CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-375/S-016

ADMINISTRATIVE DOCUMENTS

14. PATENT CERTIFICATION

A patent certification pursuant to 21 U.S.C. 355(b)(2) or (j)(2)(A) is not applicable to this supplement to NDA 20-375 for Climara® (estradiol transdermal system).

BERLEX LABORATORIES, INC.

Ted Ikeda

Ted Ikeda
General Counsel Intellectual Properties

May 1, 2000
Date

13. PATENT INFORMATION

Pursuant to 21 CFR § 314.53(d)(2)(B) the undersigned declares that the United States patent identified below, owned by 3M Pharmaceuticals, covers the Composition/Method of Use of Climara® (estradiol transdermal system) which is currently approved under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act.

Type of Patent	Patent Number	Issued to	Original Expiration Date
Composition and Method of Use	5,223,261	Riker Laboratories on June 29, 1993	June 29, 2010

BERLEX LABORATORIES, INC.

Ted Ikeda

Ted Ikeda
General Counsel Intellectual Properties

May 1, 2000
Date

gab/patents/climsmsup/037

EXCLUSIVITY SUMMARY for NDA # 20-375 SUPPL # 016

Trade Name Climara® Generic Name estradiol transdermal system

Applicant Name Berlex Laboratories HFD-580

Approval Date _____

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

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

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

   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

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

YES /___/ NO /_X__/

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

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

YES /_X__/ NO /___/

If yes, NDA # 20-417 Drug Name Fempatch

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

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

YES /___/ NO /___/

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

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

1. Single active ingredient product.

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

YES /___/ NO /___/

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

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

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

YES /___/ NO /___/

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

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

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

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

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

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

YES /___/ NO /___/

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

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

to support approval of the application, without reference to the clinical investigation submitted in the application.

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

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

YES /__/ NO /___/

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

_____

_____

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

YES /___/ NO /___/

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

YES /___/ NO /___/

If yes, explain: _____

_____

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

YES /___/ NO /___/

If yes, explain: _____

_____

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

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

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

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

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

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

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

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

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

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

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

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

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

Investigation #1

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

	_____
	_____
Investigation #2	
IND # _____ YES /___/	NO /___/ Explain: _____
	_____
	_____

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

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

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

YES /___/ NO /___/

If yes, explain: _____

_____

_____

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

/s/

Diane V. Moore
3/30/01 04:35:01 PM
CSO

Susan Allen
3/30/01 04:50:18 PM
MEDICAL OFFICER

FDA Links Searches Check Lists Tracking Links Calendars Reports Help

PEDIATRIC PAGE (Complete for all original application and all efficacy supplements)

View as Word Document

NDA Number:	020375	**Trade Name:**	CLIMARA (ESTRADIOL TRANSDERMAL SYSTEM)
Supplement Number:	016	**Generic Name:**	ESTRADIOL TRANSDERMAL SYSTEM
Supplement Type:	SE1	**Dosage Form:**	
Regulatory Action:	OP	**COMIS Indication:**	TREATMENT OF MODERATE TO SEVERE VASOMOTOR SYMPTOMS ASSOCIATED WITH THE MENOPAUSEVULVAL AND VAGINAL ATROPHY/HYPOESTROGENISM DUE TO HYPOGONADISM CASTRATION OR PRI
Action Date:	6/5/00		

Indication # 1 relief of vasomotor symptoms

Label Adequacy: Does Not Apply

Formulation Needed: NO NEW FORMULATION is needed

Comments (if any):

Ranges for This Indication

Lower Range	Upper Range	Status	Date
0 years	Adult	Waived	

Comments: For post-menopausal women only

This page was last edited on 3/28/01

LS

Signature

3/28/01

Date

16. DEBARMENT CERTIFICATION

Berlex Laboratories, Inc. hereby certifies that it did 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 supplement to NDA 20-375 for Climara® (estradiol transdermal system).

BERLEX LABORATORIES, INC.

Joan Mufascio
Regulatory Submissions &
Information Associate

May 16 2000
Date

Division Director Memorandum

NDA#	**20-375/S-016**
Sponsor:	**Berlex Laboratories**
Drug:	**Climara® (estradiol in an adhesive transdermal system)**
Dosage form:	**7-day adhesive transdermal system**
Dosage strengths and regimens:	**6.5 cm^2 transdermal system containing 2.0 mg estradiol, delivering 25 mcg of estradiol/day** **12.5 cm^2 transdermal system containing 3.8 mg estradiol, delivering 50 mcg of estradiol/day** **18.75 cm^2 transdermal system containing 5.7 mg estradiol, delivering 75 mcg of estradiol/day** **25.0 cm^2 transdermal system containing 7.6 mg estradiol, delivering 100 mcg of estradiol/day**
Approved Indications:	**Treatment of moderate-to-severe vasomotor symptoms associated with the menopause** **Treatment of vulvar and vaginal atrophy** **Treatment of abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology and only when associated with a hypoplastic or atrophic endometrium** **Prevention of postmenopausal osteoporosis**
Submission date:	**June 5, 2000**
Date of memorandum:	**April 4, 2001**

This memorandum provides for my concurrence with the recommendations of the primary and secondary reviewers of all disciplines for approval of the 6.5 cm^2 transdermal system of Climara® for the indication of the treatment of moderate to severe vasomotor symptoms associated with the menopause. The labeling submitted by the

sponsor on April 4, 2001 is acceptable and I recommend that this application be approved.

/s/

Susan Allen
4/4/01 04:06:28 PM
MEDICAL OFFICER

Climara® Team Leader Review

NDA:	**20-375, S-016**
Drug:	**Climara® (estradiol in an adhesive transdermal system)**
Approved Indications:	**1. Treatment of moderate-to-severe vasomotor symptoms associated with the menopause** **2. Treatment of vulvar and vaginal atrophy** **3. Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure** **4. Treatment of abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology and only when associated with a hypoplastic or atrophic endometrium.** **5. Prevention of postmenopausal osteoporosis**
Dosage/Form/Route:	**Proposed for Indication 1-** **6.5 cm^2 transdermal system, nominal delivery rate of 25 mcg of estradiol/day (contains 2.0 mg of estradiol)** **Approved for Indication 1-** **12.5 cm^2 transdermal system, nominal delivery rate of 50 mcg of estradiol/day (contains 3.8 mg of estradiol)** **18.75 cm^2 transdermal system, nominal delivery rate of 75 mcg of estradiol/day (contains 5.7 mg of estradiol)** **25.0 cm^2 transdermal system, nominal delivery rate of 100 mcg of estradiol/day (contains 7.6 mg of estradiol)**
Applicant:	**Berlex Laboratories**
Original Submission Date:	**June 5, 2000**
Primary Review Completed:	**March 26, 2001**
Date of Memorandum:	**March 26, 2001**

Background

The Agency has previously reviewed and approved six transdermal estradiol-containing patches for the treatment of vasomotor symptoms. The first estradiol (E_2)-containing patch to be approved, Estraderm®, had an ethanol reservoir which resulted in skin irritation. Subsequent estradiol patches have incorporated estradiol into a matrix formulation that avoids the use of ethanol and have proved to be less irritating to the skin. Berlex Laboratories has previously received approval (see regulatory history to follow) to market Climara® 50 mcg, 75 mcg and 100 mcg/day estradiol for the treatment of vasomotor symptoms. In this submission Berlex Pharmaceuticals is seeking approval of the 25

mcg/day estradiol transdermal system for the indication of treatment of moderate-to-severe vasomotor symptoms associated with the menopause. This dosage was previously approved for prevention of postmenopausal osteoporosis.

Regulatory History

NDA 20-375 submitted by 3M Pharmaceuticals for Climara® 50 mcg/day and 100 mcg/day estradiol transdermal systems was approved on December 22, 1994. The approved indications were:

1. Treatment of moderate to severe vasomotor symptoms associated with the menopause.
2. Treatment of vulvar and vaginal atrophy.
3. Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure.
4. Treatment of abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology and only when associated with a hypoplastic or atrophic endometrium.

Indications 2, 3, and 4 were granted based on estrogen class labeling.

All rights to NDA 20-375 was transferred to Berlex Laboratories on November 2, 1995. On March 23, 1998, Berlex received approval for NDA 20-375, supplement 9 (S-009) which provided for a 75 mcg/day dose for the treatment of moderate-to severe vasomotor symptoms (MSVS). On March 5, 1999, Berlex received approval for NDA 20-375, supplement 11 (S-011) for Climara® 25 mcg/day for the prevention of postmenopausal osteoporosis.

S-011 did not provide for the treatment of MSVS. On June 5, 2000, the Agency received from Berlex, NDA 20-375, supplement 16 (S-016) for the indication of the treatment of MSVS for the 25mcg/day dosage of Climara®. The application was filed on August 4, 2000.

Chemistry/Manufacturing

The following summary addresses the major points discussed in the chemistry review.

NDA 20-375, S-011 was approved for manufacturing of the 25 mcg/day (6.5 cm^2) transdermal system on March 15, 1999 for prevention of postmenopausal osteoporosis. This supplement referenced DMF —— for the chemistry, manufacturing and control information on the 25 mcg/day transdermal system. This DMF was reviewed on March 3, 1999 (by the same chemistry reviewer who reviewed this supplement [S016]) and was found to adequately support S-011.

All approved and marketed Climara® transdermal systems are manufactured from a common laminate, and all have the same formulation composition (%). The transdermal systems differ in size. The proposed formulation is die cut to 6.5 cm^2 from the common laminate, and has the same formulation composition (%) to that of the other marketed transdermal system sizes.

A communication, dated August 18, 2000 provides for a categorical exclusion request for the environmental assessment based on an expected introduction concentration of less than 1 part per billion. The recommendation is that this categorical exclusion be granted. The inspection of the drug product manufacturing site was satisfactory.

The recommendation of the chemistry reviewer is that this supplemental application can be approved.

Microbiology

A microbiology review was not necessary for this supplement.

Product Name

Climara® is the approved registered trademark.

Pre-clinical Pharmacology and Toxicology

Based on extensive clinical experience with the approved (higher) dosage strengths of Climara® for the treatment of moderate-to-severe vasomotor symptoms associated with the menopause, Pharmacology recommends that NDA 20-375, S-016 should be approved.

Biopharmaceutics

The pharmacokinetics and biopharmaceutics for the 25 mcg/day transdermal system was submitted in NDA 20-375, S-011. The same biopharmaceutics reviewer who reviewed S-011, also reviewed this supplement (S-016). No new human pharmacology or biopharmaceutic data was included in S-016. The formulation used in the clinical trials is the currently approved formulation. Therefore, no additional clinical pharmacology, pharmacokinetic, or bioavailability studies were required.

The review from the Office of Clinical Pharmacology and Biopharmaceutics/ Division of Pharmaceutical Evaluation II (HFD-870) has determined that NDA 20-375, S-016 is acceptable.

Division of Scientific Investigations (DSI)-Clinical Inspection Summary

Following the DSI guidelines regarding criteria for requesting inspection of clinical sites, the medical officer determined that this efficacy supplement had no specific safety concerns and did not require inspection

Clinical Efficacy and Safety

Efficacy

The NDA contains two well-designed primary clinical trials to evaluate the efficacy for treatment of moderate-to-severe vasomotor symptoms. In these two primary trials, 379 subjects were randomized and 187 subjects received the 25 mcg/day Climara® dosage.

Study 97074

Study 97074 was a randomized, parallel-group, double-blind, multi-center (18) study of 12 weeks duration conducted in the United States and designed to compare the efficacy and safety of Climara® 25mcg/day with that of placebo in the treatment of MSVS in 200 postmenopausal women. Each cycle was designed to be 28 days in duration. Each subject received either an active-drug or a placebo transdermal system every 7 days. Placebo patches were identical to the Climara® 25 mcg/day patch except that they contained no 17β-estradiol.

The enrollment criteria were consistent with the Clinical Evaluation of Combination Estrogen/Progestin-Containing Drug Products used for Hormone Replacement Therapy of Postmenopausal Women, 1995 Guidance (HRT Guidance) requirements for clinical trials of efficacy and safety for the treatment of vasomotor symptoms. All subjects either received an endometrial biopsy at screening or had a documented negative endometrial biopsy within 6 months of baseline. Current recommendations are that subjects receive endometrial biopsies within 3 months of baseline, however, this trial was conducted between January 1998 and January 1999 prior to institution of those recommendations. Subjects who were currently using HRT received an 8 week washout period and this is considered adequate. During a 4-week placebo run-in period, each subject received placebo transdermal systems. Subjects were eligible to enroll if they had 7 or more moderate-to-severe hot flushes per day or 60 or more moderate to severe hot flushes per week during any consecutive 7 days of the 4 week run-in period. During the treatment period, the 25 mcg/day transdermal estradiol system or a placebo system was applied every 7 days to a clean and dry location on the abdomen or buttock. Subjects were instructed to reapply any transdermal system that became detached or to replace it with a new (spare) system if the old system would not adhere. Subjects were told to follow a fairly restrictive daily activity regimen following system application that avoided swimming, tub bathing and the use of saunas and medicated soaps. Showering and the use of non-medicated soaps were allowed. Subjects were also instructed not to expose the transdermal systems to sunlight. Following randomization, subjects returned to the clinic at Week 4, Week 8 and Week 12.

A total of 186 subjects were randomized into the study. Of these 186 subjects, 92 subjects received Climara® 25 mcg/day and 94 subjects received placebo. A total of 164 (88%) subjects completed the study (defined as completing 3 cycles [each 28 days in duration] or completion of 6 successful weeks of the study before discontinuation). The most common reasons for discontinuations were lack of efficacy (10% total, 3% Climara® and 7% placebo) and voluntary withdrawal (8% total, 2% Climara® and 6% placebo). Protocol-deviation, adverse events and "other" accounted for 2%, 2%, and 3% of the total discontinuations, respectively.

The Intent-to-Treat population was defined as all randomized subjects. Despite having the entrance criterion of ≥ 7 moderate-to-severe vasomotor flushes per day or ≥ 60 per week, the Sponsor also enrolled subjects into the study who did not meet this criterion. Only those subject who met the enrollment criterion of ≥ 7 moderate-to-severe vasomotor flushes per day or ≥ 60 per week were considered in the review of efficacy for this application. Therefore, the population considered for efficacy in the clinical review was not all subjects randomized, but rather all subjects randomized with the requisite number of MSVS. The mean daily number of all hot flushes (mild, moderate and severe) at baseline (12.1-Climara® vs. 14.1-placebo) and the mean weekly number of all hot flushes at baseline (84.9- Climara® vs. 98.6-placebo) were not statistically significantly different between the two treatment groups. The mean daily number of MSVS and the change from baseline in the mean daily number of MSVS are shown in Table 1 below modified from the medical officer's review (Tables 4 and 5).

Table 1. Mean Daily Number of Moderate-to-Severe Hot Flushes and Change from Baseline During Therapy in All Subjects with Moderate-to-Severe Hot Flushes Per Day at Baseline, Intent-to-Treat Population

Week	Placebo	Climara®25 mcg/day
Baseline Mean	11.25 (n^a=92)	10.15 (n^a=89)
Week 4 Mean Mean Change[b] p-value vs. Climara®[c]	6.20 (n^a=84) -5.11 (n^a=83) 0.002	3.70 (n^a=83) -6.45 (n^a=82)
Week 8 Mean Mean Change[b] p-value vs. Climara®[c]	5.68 (n^a=72) -5.98 (n^a=71) 0.002	2.40 (n^a=85) -7.69 (n^a=84) -
Week 12 Mean Mean Change[b] p-value vs. placebo[c]	5.51 (n^a=66) -5.98 (n^a=65) 0.003	2.27 (n^a=68) -7.56 (n^a=68)

[a]n= number of subjects contributing data
[b]mean change from baseline
[c]p-value treatment effect obtained from the following model based on ranks: Y=TMT INV, where Y = outcome variable, TMT = treatment group, and INV =investigator

There is a decrease of greater than 2 moderate-to-severe hot flushes per day in the Climara® group compared to the placebo that is evident at Week 4 and maintained through Week 12.

The mean daily hot flush severity and the change from baseline in the mean daily hot flush severity is shown in Table 2, modified from the medical officer's review (Table 6), the statistician's review (Table 3), and the Sponsor's Tables 18 and 21.

Table 2. Mean Daily Severity and Change from Baseline in the Mean Daily Severity of Hot Flushes During Therapy in All Subjects with Moderate-to-Severe Hot Flushes Per Day at Baseline, Intent-to-Treat Population

Week	Placebo	Climara®25 mcg/day
Baseline Mean	2.44 (n^a=92)	2.42 (n^a=89)
Week 4 Mean Mean Change[b] p-value vs. Climara®[c]	2.27 (n^a=84) -0.18 (n^a=83) ≤0.001	1.61 (n^a=83) -0.81 (n^a=82)
Week 8 Mean Mean Change[b] p-value vs. Climara®[c]	2.09 (n^a=72) -0.36 (n^a=71) ≤0.001	1.36 (n^a=85) -1.05 (n^a=84)
Week 12 Mean Mean Change[b] p-value vs. Climara®[c]	1.91 (n^a=66) -0.53 (n^a=65) ≤0.001	1.35 (n^a=68) -1.08 (n^a=68)

[a]n= number of subjects contributing data
[b]mean change from baseline.
[c]p-value treatment effect obtained from the following model based on ranks: Y=TMT INV, where Y = outcome variable, TMT = treatment group, and INV =investigator

Clearly, there is a clinically and statistically significant reduction in the frequency and severity of hot flushes in the Climara® 25 mcg/day group when compared to placebo. This reduction is evident by Week 4 and is maintained through Week 12.

Safety

There were no deaths in study 97074. There were two serious adverse events requiring hospitalization; a rotator cuff injury, and a dermatologic surgery for removal of skin cancer. These two events were both in subjects who had been treated with Climara®, but the events were considered appropriately as unrelated to study drug treatment. There were 6 other serious events that did not require hospitalization. Two of these events, an accidental injury and a case of erythema nodosum, were in the 25 mcg/day Climara® treatment group and 4 of the 6 serious adverse events, not requiring hospitalization, were in the placebo treatment arm and consisted of 1 case each of abdominal pain, diarrhea, severe migraine headache and an abnormal laboratory value. Only 2 subjects out of the 186 randomized subjects discontinued the study because of adverse events. The adverse event experienced by the two subjects was one case each of moderate generalized edema and nausea. Of the186 subjects, 52.7% experienced 1 or more adverse events. The most common adverse events were upper respiratory infection (8.6% of the total) and application site reaction (5.4% total, 5.4 % of the 25 mcg/day Climara® treatment group and 5.3% of the placebo treatment group). Overall, there was a low incidence of adverse events in the 25 mcg/day Climara® treatment group (and placebo), and this is consistent with that expected for a low dose transdermal estrogen product.

Clinical Study 97095

Study 97095 was a Phase 3, randomized, double-blind, double-dummy, active-comparator, multi-center study of 12 weeks duration conducted in the United States and designed to compare the

efficacy and safety of 25 mcg/day Climara® with that of oral Premarin® (0.3 mg) in the treatment of moderate-to-severe vasomotor symptoms in postmenopausal women. Each cycle was designed to be 28 days in duration. Each subject received a transdermal system (with active-drug or placebo) and a capsule (containing a 0.3mg Premarin® tablet or placebo) every 7 days. Transdermal systems were applied to a location on the abdomen or buttock every 7 days. One capsule was taken daily upon retiring. Enrollment requirements and study procedures were identical to those of Protocol 97074 (except for the use of an active control) and were consistent with those of the 1995 HRT Guidance document.

One hundred ninety three (193) subjects were randomized at 19 centers in the U.S. Of these 193 subjects, 95 subjects were randomized to receive 25 mcg/day Climara® and 98 were randomized to receive Premarin®. One hundred seventy three (173) subjects completed the study according to the definition of completer as either a subject completing 3 cycles (each cycle being 28 days in duration) or a subject completing 6 successful weeks of the study before discontinuation. The most common reasons for discontinuations were adverse events (5.7% total, 5.3% Climara® and 6.1 % Premarin®) and "other" (4.7% total, 4.2% Climara® and 5.1% Premarin®). Protocol-deviation, lack of efficacy and voluntary withdrawal accounted for 2.1%, 1.6%, and 2.1% of the total discontinuations, respectively.

The Intent-to-Treat population was defined as all randomized subjects. As stated above for Study 97074, the Sponsor enrolled some subjects with only mild vasomotor symptoms, even though the protocol enrollment criterion required subjects to have ≥ 7 moderate-to-severe vasomotor flushes per day or ≥ 60 per week. The medical officer in his efficacy analysis considered only subjects who met the requisite number of moderate-to severe-vasomotor symptoms at baseline. The mean daily number of all hot flushes (mild, moderate and severe) at baseline (13.4-Climara® vs. 13.4-Premarin®) and the mean weekly number of all hot flushes at baseline (94.1-Climara® vs. 94.1-Premarin®) were not statistically significantly different between the two treatment groups. The mean daily number of MSVS and the change from baseline in the mean daily number of MSVS is shown in Table 3 below modified from the medical officer's review (Tables 12 and 13).

Table 3. Mean Daily Number of Moderate-to-Severe Hot Flushes and Change from Baseline During Therapy in All Subjects with Moderate-to-Severe Hot Flushes Per Day at Baseline, Intent-to-Treat Population

Week	Premarin®	Climara®25 mcg/day
Baseline		
n[a]	98	95
Mean	10.99	11.09
Week 4		
n[a]	91	88
Mean	4.07	3.86
Mean Change[b]	-6.97	-7.07
Week 8		
n[a]	83	83
Mean	2.18	2.94
Mean Change[b]	-8.14	-7.91
Week 12		
n[a]	74	75
Mean	1.83	2.27
Mean Change[b]	-8.44	-8.29

[a]n= number of subjects contributing data
[b]Mean change from Baseline

The mean daily hot flush severity and the change from baseline in the mean daily hot flush severity is shown in Table 4, modified from the medical officer's review (Table 14) and the Sponsor's Table 22.

Table 4. Mean Daily Severity and Change from Baseline in the Mean Daily Severity of Hot Flushes During Therapy in All Subjects with Moderate-to-Severe Hot Flushes Per Day at Baseline Intent-to-Treat Population

Week	Premarin®	Climara®25 mcg/day
Baseline		
n[a]	98	95
Mean	2.40	2.43
Week 4		
n[a]	91	88
Mean	1.66	1.75
Mean Change[b]	-0.74	-0.67
Week 8		
n[a]	83	83
Mean	1.33	1.42
Mean Change[b]	-1.06	-1.02
Week 12		
n[a]	74	75
Mean	1.07	1.11
Mean Change[b]	-1.32	-1.33

[a]n= number of subjects contributing data
[b]Mean change from Baseline

The Sponsor's original protocol planned for within group paired tests for week 4 and week 12 compared to baseline. As per comments from the statistical reviewer, within-group comparisons are not appropriate to assess efficacy for this indication. The indication of interest is assessed on between-group comparisons. Comparisons between the Climara® treatment arm and the Premarin® treatment arm are not appropriate because the study was not adequately designed to reach efficacy conclusions based on those comparisons. No clinically meaningful difference was prospectively proposed for the comparison of Climara® to Premarin®. Study 97095 did not have a placebo treatment arm, so the Climara treatment arm can not be compared to placebo. However, based on the descriptive statistical results for the Climara® treatment arm only, the results of Study 97095 appear to be supportive of the efficacy of the 25mcg/day Climara® dosage.

Safety

There were no deaths in Study 97075. There were three serious adverse events requiring hospitalization. Two of the three subjects with serious adverse events requiring hospitalization received Premarin®. The serious adverse events in these two subjects were 1 case of severe constipation and one case of polymicrobial bacteremia following repair of an oral antral fistula and tooth extraction. Investigators categorized these two serious adverse events as not related to study drug administration. The third case of a serious adverse event requiring hospitalization occurred in a subject treated with 25 mcg/day of Climara®. She experienced severe leg cramps, hypertension, dizziness, and chest pain. The hypertension was considered as possibly related to study drug administration. There were 13 other serious events that did not require hospitalization. Seven of these 13 serious events that did not require hospitalization occurred in the 25 mcg/day Climara® treatment group and 6 in the 0.3 mg Premarin® treatment group. These adverse events

included back pain, headache, insomnia, colitis, constipation, sinusitis, acne, taste perversion and an abnormal liver function test. One subject in the 25 mcg/day Climara® treatment group reported an application site reaction. Eleven subjects out of the 193 randomized subjects discontinued the study because of adverse events. Six of the subjects who discontinued prematurely because of adverse events were in the 0.3 mg Premarin® group and 5 were in the 25 mcg/day Climara® treatment group. Only 1 of the 11 adverse events leading to discontinuation, an application site reaction in a subject in the 25 mcg/day Climara® treatment group, was definitely related to study drug administration. Of the 193 subjects, 56.5% experienced 1 or more adverse events. The most common adverse events were headache (6.7% of the total) and application site reaction (6.2% total, 7.4 % of the 25 mcg/day Climara® treatment group and 5.1% of the Premarin® treatment group). Overall, there was a low incidence of adverse events in the 25 mcg/day Climara® treatment group and the 0.3 mg/day Premarin® treatment group and this is consistent with that expected for a low dose transdermal estrogen product and the lowest approved Premarin dose.

Discussion and Conclusions

The results of Study 97074 demonstrate that the 25 mcg/day Climara® dose produces a clinically and statistically significant reduction in the frequency and severity of hot flushes, when compared to placebo, and this reduction is evident by Week 4 and is maintained through Week 12. Therefore, the 25mcg/day Climara® dose is efficacious in the treatment of moderate-to-severe vasomotor symptoms. The safety of this dose of Climara® is comparable to that of other low dose estrogen products. Application site reactions were low. I concur with the reviewing chemist, medical officer and statistician that this dose can be approved.

The agreed upon label is included in this action package. The approved label was modified to bring it into compliance with the Non-Contraceptive Estrogen Drug Products Labeling-1999 Draft Guidance. Consistent with this guidance, the DESI indication of "Treatment of abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology and only when associated with a hypoplastic or atrophic endometrium" was removed. This indication is no longer considered appropriate for this class of drugs.

In addition to the above changes, the following changes were also made. These changes are being added to the Draft Guidance on Non-Contraceptive Estrogen Drug Product Labeling.

1. Inclusion of the following language under **WARNINGS 1.b. Breast Cancer.** While some epidemiologic studies suggest a very modest increase in breast cancer risk for estrogen alone users versus non-users, other studies have not shown any increased risk. The addition of a progestin to estrogen may increase the risk for breast cancer over that noted in non-hormone users more significantly (by about 24-40%), although this is based solely on epidemiologic studies, and definitive conclusions await prospective controlled clinical trials.

   Women without a uterus who require hormone replacement should receive estrogen-alone therapy, and should not be exposed unnecessarily to progestins. Women with a uterus who are candidates for short-term combination estrogen/progestin therapy (for relief of vasomotor symptoms) are not felt to be at a substantially increased risk for breast cancer. Women with a uterus who are candidates for long-term use of estrogen/progestin therapy should be advised of potential benefits and risks (including the potential for an increased risk of breast cancer). All women should receive yearly breast exams by a

healthcare provider and perform monthly breast-self examinations. In addition, mammography examinations should be scheduled as suggested by providers based on patient age and risk factors.

2. Inclusion of the following language under **PRECAUTIONS A. GENERAL** 2. Cardiovascular risk. The effects of estrogen replacement on the risk of cardiovascular disease have not been adequately studied. However, data from the Heart and Estrogen/Progestin Replacement Study (HERS), a controlled clinical trial of secondary prevention of 2,763 postmenopausal women with documented heart disease, demonstrated no benefit. During an average follow-up of 4.1 years, treatment with oral conjugated estrogen plus medroxyprogesterone acetate did not reduce the overall rate of coronary heart disease (CHD) events in postmenopausal women with established coronary disease. There were more CHD events in the hormone treated group than in the placebo group in year 1, but fewer events in years 3 through 5.

3. A new table that presents the efficacy of the 25 mcg/day dose for the treatment of vasomotor symptoms at 4, 8 and 12 weeks.

Shelley R. Slaughter, MD, Ph.D.
Reproductive Medical Team Leader

cc: Division File NDA 20-375
S. Allen, MD
D. Shames, MD
P. Price, MD
K. Meaker, M.S.
A. Parekh, Ph.D.
R. Kavanaugh
A. Mitra, Ph.D.
D. Moore
S. Slaughter, M.D., Ph.D.

/s/

Shelley Slaughter
7/27/01 03:55:20 PM
MEDICAL OFFICER

MEMORANDUM

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

DATE: March 21, 2001

FROM: Kim Colangelo
Senior Regulatory Associate
Division of Reproductive and Urologic Drug Products (HFD-580)

Subject: Review of Financial Disclosure documents

To: NDA 20-375/S-016

I have reviewed the financial disclosure information submitted by Berlex Laboratories in support of their supplemental NDA, NDA 20-375/S-016.

Two studies were conducted to support the safety and efficacy of Climara (estradiol transdermal system) for the treatment of moderate to severe vasomotor symptoms associated with menopause at a dose of 0.025 mg estradiol/day. 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 97074, "A Multicenter, Double-Blind, Placebo-Controlled, Randomized Study to Determine Efficacy in the Relief of Hot Flushes in Women Receiving Transdermal Estradiol"	Study ongoing as of February 2, 1999	Appropriate documentation received, financial disclosure submitted (no significant finding), reporting rate acceptable
Study 97095, "A Multicenter, Double-Blind, controlled, Randomized Study to Determine Efficacy in the Relief of Hot Flushes in Women Receiving Transdermal Estradiol Compared to Oral Conjugated Estrogens"	Study ongoing as of February 2, 1999	Appropriate documentation received, no financial disclosure submitted, reporting rate acceptable

Documents reviewed:

Financial disclosure certification dated May 31, 2000
Financial disclosure certification dated June 13, 2000
Facsimile to Ms. Lana Pauls dated July 20, 2000, providing the number of patients at each site for both "pivotal" trials
Facsimile dated September 15, 2000, describing Berlex's efforts at "due diligence"
Submission dated February 13, 2001, providing additional information requested February 2, 2001

Study 97074

I was troubled by the high rate of non-compliance by the investigators for this Study, and the lack of diligence on the part of the sponsor to obtain the information. The sponsor had described their due diligence in obtaining the information as follows:

> A letter was sent to each study site on February 23, 2000. Since all sites closed between March and September 1999, the letters were not sent CERTIFIED, nor was any additional action taken to obtain outstanding Financial Disclosure forms.

Bias on the part of these seven investigators, affecting 34% of the patients enrolled, could feasibly impact the outcome of Study 97074. I contacted Ms. Linda Carter, Office of Drug Evaluation I, for guidance on Center policy.

Based on my discussion with Ms. Carter, I contacted Mr. Geoff Millington of Berlex on February 2, 2001. I strongly recommended additional efforts (e.g., contacting sites for forwarding addressed, Internet searches, professional society database searches) to contact and obtain financial disclosure information from all non-compliant investigators. I requested that Mr. Millington submit correspondence to the NDA regarding their efforts, and that updated information on submitted financial disclosure documents be provided by February 26, 2001.

The sponsor submitted additional disclosure information on February 13, 2001, providing certification for five of the seven sites. One additional site provided disclosure of interests [redacted] disclosed that he is on the [redacted], and has other research grants); however, this site only enrolled one patient.

Of the 18 sites that enrolled patients in this study, one did not submit financial disclosure information. That site accounts for 5% (8/152) of the patients in this study.

Study 97095

Of the 19 sites that enrolled patients, four investigators failed to submit financial disclosure information. These four sites account for 15% (24/160) of the patients in this study. [redacted]

Conclusion:

Adequate documentation was submitted to comply with 21 CFR 54. The sponsor has acted with due diligence in attempting to obtain documentation from non-compliant investigators in Study 97074, and the rate of return is acceptable for both studies. The information disclosed by [redacted] is not significant enough to impact the study outcome.

/s/

Kim Colangelo
3/21/01 09:08:18 AM
CSO

Meeting Minutes

Date: March 20, 2001 **Time:** 11:00 AM - 12:00 PM **Place:** Parklawn; Rm. 17B-43

NDA: 20-375/S-016 **Drug Name:** Climara (estradiol transdermal system) 0.025 mg estradiol/day

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

Type of Meeting: labeling

Sponsor: Berlex Laboratories, Inc.

FDA Lead: Dr. Shelley Slaughter

Meeting Recorder: Ms. Diane Moore

FDA Participants:
Shelley Slaughter, M.D., Ph.D. - Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Phill Price, M.D. - Medical Officer, DRUDP (HFD-580)
Diane Moore - Regulatory Project Manager, DRUDP (HFD-580)
Amit Mitra, Ph.D. - Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Venkateswar R. Jarugula, Ph.D. - Pharmacokinetic Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Kate Meaker, M.S. - Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
Lisa Stockbridge, Ph.D. - Regulatory Reviewer, Division of Drug Marketing, Advertising and Communications (DDMAC; HFD-42)

Meeting Objective: To discuss the labeling comments from the sponsor for the physician insert and the patient package insert for Supplement-016.

Background: A letter was sent to the sponsor on March 14, 2001, with labeling comments for Supplement 014. The comments for Supplement 014 were to also be incorporated in the labeling for Supplement 016. The sponsor submitted the labeling with revisions and further comments on March 19, 2001.

Decisions:
Physician package insert

- the Division requested that the paragraph below from the **Pharmacokinetics** section be deleted from the Climara labeling; the sponsor requested that it be retained; the Division feels that the paragraph should not be included in the labeling because the comparison to ——— does not add any relevant information to the labeling

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

- th[redacted]

Action Items	Responsible Person:	Due Date:
• send letter to sponsor with proposed labeling revisions	Ms. Moore	1-2 weeks

Signature, minutes preparer

Signature, Chair

Post Meeting Addendum: The attached labeling revisions were sent to the sponsor in a regulatory letter on March 27, 2001.

drafted: dm/3.27.01/N20375S16LM32001.doc

Concurrence:
J.Best, V.Jarugula, K.Meaker 3.28.02/S.Slaughter 4.3.01
L.Stockbridge, A.Mitra, P.Price
4.5.01

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

/s/

Diane V. Moore
1/5/01 12:51:56 PM

Shelley Slaughter
4/5/01 03:10:44 PM

Meeting Minutes

Date: March 7, 2001 **Time:** 11:00 - 11:45 AM **Place:** Parklawn; Rm. 17B-43

NDA: 20-375/S-016 **Drug Name:** Climara (estradiol transdermal system) 0.025 mg estradiol/day

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

Type of Meeting: 9-month status/labeling

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, 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.D., Ph.D. – Pharmacokinetics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Kate Meaker, M.S. - Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
Aurora Breaza, Ph.D.- Statistician, DBII (HFD-705)

Meeting Objective: To discuss the labeling and the status of reviews for Supplement-016.

Background: Previously approved doses for MSVS include 0.05 mg, 0.075 mg and 0.10 mg. Supplement-016 was submitted on June 2, 2000. The 10-month goal date is April 5, 2001; the 12-month goal date is June 5, 2001.

Decisions:
- the anhydrous form of estradiol was revised in Supplement-013 (approved May 20, 1999)
-
-
-
-
-
  - the sponsor has submitted additional financial disclosure information

- Pharmacology:
  - since higher doses of these ingredients have been approved, a memo to the file by the Pharmacologist will be submitted, a formal review is not necessary
- Chemistry, Manufacturing and Quality Control
  - review pending
- Clinical
  - review pending
  - the **Adverse Events** section will be reworded to add additional events from Study 97074
- Clinical Pharmacology and Biopharmaceutics
  - revisions made to Supplement-014 will also be included in revisions to the labeling for Supplement-016; other revisions to Supplement-016 will be added as appropriate
  - the Biopharmaceutics Team Leader will sign off on the action package for the reviewer

Action Items	**Responsible Person:**	**Due Date:**
• send letter to sponsor with proposed labeling revisions	Ms. Moore	1-2 weeks

Signature, minutes preparer

Signature, Chair

drafted: dm/3.7.01/N20375S16SM3701.doc

Concurrence:

T.Rumble 3.19.01/R.Kavanagh, K.Meaker 3.20.01/A.Mitra 3.23.01/S.Slaughter 3.27.01
P.Price 3.29.01/S.Allen 3.30.01

Response not received from A.Breaza

/s/

Diane V. Moore
3/30/01 01:09:51 PM

Susan Allen
3/30/01 01:40:42 PM

Meeting Minutes

Date: February 7, 2001 **Time:** 11:05 - 10:20 AM **Place:** Parklawn; Rm. 17B-43

NDA: 20-375/S-016 **Drug Name:** Climara (estradiol transdermal system) 0.025 mg estradiol/day

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

Type of Meeting: 8-month status

Sponsor: Berlex Laboratories, Inc.

FDA Lead: Dr. Shelley Slaughter

Meeting Recorder: Ms. Diane Moore

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

Meeting Objective: To discuss the status of reviews for Supplement 16.

Background: Previously approved doses for MSVS include 0.05 mg, 0.075 mg and 0.10 mg. Supplement 16 was submitted on June 2, 2000. The primary goal date is April 5, 2001; the secondary goal date is June 5, 2001.

Decisions:

- Regulatory:
  - the goal date for all primary reviews to be completed, including Team Leader sign-off is on or before March 1, 2001
  - upon review of the financial disclosure information, it was found that 34% of the investigator information was submitted; the sponsor has been requested to seek the remainder of the investigator information with due diligence
- Pharmacology:
  - since higher doses of these ingredients have been approved, Pharmacology has no toxicological concerns, per the Pharmacology reviewer, Dr. Raheja
- Chemistry, Manufacturing and Quality Control
  - review pending
  - the inspection of the 3M manufacturing facility has been completed and is satisfactory

- EA
  - the sponsor has submitted the requested EA information; a categorical exclusion request was submitted on August 18, 2000, for environmental assessment; the decision of the exclusion needs to be clarified
- Clinical
  - review pending
  - the **Adverse Event** section will be reworded to add additional events from Study 97074
- DSI inspection
  - a DSI inspection is not warranted for this supplement because this is a lower dose of an approved drug product and there was no suspected issues regarding the study sites
- Clinical Pharmacology and Biopharmaceutics
  - Supplement 14 for this NDA contains proposed labeling which is also included in Supplement 16; the study data was sent to the IND, but was not included in the supplement; the sponsor was requested to submit the data to the NDA supplement; the sponsor submitted the study data and it is being reviewed
  - the Biopharmaceutics Team Leader will sign off on the action package for the reviewer

Action Items	**Responsible Person:**	**Due Date:**
• check on environmental exclusion status	Dr. Mitra	1-2 weeks

Signature, minutes preparer

Signature, Chair

drafted: dm/2.24.01/N20375S16SM2701.doc

Concurrence:

T.Rumble 2.28.01/A.Mitra 3.2.01/S.Slaughter, R.Kavanagh 3.5.01

Response not received from P.Price

/s/

Diane V. Moore
3/15/01 09:12:25 PM

Shelley Slaughter
3/19/01 03:16:39 PM

Meeting Minutes

Date: January 8, 2001 **Time:** 10:30 - 10:45 AM **Place:** Parklawn; Rm. 17B-43

NDA: 20-375/S-016 **Drug Name:** Climara (estradiol transdermal system) 0.025 mg estradiol/day

Indications: Treatment of moderate-to-severe vasomotor symptoms (MSVS) 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, DRUDP (HFD-580), 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.D., Ph.D. – Pharmacokinetics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (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 Supplement 16.

Background: Previously approved doses for MSVS include 0.05 mg, 0.075 mg and 0.10 mg. Supplement 16 was submitted on June 2, 2000. The primary goal date is April 5, 2001; the secondary goal date is June 5, 2001.

Decisions:
- Regulatory:
  - the sponsor has submitted the additional requested financial disclosure information
  - the goal date for all reviews to be completed, including Team Leader sign-off is March 1, 2001
- Pharmacology:
  - since higher doses of these ingredients have been approved, Pharmacology has no toxicological concerns, per Pharmacology reviewer
- Chemistry, Manufacturing and Quality Control
  - review pending; a review was completed on this dose for a prevention of osteoporosis indication in DMEDP (HFD-510); no new issues have arisen since that review; a memorandum may be sufficient in lieu of a full review
  - manufacturing sites were inspected about two years ago

- EA
  - the sponsor has submitted the requested EA information; a categorical exclusion request was submitted on August 18, 2000, for environmental assessment
- Clinical
  - review pending
- DSI inspection
  - a DSI inspection is not warranted for this supplement because this is a lower dose of an approved drug product and there was no suspected issues regarding the study sites
- Clinical Pharmacology and Biopharmaceutics
  - no new biopharmaceutical information has been submitted; the data for this dosage was reviewed in the Division of Metabolic and Endocrine Drug Products (HFD-510); labeling comments will follow in a memorandum to the file with reference to the previous review
- Statistics
  - review pending with targeted goal date of March 1, 2001
  - the missing sections have been submitted to the NDA
  - the review will include an evaluation of unexpected dropout rates and unexpected reasons for dropouts in the clinical review; otherwise, the statistical evaluation appears to be adequate

Action Items	**Responsible Person:**	**Due Date:**
• schedule labeling meeting for end of January	Ms. Moore	one week
• check on GMP status	Dr. Mitra	1-2 weeks

_____ _____

Signature, minutes preparer Signature, Chair

Post Meeting Status: An inspection request for the 3M facility was submitted on January 13, 2000.

drafted: dm/1.9.01/N20375S16SM1801.doc

Concurrence:
T.Rumble, DShames, RKavanagh, KMeaker 1.10.01/P.Price 1.11.01

cc:
Archival NDA 20-375/S-016
HFD-580/Div File
HFD-580/DMoore/TRumble
HFD-580/SAllen/DShames/SSlaughter/PPrice/AParekh/VJarugula/RKavanagh/MRhee/AMitra
HFD-580/LKammerman/MWelch

/s/

Diane V. Moore
1/17/01 02:21:38 PM

Daniel A. Shames
1/18/01 02:59:02 PM

Moore

Meeting Minutes

Date: August 1, 2000 **Time:** 11:30 - 11:40 AM **Place:** Parklawn; Rm. 17B-43

NDA: 20-375/S-016 **Drug Name:** Climara (estradiol transdermal system) 0.025 mg estradiol/day

Indications: Treatment of moderate-to-severe vasomotor symptoms (MSVS) 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)
Daniel Shames, M.D. – Acting Deputy, DRUDP (HFD-580)
Shelley Slaughter, M.D., Ph.D. – Team Leader, 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, DNDC II @ DRUDP (HFD-580)
Ron Kavanagh, B.S., Pharm.D., Ph.D. – Pharmacokinetics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Lisa Kammerman, Ph.D. - Team Leader, Division of Biometrics II (DBII) @ DRUDP (HFD-580)

Meeting Objective: To discuss the fileability of Supplement 16 to add a new low strength transdermal system (6.5 mg^2 delivering 0.025 mg estradiol/day).

Background: Previously approved doses for MSVS include 0.05 mg, 0.75 mg and 0.10 mg. Supplement 16 was submitted on June 2, 2000. The primary goal date is April 5, 2001, the secondary goal date is June 5, 2001.

Discussion Items:
- the 0.025 mg strength has been approved for the prevention of osteoporosis

Decisions:

- Regulatory:
  - Fileable
  - the sponsor has been requested to submit additional financial disclosure information in regard to the number of patients at each site in which information was not received
- Pharmacology:
  - fileable per electronic message from Pharmacology reviewer
- Chemistry, Manufacturing and Quality Control
  - fileable
- EA
  - the sponsor needs to submit a copy of the original EA/AEA and from the original NDA application and a discussion of the differences/changes from the original application and the impact of these differences on the environment from those described in the original EA/AEA; this is a fileability issue
- Clinical
  - fileable
  - the sponsor has submitted two Phase 3 double-blinded randomized trials
- DSI inspection
  - a DSI inspection is not warranted for this supplement
- Clinical Pharmacology and Biopharmaceutics
  - fileable
  - no new biopharmaceutical information has been submitted; the data for this dosage was reviewed in the Division of Metabolic and Endocrine Drug Products (HFD-510); labeling comments will follow
- Statistics
  - Fileable
  - the table of contents on page 736 in the statistics section (Item 8, Vol. 7) lists Statistical Appendixes 1.1, 1.2, 2.1 and 2.2; these appear to be missing; the location should be clarified or the missing pages submitted to the file

Action Items	**Responsible Person:**	**Due Date:**
• request items from sponsor	Ms. Moore	one week

/S/

/S/

Signature, Chair

drafted: dm/8.7.00/N20375S16FM8100.doc

Concurrence:

MRhee, LKammerman, SAllen 8.21.00/RKavanagh, DShames, SSlaughter 8.23.00
TRumble 8.24.00/AMitra 8.29.00

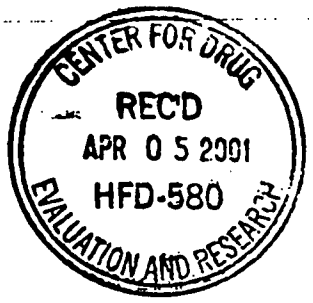
cc:
Archival NDA 20-375/S-016
HFD-580/Div File

HFD-580/DMoore/TRumble
HFD-580/SAllen/DShames/SSlaughter/PPrice/AParekh/VJarugula/RKavanagh/MRhee/AMitra
HFD-580/LKammerman

UPS OVERNIGHT

ORIGINAL

BERLEX



Drug Development & Technology
Division of Berlex Laboratories, Inc.

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

April 4, 2001

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

SC-1-016-BL

Dear Dr. Allen:

RE: NDA 20-375 S-016
Climara® (Estradiol Transdermal System)
Response to a Request for Information

Reference is made to Berlex NDA 20-375 for Climara® (estradiol transdermal system). Additional reference is made to Supplement 016 which was submitted on June 2, 2000 and which provided for the indication, relief from vasomotor symptoms, for the lowest (0.025 mg/day) Climara® patch strength.

Additional reference is made to our submission of April 4, 2001 and to April 4, 2001 phone conversations between Ms. Moore and the undersigned wherein Ms. Moore requested corrections on two pages, one from the physician insert and one from patient insert.

Attached to this correspondence are the two corrected pages as requested.

Please contact the undersigned at (973) 487-2254 with any questions.

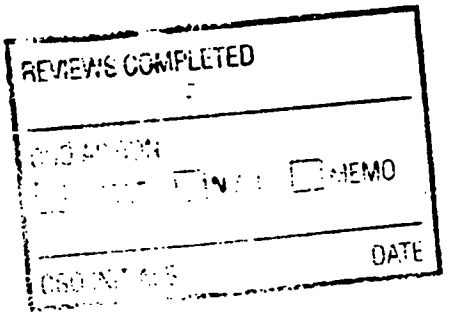
Sincerely,

BERLEX LABORATORIES, INC.

Geoffrey Millington
Manager, Drug Regulatory Affairs

GPM/055

CC: fax (with attachments) to Diane Moore



TELEFAX
UPS OVERNIGHT

BERLEX

ORIGINAL

April 3, 2001

Drug Development & Technology
Division of Berlex Laboratories, Inc.

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

NDA SUPP AMEND

21-016-BL

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 20-375 S-016
Climara® (Estradiol Transdermal System)
Response to a Request for Information

Reference is made to Berlex NDA 20-375 for Climara® (estradiol transdermal system). Additional reference is made to Supplement 016 which was submitted on June 2, 2000 and which provided for the indication, relief from vasomotor symptoms, for the lowest (0.025 mg/day) Climara® patch strength.

Additional reference is made to an Information Request Letter which was faxed to Berlex by your representative, Ms. Diane Moore on March 30, 2001, and to April 2-3, 2001 phone conversations between Ms. Moore and the undersigned.

Attached to this correspondence is our response to the Division comments and requests on the physician and patient package inserts. We have accepted all of the Division additions and deletions and have added the requested adverse event table.

Please contact the undersigned at (973) 487-2254 with any questions.

Sincerely,

BERLEX LABORATORIES, INC.

Geoffrey Millington
Manager, Drug Regulatory Affairs

GPM/048

CC: fax (with attachment) to Diane Moore

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

BERLEX

UPS OVERNIGHT
FACSIMILE

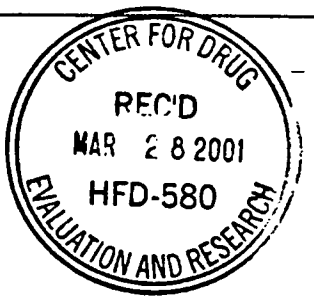
Drug Development & Technology
Division of Berlex Laboratories, Inc.

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

March 27, 2001

DUPLICATE

NDA SUPP AMEND



Susan Allen, MD, MPH, Director
Division of Reproductive and Urologic Drug Products, HFD-580
Office of Drug Evaluation II
Center for Drug Evaluation & Research
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857-1706

Sel-16-54

Dear Dr. Allen:

Re NDA 20-375 – S-016
Climara® (Estradiol Transdermal System)
Other: Safety Update Report

Reference is made to Berlex NDA 20-375 for Climara® (estradiol transdermal system). Additional reference is made to Supplement 016 which was submitted on June 2, 2000 and which provided for the indication, relief of vasomotor symptoms, for the smallest approved strength (6.5 cm^2, 0.025 mg/day of estradiol) of Climara®.

Additional reference is made to a phone conversation of March 20, 2001 between the undersigned and your representative, Ms. Diane Moore wherein Ms. Moore requested that Berlex submit a safety update report. Attached to this correspondence is the requested information.

Should you have any questions regarding this submission, please call me at (973) 487-2254.

Sincerely,

BERLEX LABORATORIES

Geoffrey Millington
Manager
Drug Regulatory Affairs

GPM/042

Desk copy (fax): Ms. Diane Moore

BERLEX

UPS OVERNIGHT

March 21, 2001

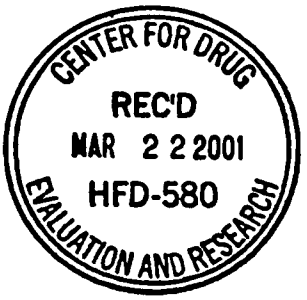
ORIGINAL
SUPPL NEW CORRESP
NEW CORRESP

NDA SUPP AMEND
PW

Drug Development & Technology
Division of Berlex Laboratories

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

Susan Allen, MD, MPH, Director
DIVISION OF REPRODUCTIVE AND UROLOGIC
DRUG PRODUCTS, HFD-580
Office of Drug Evaluation II
Center for Drug Evaluation & Research
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857-1706



Dear Dr. Allen:

Re NDA 20-375 – S-016
Climara® (Estradiol Transdermal System)
Other: Request for Waiver of Pediatric Studies

Reference is made to Berlex NDA 20-375 for Climara® (estradiol transdermal system). Additional reference is made to Supplement 016 which was submitted on June 2, 2000 and which provided for the indication, relief of vasomotor symptoms, for the smallest approved strength (6.5 cm^2) of Climara® .

Additional reference is made to a phone conversation of March 19, 2001 between the undersigned and your representative, Ms. Diane Moore wherein Ms. Moore requested that Berlex submit a request for a waiver of pediatric requirements.

Request for a Waiver from the Requirement to Assess the Safety and Effectiveness of New Drugs in Pediatric Patients

Berlex Laboratories requests a full waiver from the requirement to submit data adequate to assess the safety and efficacy of the drug product in all relevant pediatric subpopulations in accordance with 21 CFR 314.55(c)(2)(ii), i.e., necessary studies are impossible or highly impractical because the number of such patients is so small

Berlex hopes that the above satisfies the Division's request for the waiver for pediatric studies and that no further action is required on the part of Berlex.

REVIEWS COMPLETED

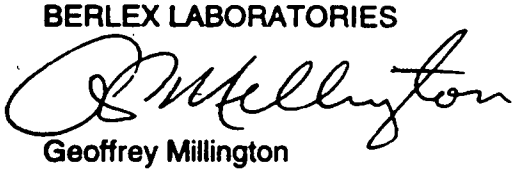
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Should you require any additional information or have any questions regarding this submission, please feel free to call me at (973) 487-2254.

Sincerely,

BERLEX LABORATORIES



Geoffrey Millington
Manager
Drug Regulatory Affairs

GPM/038

Desk copy (e-mail): Ms. Diane Moore

UPS OVERNIGHT

ORIGINAL

BERLEX

Drug Development & Technology
Division of Berlex Laboratories, Inc.

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

March 19, 2001

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

NDA SUPP AMEND
SCI-016- BL

Dear Dr. Allen:

RE: NDA 20-375 S-016
Climara® (Estradiol Transdermal System)
Response to a Request for Information

Reference is made to Berlex NDA 20-375 for Climara® (estradiol transdermal system). Additional reference is made to Supplement 016 which was submitted on June 2, 2000 and which provided for the indication, relief of vasomotor symptoms, for the smallest approved strength (6.5 cm^2) of Climara®.

Additional reference is made to a phone conversation of March 15, 2001 between the undersigned and your representative, Ms. Diane Moore wherein Ms. Moore provided guidance for revision of the patient package insert.

Attached to this correspondence is the revised patient package insert.

Please contact the undersigned at (973) 487-2254 with any questions.

Sincerely,

BERLEX LABORATORIES, INC.

Geoffrey Millington
Manager, Drug Regulatory Affairs

GPM/035

CC: e-mail of cover letter and file to Diane Moore

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

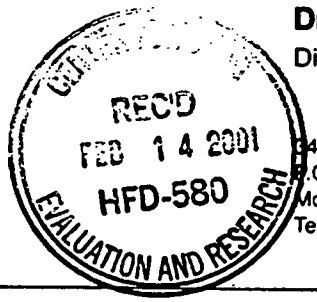
UPS OVERNIGHT

ORIGINAL

BERLEX

Drug Development & Technology
Division of Berlex Laboratories, Inc.

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



February 13, 2001

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

SUPPL NEW CORRESP

SE1-016-C

Dear Dr. Allen:

RE: NDA 20-375 S-016
Climara® (Estradiol Transdermal System)
Response to a Request for Information

Reference is made to Berlex NDA 20-375 for Climara® (estradiol transdermal system). Additional reference is made to Supplement 016 which was submitted on June 2, 2000 providing for the indication, treatment of moderate to severe vasomotor symptoms associated with menopause, for the lowest approved patch strength.

Additional reference is made to a February 2, 2001 telephone conversation between your representative, Ms. Kim Colangelo and the undersigned wherein Ms. Colangelo addressed the issue of our financial disclosure compliance for study 97074. Ms. Colangelo stated that Berlex must take additional steps to obtain financial disclosure information for the study.

The attached information documents the additional Berlex due diligence efforts to obtain financial disclosure information for the 7 study 97074 sites which did not comply.

- Attachment A – internal Berlex memo of February 6, 2001 documenting successful efforts to locate the current addresses for all 7 Investigators.
- Attachment B – internal Berlex memo of February 8, 2001 documenting shipment of letters and financial disclosure forms to all 7 Investigators. This attachment contains copies of the letters and forms as well as UPS Overnight Delivery Confirmations.
- Attachment C – internal Berlex memo of February 8, 2001 documenting follow-up telephone calls to each of the 7 sites.

- Attachment D – internal Berlex memo of February 9, 2001 providing copies of faxed, signed financial disclosure forms from 5 of the 7 sites plus follow-up efforts for the remaining 2 sites.

- Attachment E – internal Berlex memo of February 12, 2001 providing a copy of an additional faxed, signed financial disclosure form.

As documented, 6 of the 7 outstanding financial disclosure forms have been obtained and strong efforts are underway to obtain the seventh form.

Please contact the undersigned at (973) 487-2254 with any questions.

Sincerely,

BERLEX LABORATORIES, INC.

Geoffrey Millington
Manager, Drug Regulatory Affairs

Desk copies (faxed) to:

Ms. Kim Colangelo
Ms. Diane Moore

GPM/023

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

ORIGINAL

UPS OVERNIGHT

BERLEX

Drug Development & Technology
Division of Berlex Laboratories, Inc.

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

January 5, 2001

SUPPL NEW CORRESP

SAT-016-C

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 20-375 S-016
Climara® (Estradiol Transdermal System)
Response to a Request for Information

Reference is made to Berlex NDA 20-375 for Climara® (estradiol transdermal system). Additional reference is made to Supplement 016 which was submitted on June 2, 2000 providing for the indication, treatment of moderate to severe vasomotor symptoms associated with menopause, for the lowest approved patch strength.

Additional reference is made to a January 3, 2001 telephone conversation between your representative, Ms. Diane Moore and the undersigned wherein Ms. Moore requested that we provide a Word file on diskette containing the draft package insert for this product.

Enclosed please find a diskette which contains the draft labeling (package insert) for Climara S-016 as a Word file. The diskette has been virus scanned and found to be clean.

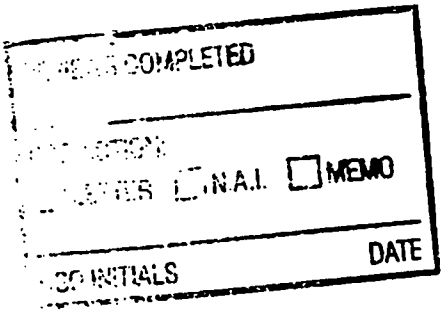
Please contact the undersigned at (973) 276-2254 with any questions.

Sincerely,

BERLEX LABORATORIES, INC.

Geoffrey Millington
Manager, Drug Regulatory Affairs

GPM/005



TELEFAX
CERTIFIED MAIL
RETURN RECEIPT REQUESTED

ORIGINAL

BERLEX

NDA SUPPLEMENT

Drug Development & Technology
Division of Berlex Laboratories, Inc.

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

September 15, 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

SE1-016-BC

9-28-00

REVIEWS COMPLETED

DATE

Dear Dr. Allen:

RE: NDA 20-375 S-016
Climara® (Estradiol Transdermal System)
Response to a Request for Information

Reference is made to Berlex NDA 20-375 for Climara® (estradiol transdermal system). Additional reference is made to Supplement 016 which was submitted on June 2, 2000 providing for the indication, treatment of moderate to severe vasomotor symptoms associated with menopause, for the lowest approved patch strength (6.5 cm^2 patch delivering 0.025 mg of estradiol/day).

Reference is also made to our submission of July 20, 2000 wherein Berlex provided, at the request of your representative, Ms. Lana Pauls, a summary of financial disclosure compliance for each of the Investigators conducting the two pivotal studies.

Reference is also made to a telephone conversation on August 31, 2000 between your representative, Kim Colangelo, and the undersigned wherein the Division requested that Berlex provide information regarding steps taken in exercising due diligence to obtain financial disclosure from investigators conducting the two pivotal studies.

In response to the Division request we are providing the following information:

Study 97074:

This study was initiated in September, 1997. All 19 sites were closed between March, 1999 and September, 1999. The financial disclosure letter, a copy of which is attached to this correspondence, was sent to each site on February 23, 2000. Since all sites were closed at the time the letter was sent, the letters were not sent CERTIFIED nor was any additional action taken to obtain outstanding Financial Disclosure Forms.

A self-addressed, stamped envelope was provided to each Investigator for ease in returning the forms to Berlex.

Study 97095:

This study was initiated in September, 1997. All 21 sites were closed between November, 1998 and October, 1999. The financial disclosure letter, a copy of which is attached to this correspondence, was sent to each site on February 28, 2000. Since all sites were closed at the time the letter was sent, the letters were not sent CERTIFIED nor was any additional action taken to obtain outstanding Financial Disclosure Forms. A self-addressed, stamped envelope was provided to each Investigator for ease in returning the forms to Berlex.

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

Sincerely,

BERLEX LABORATORIES, INC.

Geoffrey Millington
Manager, Drug Regulatory Affairs

GPM/104