not needed

· Statistics
· fileable

Action Items
- none

Signature, minutes preparer Signature, Chair

drafted: dm/8.16.00/N21258FM81500.doc
Concurrence:
LKammerman, RBlay, SAllen 8.21.00/SSlaughter 8.23.00/AMitra, RKavanagh 9.7.00
MRhee 9.18.00/TRumble 9.19.00
Response not received from AParekh
cc:
Archival: NDA 21-258
HFD-580/Div File
HFD-580/DMoore/TRumble
HFD-580/SAllen/DShames/SSlaughter/PPrice/AParekh/RKavanagh/MRhee/AMitra
HFD-580/AJordan

Regulatory Project Manager, HFD-580

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

1. APPLICANT'S NAME AND ADDRESS

Berlex Laboratories, Inc
P.O. Box 1000
Montville, New Jersey 07045-1000

2. TELEPHONE NUMBER *(Include Area Code)*

(973) 276 - 2157

3. PRODUCT NAME

ClimaraPro [Estradiol/ Levonorgestrel Transdermal Delivery System]

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:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.
☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA).

5. USER FEE I.D. NUMBER

3926

6. LICENSE NUMBER / NDA NUMBER

NDA 21-258

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

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, on reverse side before checking box.)*

☐ 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.)*

☐ 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.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT

☐ 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.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Jean R. Bertin	Manager, Regulatory Submissions and Information	06/06/00

FORM FDA 3397 (5/98)

I

4 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
DA 21-258	Efficacy Supplement Type SE-	Supplement Number
Drug: Climara Pro™ (estradiol/levonorgstrel) transdermal system	Applicant: Berlex Laboratories, Inc.	
RPM: K. Sherrod	HFD-580	Phone # 301-827-4260
Application Type: (×) 505(b)(1) ( ) 505(b)(2)	Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	(*) Standard ( ) Priority
• Chem class (NDAs only)	4S
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	April 29, 2001, June 29, 2001, November 21, 2003
❖ Special programs (indicate all that apply)	(*) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	(*) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (*) No
• This application is on the AIP	( ) Yes (*) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(*) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(*) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of	( ) Verified

notice).	
Exclusivity Summary (approvals only)	×
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	×
General Information	
❖ Actions	
• Proposed action	(×) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	(×) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (×) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(×) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling	
• Original applicant-proposed labeling	
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	DMETS-11/14/03
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	10/24/03
• Reviews	
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	11/14/03
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	
❖ Memoranda and Telecons	
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	
• Pre-NDA meeting (indicate date)	
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other	
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	

Clinical and Summary Information	
Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	
❖ Clinical review(s) *(indicate date for each review)*	×
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	×
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	×
❖ Statistical review(s) *(indicate date for each review)*	×
❖ Biopharmaceutical review(s) *(indicate date for each review)*	
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	
• Bioequivalence studies	
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	
• Review & FONSI *(indicate date of review)*	
• Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	
❖ Facilities inspection (provide EER report)	Date completed: (*) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	
❖ Nonclinical inspection review summary	
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	
❖ CAC/ECAC report	

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-258	Efficacy Supplement Type SE-	Supplement Number
Drug: Climara Pro™ (estradiol/levonorgstrel) transdermal system	Applicant: Berlex Laboratories, Inc.	
RPM: K. Sherrod	HFD-580	Phone # 301-827-4260
Application Type: (×) 505(b)(1) ( ) 505(b)(2)	Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	(*) Standard ( ) Priority
• Chem class (NDAs only)	4S
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	April 29, 2001, June 29, 2001, November 21, 2003
❖ Special programs (indicate all that apply)	(*) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	(*) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (*) No
• This application is on the AIP	( ) Yes (*) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(*) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(*) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of	( ) Verified

notice).	
Exclusivity Summary (approvals only)	×
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	×
General Information	
❖ Actions	
• Proposed action	(×) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	(×) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (×) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(×) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	
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❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	×
❖ Statistical review(s) *(indicate date for each review)*	×
❖ Biopharmaceutical review(s) *(indicate date for each review)*	
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	
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NDA 21-258
Climara Pro™ transdermal system
(estradiol/levonorgestrel) 0.045/0.015, 0.045/0.030, and 0.045/0.040 mg/day
Berlex laboratories, Inc.

Pharmacology Review

No pharmacology review was required for this review cycle 2.

NDA 21-258
Climara Pro™ transdermal system
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Berlex laboratories, Inc.

CAC/ECAC Report

No CAC/ECAC report was needed for this product this review cycle 2.

NDA 21-258
Climarapro™ (estradiol transdermal system) estradiol/levonorgestrel 0.045/0.015, 0.045/0.030 and 0.045/0.040 mg per day
Berlex laboratories, Inc.

CAC/ECAC Report

No CAC/ECAC report was needed for this product. Diane Moore 6/11/01

NDA 21-258
Climarapro™ (estradiol transdermal system) estradiol/levonorgestrel 0.045/0.015, 0.045/0.030 and 0.045/0.040 mg per day
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Abuse Liability review(s)

This product does not require an abuse liability review. Diane Moore 6/11/01

NDA 21-258
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DSI Inspections

No DSI inspections were requested for this review cycle 2.

NDA 21-258
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Safety Update

See Medical Officer Review Page _____.

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Safety Update Review

The safety update is included in Medical Officer review dated June 26, 2001, on page 26.

Diane Moore
6/27/01

NDA 21-258
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Advisory Committee

This application was not the subject of an advisory committee during this review cycle 2.

NDA 21-258
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Advisory Committee Meeting Minutes

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

Diane Moore 6/1/01

NDA 21-258
Climara Pro™ transdermal system
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Berlex laboratories, Inc.

Federal Register Notices

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NDA 21-258
Climarapro™ (estradiol transdermal system) estradiol/levonorgestrel 0.045/0.015, 0.045/0.030 and 0.045/0.040 mg per day
Berlex laboratories, Inc.

Federal Register Notices

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

Diane Moore 9/11/01