TELEFAX
CERTIFIED MAIL
RETURN RECEIPT REQUESTED

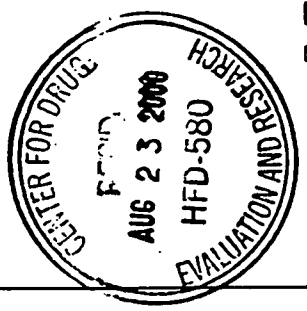
BERLEX

**Drug Development & Technology**
Division of Berlex Laboratories, Inc.

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

August 18, 2000

ORIGINAL




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
S(1-016 JC

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 a telephone conversation on August 14, 2000 between your representative, Diane Moore, and the undersigned wherein the Division requested that Berlex provide additional information regarding the environmental assessment for the Climara® 25 patch (6.5 $cm^2$ patch delivering 0.025 mg of estradiol/day). Specifically, it was agreed that Berlex would provide the calculation of drug substance introduced into the aquatic environment as a basis for claiming a categorical exclusion. This calculation is based on the projected distribution of the Climara® 25 patch and includes any anticipated distribution increases which would result from the approval of S-016 (additional indication). The requested calculation is attached.

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

Sincerely,

BERLEX LABORATORIES, INC.
Geoffrey Millington
Manager, Drug Regulatory Affairs
GPM/094

REVIEWS COMPLETED
CSO INITIALS DATE

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

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

BERLEX


**Drug Development & Technology**
Division of Berlex Laboratories, Inc.

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

August 17, 2000

ORIGINAL

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
1 016 BS

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 a telephone conversation on August 14, 2000 between your representative, Diane Moore, and the undersigned wherein the Division requested that Berlex provide the location of the Statistical Appendices which are referenced on page 736 of Item 8 (volume 7).

The requested Statistical Appendices were inadvertently omitted from Supplement 016 and are therefore enclosed. The attached 23-page document is paginated as follows: Item 8, Vol. 7, Pages 736-1 through 736-23.

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

Sincerely,

BERLEX LABORATORIES, INC.

Geoffrey Millington
Manager, Drug Regulatory Affairs
GPM/092

REVIEWS COMPLETED

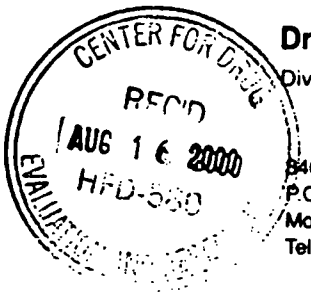
CSO INITIALS DATE

**TELEFAX**
**CERTIFIED MAIL**
**RETURN RECEIPT REQUESTED**

BERLEX

**Drug Development & Technology**
Division of Berlex Laboratories, Inc.

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




August 10, 2000

ORIGINAL

NDA SUPPLEMENT

S011 - CLIMARA

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:

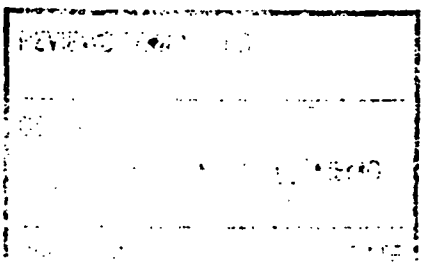
**RE: NDA 20-375 S-016**
**Climara® (Estradiol Transdermal System)**
**Response to a Request for Information**

Reference is made to Berlex NDA 20-375 for Climara® (estradiol transdermal system). Additional reference is made to S011 which was submitted for the prevention of osteoporosis and included the 6.5 $cm^2$ patch. Supplement 011 was approved on March 5, 1999.

Further reference is also 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. This indication also utilizes the lowest approved patch strength (6.5 $cm^2$ patch delivering 0.025 mg of estradiol/day).

Reference is also made to a telephone voicemail of August 9, 2000 from your representative, Diane Moore. Ms. Moore requested that Berlex provide information regarding environmental impact.

3M Pharmaceuticals is the manufacturer of this drug product. Please refer to DMF —— submitted April 27, 1998, volume 1, page 312. A copy of the 3M letter of authorization is attached for your convenience. This letter was submitted in Supplement 011. 3M Pharmaceuticals informed Berlex today that a categorical exclusion pursuant to 21 CFR 25.31(a) was requested. Attached is a copy of a telefax to Ms. Moore dated July 19, 2000 in which this information was previously provided.



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

Sincerely,

BERLEX LABORATORIES, INC.

Geoffrey Millington
Manager, Drug Regulatory Affairs

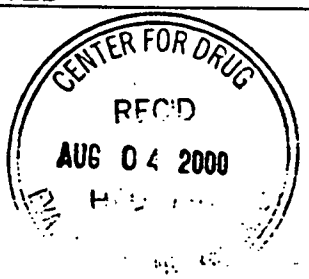
GPM/090

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

ORIGINAL

BERLEX

**CERTIFIED MAIL**
**RETURN RECEIPT REQUESTED**




July 31, 2000

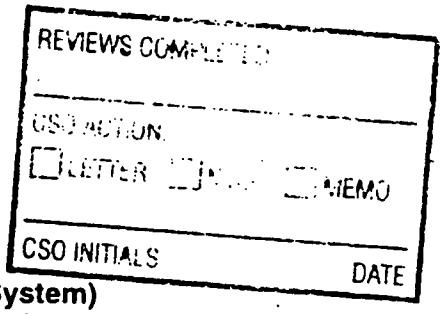
**Drug Development & Technology**
Division of Berlex Laboratories, Inc.

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

**NDA SUPPLEMENT**

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 BZ




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). Reference is also made to Supplement 016 which was submitted on June 2, 2000 and which provided 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 a telephone conversation of July 20, 2000 between your representative, Diane Moore, and the undersigned wherein the Division requested information about the drug product formulations used in the clinical trials for S-016. Specifically, the Division requested confirmation that the drug product used in clinical trials was not the same formulation that was presented in NDA 20-375 prior approval chemistry supplement —— \ ——— .

The formulation presented in prior-approval chemistry supplement ——— of ——— for Climara, and the formulations used in the clinical trials (studies 97074 and 97095) on which supplement S-016 was based, are not the same drug product. The formulation in —— has not been used in clinical trials; it has been formulated for the purpose of the prior approval chemistry supplement ———

Ms. Moore had also requested that Berlex provide the lot numbers, manufacturing site and composition for the drug product used in the clinical trials for S-016.

The active drug product lot used in studies 97074 and 97095 is ——— This product was manufactured for Berlex by 3M Pharmaceuticals in their Northridge, CA facility, the same facility approved in NDA 20-375 for the manufacture of Climara®.

Information regarding the qualitative and quantitative composition for the drug product is provided in the attached pages (extracted from IND 40,928).

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/080

BERLEX

UPS OVERNIGHT

Drug Development & Technology
Division of Berlex Laboratories, Inc.

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

June 2, 2000

Susan Allen, M.D., Acting 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**
**Climara® (Estradiol Transdermal System)**
**Efficacy Supplement**

Reference is made to Berlex NDA 20-375 for Climara® (estradiol transdermal system) which was submitted by 3M Pharmaceuticals and which was approved on December 22, 1994. Reference is also made to Supplement 011 which was approved on March 5, 1999 and which provided for a fourth patch strength of 0.025 mg estradiol/day. Supplement 011 also provided for the indication, prevention of postmenopausal osteopororsis, for all 4 patch strengths. However, Supplement 011 did not provide for the indication, treatment of vasomotor symptoms associated with menopause, for the fourth (lowest, approved) patch strength.

Pursuant to 21 CFR §314.70, Berlex is submitting an efficacy supplement, the purpose of which is to modify the existing Climara® labeling to provide 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).

This indication is supported by 2 clinical studies:

**Study 97074 (Report B583)**: A multicenter, double-blind, placebo-controlled, randomized study to determine efficacy in the relief of hot flushes in women receiving transdermal estradiol compared to placebo.

**Study 97095 (Report 98184)**: 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.

Reference is made to a telephone conversation of July 19, 1999 between Ms. Diane Moore and the undersigned wherein the format for this submission was discussed. Ms. Moore requested that Berlex address each NDA Item for reviewing convenience and clarity. Therefore, the enclosed 38-volume supplemental application is organized in the conventional NDA format. However, Items 4 (CMC), 5 (Non-clinical) and 6 (Human PK) of this submission do not contain review information. They each simply provide a statement that there is no new information within each of these review categories.

Pursuant to the Guidance for Industry; Providing Regulatory Submissions in Electronic Format, Items 8 and 10 of this submission are identical. Documents describing statistical methods are included in Item 8. The submission also includes a 38 volume Archival copy and a 66 volume Review copy.

Reference is also made to Berlex correspondence of May 2, 2000 wherein, pursuant to the Prescription Drug User Fee Act, check No. 107780 for $142,870.00 ( the full amount of the fee rate in FY 2000 for supplements requiring clinical data) was provided. User [redacted] had been assigned to this supplement by FDA, Central Documents and Records on March 21, 2000.

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/061

BERLEX

February 28, 2000

David Baylink, MD
Jerry L. Pettis VAMC & Loma Linda U. Osteoporosis Center
11165 Mt. View Ave., Suite 137
Loma Linda, CA 92354

**Berlex Laboratories**
Division of Berlex Laboratories, Inc.

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

**Re: Financial Disclosure Form (Protocol 97095)**

Dear Dr. Baylink:

The FDA issued a rule (21 CFR part 54) requiring companies that sponsor studies for marketing applications to provide information about compensation to, and financial interests of, any investigator conducting a clinical trial for the sponsor. This rule, which went into effect on February 2, 1999, is designed to minimize the potential for investigator bias by requiring disclosure of any interest the investigator, investigator's spouse, or investigator's dependent children may have on the outcome of the clinical trial. Failure to comply with the rule could result in the FDA's refusal to file an application.

Since it is not possible for Berlex to determine the extent of an investigator's or sub-investigator's financial interest in a study, all personnel listed in block 6, of all FDA Form 1572 completed by your site, must complete and sign the enclosed Financial Disclosure Forms. A separate form has been provided for each individual listed on the 1572 form. This will enable Berlex to meet the FDA's requirement by certifying the absence of investigator financial interests or making disclosure of these interests. The Financial Disclosure Form requires you to inform us of any changes to the information on the form for a period of up to one year following the completion of the clinical trial.

This information needs to be provided to the sponsor by the investigator and all sub-investigators as soon as possible. For more information and instructions for completing the form, please see the enclosed information sheet. We appreciate your cooperation in meeting these new regulatory requirements. If you have any questions please contact your Study Monitor.

A prepaid envelope has been provided for your convenience.

Sincerely,

BERLEX LABORATORIES

Grexan Wulff
Female Health Care

BERLEX

February 23, 2000

David Archer, MD
Jones Institute for Reproductive Medicine
601 Colley Avenue
Norfolk, VA 23507-1912

Re: Financial Disclosure Form (Protocol 97074)

**Berlex Laboratories**
Division of Berlex Laboratories, Inc.

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

Dear Dr. Archer:

The FDA issued a rule (21 CFR part 54) requiring companies that sponsor studies for marketing applications to provide information about compensation to, and financial interests of, any investigator conducting a clinical trial for the sponsor. This rule, which went into effect on February 2, 1999, is designed to minimize the potential for investigator bias by requiring disclosure of any interest the investigator, investigator's spouse, or investigator's dependent children may have on the outcome of the clinical trial. Failure to comply with the rule could result in the FDA's refusal to file an application.

Since it is not possible for Berlex to determine the extent of an investigator's or sub-investigator's financial interest in a study, all personnel listed in block 6, of all FDA Form 1572 completed by your site, must complete and sign the enclosed Financial Disclosure Forms. A separate form has been provided for each individual listed on the 1572 form. This will enable Berlex to meet the FDA's requirement by certifying the absence of investigator financial interests or making disclosure of these interests. The Financial Disclosure Form requires you to inform us of any changes to the information on the form for a period of up to one year following the completion of the clinical trial.

This information needs to be provided to the sponsor by the investigator and all sub-investigators as soon as possible. For more information and instructions for completing the form, please see the enclosed information sheet. We appreciate your cooperation in meeting these new regulatory requirements. If you have any questions please contact your Study Monitor.

A prepaid envelope has been provided for your convenience.

Sincerely,

**Berlex Laboratories**

Grexan Wulff

Grexan Wulff
Female Health Care

UPS OVERNIGHT

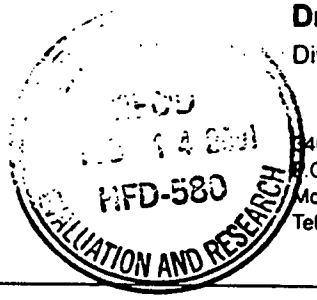
ORIGINAL

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

20-375-016-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

BERLEX
Laboratories

Facsimile
Transmittal Sheet

| | |
|---|---|
| FROM: Geoffrey Millington/Sharon Brown | TELEPHONE: (973) 276-2254 |
| ADDRESS: ⌦ 340 Changebridge Road, P. O. Box 1000, Montville, NJ 07045-1000 | |
| FAX NUMBER: ⌦ Drug Regulatory Affairs (973) 276-2016 | |
| TO: Diane Moore, Project Manager<br>Division of Reproductive and Urologic Drug Products | TELEPHONE: 301-827-4236 |
| SUBJECT: Climara Transdermal –NDA 20-375 - Supplement 016 | FAX NUMBER: 301-827-4267 |
| | DATE: July 19, 2000 |
| | TOTAL NUMBER OF PAGES (INCLUDING COVER SHEET): 1 |

Dear Ms. Moore,

Please refer to your question on July 18 regarding the environment assessment waiver. The waiver request is located in volume 1 of DMF [redacted] on page 312 submitted by 3M Pharmaceutical on April 27, 1998.

Sincerely,

Geoffrey Millington
Manager, Drug Regulatory Affairs
BERLEX LABORATORIES

GPM/073

**BERLEX**
Laboratories

Facsimile
Transmittal Sheet

| | |
|---|---|
| FROM: Geoffrey Millington | TELEPHONE: (973) 276-2254 |
| ADDRESS: ⌦ 340 Changebridge Road, P. O. Box 1000, Montville, NJ 07045-1000 | |
| FAX NUMBER: ⌦ Drug Regulatory Affairs (973) 276-2016 | |
| TO: Diane Moore, Project Manager<br>Division of Reproductive and Urologic Drug Products | TELEPHONE: 301-827-4236 |
| SUBJECT: Climara Transdermal –NDA 20-375 - Supplement 016 – Financial Disclosure Information | FAX NUMBER: 301-827-4267 |
| | DATE: August 4, 2000 |
| | TOTAL NUMBER OF PAGES (INCLUDING COVER SHEET): 3 |

Dear Ms. Moore,

As you requested, here is the information which was faxed to Lana Pauls on July 20, 2000.

Dear Ms. Pauls,

Please refer to your July 7, 2000 phone request for a breakdown of financial disclosure information for NDA 20-375 S016. Attached are 2 tables which provide the requested information for the 2 pivotal studies which were the basis of the submission.

If you need additional information please contact me.

Sincerely,

Geoffrey Millington
Manager, Drug Regulatory Affairs
BERLEX LABORATORIES

GPM/086

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

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20375/S-016

**INFORMATION REQUEST 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 supplemental new drug application dated June 2, 2000, received June 5, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Climara® (Estradiol transdermal System) 0.025, 0.05, 0.075, 0.1 mg/day.

We have completed the review of this supplemental application including the submitted draft labeling and have several comments. Revisions have been incorporated directly into the enclosed Physician Package Insert and Patient Package Insert. Additions have been noted with double underlining, deletions have been noted as ~~strikeouts~~. Additional comments requiring response are denoted in **14 point** bold face type.

Please submit your revised package insert as soon as available so that we can continue the evaluation of your supplemental NDA.

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

Sincerely,

*{See appended electronic signature page}*

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

Enclosure:

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

/s/
---
Susan Allen
3/30/01 05:05:06 PM

NDA 20-375/S-016

**PRIOR APPROVAL SUPPLEMENT**

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

JUN - 9 2000

Dear Mr. Millington:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

| | |
|---|---|
| Name of Drug Product: | Climara (estradiol transdermal system) 0.025 mg / day |
| NDA Number: | 20-375 |
| Supplement Number: | S-016 |
| Therapeutic Classification: | Standard (S) |
| Date of Supplement: | June 2, 2000 |
| Date of Receipt: | June 5, 2000 |

This supplement proposes the following change(s):

- To modify the labeling to provide for the indication of 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 estradiol / day.

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 4, 2000 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be April 5, 2001 and the secondary user fee goal date will be June 2, 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 application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application 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, Regulatory Project Manager, at (301) 827-4260.

Sincerely.

/S/

for Tem 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 20-375
HFD-580/Div. Files
HFD-580/Moore
HFD-580/Allen/Slaughter/Price/Rhee/Mitra/Parekh/Raheja/Rumble

DISTRICT OFFICE

Drafted by: dsl/June 6, 2000
Initialed by: Rumble, 6.7.00
final:Spell-LeSane, 6.8.00
filename: NDA/20375/letter/AC016

PRIOR APPROVAL SUPPLEMENT ACKNOWLEDGEMENT (AC)

Moore

JUN 26 2000



# Division of Reproductive and Urologic Drug Products

## ADMINISTRATIVE REVIEW OF APPLICATION

**Application Number:** **NDA 20-375/S-016**

**Name of Drug:** Climara (estradiol transdermal system) 0.025 mg/day

**Sponsor:** **Berlex**

**Material Reviewed:** **NDA volumes**

**Submission Date:** **June 2, 2000**

**Receipt Date:** **June 5, 2000**

**Filing Date:** **August 4, 2000**

**User-Fee Goal Date(s):** **April 5, 2001, June 2, 2001**

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

**Other Background Information:** Previous approval for VMS indication for 0.025, 0.05, 0.075 or 0.1 mg estradiol/day

**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 | | Item 1, Vol. 1, Page 3 |
| 2. Form FDA 356h (original signature) | X | | Item 1, Vol. 1, Page 4 |
| a. Reference to DMF(s) & Other Applications | X | | Item 1, Vol. 1, Page 4 |
| 3. Patent information & certification | X | | Item 14, Vol. 1, Page 1 |
| 4. Debarment certification (note: must have a definitive statement) | X | | Item 16, Vol. 1, Page 1 |
| 5. Financial Disclosure | X | | Item 19, Vol. 1, Page 2 |

| | | | |
|---|---|---|---|
| 6. Comprehensive Index | X | | Item 1, Vol. 1, Page 1 |
| | | | |
| 8. Summary Volume | X | | Item 3, Vol.1, Page 1 |
| 9. Review Volumes | X | | |
| 10. Labeling (PI, container, & carton labels) | X | | Item 2, Vol. 1, Page 2 |
| a. unannotated PI | X | | Item 2, Vol. 1, Page 2 |
| b. annotated PI | | X | |
| c. immediate container | | X | |
| d. carton | | X | |
| e. foreign labeling (English translation) | | X | |
| 11. Foreign Marketing History | | X | |
| 12. Case Report Tabulations (CRT) (paper or electronic) (by individual patient data listing or demographic) | X | | electronic CRT<br>in clinical study reports |
| 13. Case Report Forms (paper or electronic) (for death & dropouts due to adverse events) | X | | electronic CRT<br>in clinical study reports |

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 | | Item 3, Vol. 1, Page 86 |
| 2. Summary of Each Technical Section | | | |
| a. Chemistry, Manufacturing, & Controls (CMC) | X | | Item 3, Vol. 1, Page 27 |
| b. Nonclinical Pharmacology/Toxicology | | X | Not applicable, higher doses previously approved |
| c. Human Pharmacokinetic & Bioavailability | | X | Not applicable, higher doses previously approved |
| d. Microbiology | | X | |
| e. Clinical Data & Results of Statistical Analysis | X | | Item 8, Vol. 5, Page 20<br>Item 3, Vol. 1. Page 28 |
| 3. Discussion of Benefit/Risk Relationship & Proposed Postmarketing Studies | X | | Item 3, Vol. 1, Page 86 |
| 4. Summary of Safety | X | | Item 8, Vol. 38, Page 12759-12909 |
| 5. Summary of Efficacy | X | | Item 8, Vol. 38, Page 12910-13058 |

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 | | Item 19, Vol. 1, Page 2<br>Item 8, Vol. 5, Page 7-9 |
| 2. Controlled Clinical Studies | X | | Volume 5-38 |
| a. Table of all studies | X | | Item 3, Vol. 1, Page 29 |
| b. Synopsis, protocol, related publications, list of investigators, & integrated clinical & statistical report for each study (including completed, ongoing, & incomplete studies) | | | Synopsis- Item 8, Vol. 5, Page 2<br>no publications submitted<br>list of investigators --in Financial disclosure (Vol. 1, Page 2 and Item 8, Vol. 5, Page 4-9<br>NDA Study reports Item 8, Vol. 5, Page 22 |
| c. Optional overall summary & evaluation of data from controlled clinical studies | | | Item 3, Vol. 1, page 28-85 |
| 3. Integrated Summary of Efficacy (ISE) | X | | Item 8, Vol. 38, Page 12910 |
| 4. Integrated Summary of Safety (ISS) | X | | Item 8, Vol. 38, Page 12759 |
| 5. Drug Abuse & Overdosage Information | | X | Not applicable, higher doses previously approved |
| 6. Integrated Summary of Benefits & Risks of the Drug | X | | Item 3, Vol. 1, page 86-88<br>Item 8, Vol. 38, pages 13054-13058 |
| 7. Gender/Race/Age Safety & Efficacy Analysis Studies | X | | Item 8, Vol. 38, page 12926 references individual study reports |

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 |
| 2. Diskettes | X | | |
| a. Proposed unannotated labeling in MS WORD 8.0 | X | | Item 2, electronic |
| b. Stability data in SAS data set format | | X | Not applicable |
| c. Efficacy data in SAS data set format | X | | electronic form, Item 8 |
| d. Biopharmacological information & study summaries in MS WORD 8.0 | | X | Not applicable; approved at higher doses |
| e. Animal tumorigenicity study data in SAS data set format | | X | Reference to earlier submissions |
| 3. User-fee payment receipt | X | | Item 18, Vol. 1, Page 1 |

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:**
**Ethical Conduct of study: Item 8, Vol. 5, page 12.**

**Conclusions: Fileable**

/S/

/S/

Concurrence

cc:
Original NDA
HFD-580/Div. Files
HFD-580/PM/
HFD-580/Allen/Mann
HFD-%80/Reviewers
draft:
r/d Initials:
final:

**ADMINISTRATIVE REVIEW**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
FOOD AND DRUG ADMINISTRATION

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

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

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY
APPLICATION NUMBER

## APPLICANT INFORMATION

NAME OF APPLICANT
Berlex Laboratories, Inc.

DATE OF SUBMISSION
June 2, 2000

TELEPHONE NO. *(Include Area Code)*
(973) 276-2254

FACSIMILE (FAX) Number *(Include Area Code)*
(973) 276-2016

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:
340 Changebridge Road
P.O. Box 1000
Montville, New Jersey 07450 –1000

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
N/A

## PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 20-375

ESTABLISHED NAME (*e.g., Proper name, USP/USAN name*)
Estradiol

PROPRIETARY NAME (*trade name*) IF ANY
Climara® (estradiol transdermal system)

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (*If any*)
Estra-1,3,5(10) triene-3, 17-diol, (17)β

CODE NAME (*If any*)
N/A

DOSAGE FORM:
Adhesive Transdermal System

STRENGTHS:
0.025, 0.05, 0.075, 0.1 mg/day

ROUTE OF ADMINISTRATION:
Transdermal

(PROPOSED) INDICATION(S) FOR USE:
Treatment of vasomotor symptoms

## APPLICATION INFORMATION

APPLICATION TYPE
(check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

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

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

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

REASON FOR SUBMISSION
To provide for the indication, treatment of moderate to severe vasomotor symptoms associated with menopause, for the 0.025 mg/day patch.

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

NUMBER OF VOLUMES SUBMITTED 38

THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

## ESTABLISHMENT INFORMATION

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

Please refer to 3M Pharmaceuticals

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

IND 40,928 DMF —
NDA 20-375

| This application contains the following items: *(Check all that apply)* | | |
|---|---|---|
| ☒ | 1. | Index |
| ☒ | 2. | Labeling (check one) ☒ Draft Labeling ☐ Final Printed Labeling |
| ☒ | 3. | Summary (21 CFR 314.50 (c)) |
| ☒ | 4. | Chemistry section |
| ☐ | | A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2) |
| ☐ | | B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request) |
| ☐ | | C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2) |
| ☒ | 5. | Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2) |
| ☒ | 6. | Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2) |
| ☐ | 7. | Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4)) |
| ☒ | 8. | Clinical data section (e.g. 314.50 (d) (5), 21 CFR 601.2) |
| ☐ | 9. | Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2) |
| ☒ | 10. | Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2) |
| ☒ | 11. | Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2) |
| ☒ | 12. | Case report forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2) |
| ☒ | 13. | Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c)) |
| ☒ | 14. | A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A)) |
| ☐ | 15. | Establishment description (21 CFR Part 600, if applicable) |
| ☒ | 16. | Debarment certification (FD&C Act 306 (k)(1)) |
| ☒ | 17. | Field copy certification (21 CFR 314.5 (k) (3)) |
| ☒ | 18. | User Fee Cover Sheet (Form FDA 3397) |
| ☐ | 19. | OTHER (Specify) FINANCIAL DISCLOSURE FORM 3454 |

CERTIFICATION

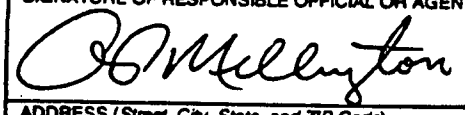
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA.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

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

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

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

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

| SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT | TYPED NAME AND TITLE | DATE |
|---|---|---|
|  | Geoffrey Millington<br>Manager | June 2, 2000 |

| ADDRESS (*Street, City, State, and ZIP Code*) | Telephone Number |
|---|---|
| 340 Changebridge Road<br>P.O. Box 1000<br>Montville, New Jersey 07450 – 1000 | ( 973 ) 276-2254 |

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

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

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**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
FOOD AND DRUG ADMINISTRATION

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

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

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY
APPLICATION NUMBER

## APPLICANT INFORMATION

| NAME OF APPLICANT | DATE OF SUBMISSION |
|---|---|
| Berlex Laboratories, Inc. | February 13, 2001 |
| **TELEPHONE NO.** *(Include Area Code)* | **FACSIMILE (FAX) Number** *(Include Area Code)* |
| (973) 487-2254 | (973) 487-2016 |

| APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: | AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE |
|---|---|
| 340 Changebridge Road<br>P.O. Box 1000<br>Montville, New Jersey 07450 –1000 | N/A |

## PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 20-375 S-016

| ESTABLISHED NAME (*e.g., Proper name, USP/USAN name*) | PROPRIETARY NAME (*trade name*) IF ANY |
|---|---|
| Estradiol | Climara® (estradiol transdermal system) |

| CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (*If any*) | CODE NAME (*If any*) |
|---|---|
| Estra-1,3,5(10) triene-3, 17-diol, (17)β | N/A |

| DOSAGE FORM: | STRENGTHS: | ROUTE OF ADMINISTRATION: |
|---|---|---|
| Adhesive Transdermal System | 0.025, 0.05, 0.075, 0.1 mg/day | Transdermal |

(PROPOSED) INDICATION(S) FOR USE:
Treatment of vasomotor symptoms, prevention of osteoporosis

## APPLICATION INFORMATION

APPLICATION TYPE
(check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

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Name of Drug — Holder of Approved Application

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

REASON FOR SUBMISSION
Response to a Request for Information

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

NUMBER OF VOLUMES SUBMITTED_____ THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

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Please refer to 3M Pharmaceuticals

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IND 40,928 DMF —
NDA 20-375

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| ☐ | 16. Debarment certification (FD&C Act 306 (k)(1)) |
| ☐ | 17. Field copy certification (21 CFR 314.5 (k) (3)) |
| ☐ | 18. User Fee Cover Sheet (Form FDA 3397) |
| ☐ | 19. OTHER (Specify) |

CERTIFICATION

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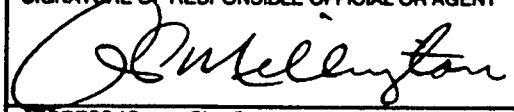
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

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

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

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

| SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT | TYPED NAME AND TITLE | DATE |
|---|---|---|
|  | Geoffrey Millington<br>Manager | February 13, 2001 |

| ADDRESS (*Street, City, State, and ZIP Code*) | Telephone Number |
|---|---|
| 340 Changebridge Road<br>P.O. Box 1000<br>Montville, New Jersey 07450 – 1000 | ( 973 ) 487-2254 |

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

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

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**BERLEX LABORATORIES, INC.**

**CLIMARA® (0.025 mg/day) – NDA 20-375 S-016**

**Safety Update Report**

Reporting Period: June 2, 2000 – March 20, 2001

---

As described in the Guideline for the Format and Content of the Clinical and Statistical Sections of an Application (July 1988), this report refers only to new data obtained during the reporting period. These additional data are relatively few, therefore, only serious or potentially serious adverse events (AE), an unusually high frequency of a less serious event, subjects who died, and subjects who failed to complete a clinical study due to an AE are described. Commercial marketing experience, foreign regulatory actions and the results of literature searches are also provided for your information.

**It was concluded that there is no new safety information learned about Climara (0.025 mg/day) that may reasonably affect the statement of Contraindications, Warnings and Adverse Reactions in the labeling.**

## 1.1 Serious Or Potentially Serious AEs (SAEs)

No studies were ongoing during the reporting period.

## 1.2 Unusually High Frequency Of A Less Serious Event

No studies were ongoing during the reporting period.

## 1.3 Subjects Who Died Or Discontinued A Clinical Study Due To An AE

### 1.3.1 Deaths

No studies were ongoing during the reporting period.

### 1.3.2 Discontinuations Due to AEs

No studies were ongoing during the reporting period.

## 1.4 Commercial Marketing Experience And Foreign Regulatory Actions

### 1.4.1 List Of Countries In Which The Drug Has Been Approved

Climara (0.025 mg/day) has been approved in the United States (March 1999 S-011 for osteoporosis), New Zealand (April 1999) and Australia (October 2000).

### 1.4.2 List Of Countries In Which The Drug Has Been Submitted For Approval And The Applications Are Pending

An application is pending in the [redacted]

### 1.4.3 Reports from Foreign Regulatory Authorities, Foreign Affiliates, Licensors or Licensees of the Applicant

There are no reports of, or analyses of, AEs, warning letters sent to physicians, and major changes in marketing status or labeling information resulting from marketing or other experience with Climara (0.025 mg/day) from foreign regulatory authorities, foreign affiliates, licensors or licensees of the applicant.

### 1.4.4 Epidemiological Studies

There are no reports of epidemiological studies or studies underway.

### 1.4.5 Spontaneous Reports From Marketing Experience

There was one spontaneous report from marketing experience (USA). A female of unspecified age and race was using Climara at 0.025 mg/day from March of 2000 to July of 2000. She discontinued use due to cramping and was admitted to the hospital for an appendectomy (date unspecified) for appendicitis. The physician reports no causal relationship between appendectomy and Climara.

## 1.5 Reports From Literature

Nonclinical and clinical literature searches were performed for the reporting period. The searches revealed that there is no new safety information in the literature that may reasonably affect the statement of contraindications, warnings, precautions and adverse reactions in the labeling.

NDA 20-375/S-016
Climara® (estradiol transdermal system) 0.025 mg/day
Berlex Laboratories, Inc.

**End of Phase 2 and Pre-NDA meetings**

No End of Phase 2 or Pre-NDA meetings were held for this efficacy supplement.

NDA 20-375/S-016
Climara® (estradiol transdermal system) 0.025 mg/day
Berlex Laboratories, Inc.

**Advisory Committee Meeting Minutes**

This supplemental application was not the subject of an Advisory Committee Meeting.

NDA 20-375/S-016
Climara® (estradiol transdermal system) 0.025 mg/day
Berlex Laboratories, Inc.

**Federal Register Notices**

This supplemental application was not the subject of any Federal Register Notices.

MEMO TO THE FILE

NDA 20-375 S016

Name of Drug: Climara®

Sponsor: Berlex Laboratories

Comment:

A revised label, dated April 4, 2001, has been received from the sponsor and has been reviewed. Appropriate changes have been incorporated into label per HFD-580 request.

Recommendation:

Label for Climara S-016 approved.

Phill H. Price, M.D.
April 5, 2001

/s/
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Phill H. Price
4/5/01 01:47:15 PM
MEDICAL OFFICER

Shelley Slaughter
4/5/01 03:19:09 PM
MEDICAL OFFICER
I concur with the primary reviewer.

**Memorandum**

NDA 20375/SLR-016

Drug: Climara (estradiol transdermal system)

Sponsor: Berlex

Through: Ameeta Parekh, Ph.D., Team Leader, HFD-870

From: Venkat Jarugula, Ph.D., Reviewer, HFD-870

Date: 04/05/01

The purpose of this memo is to provide the appropriate labeling language for adhesion information based on the results of adhesion study (report #99001) submitted by the sponsor. The adhesion information included in the proposed label should be replaced by the following:

*An open-label study of adhesion potential of placebo transdermal systems that correspond to the 6.5 $cm^2$ and 12.5 $cm^2$ sizes of Climara® was conducted in 112 healthy women of 45-75 years of age. Each woman applied both transdermal systems weekly, on the upper outer abdomen, for 3 consecutive weeks. It should be noted that lower abdomen and upper quadrant of the buttock are the approved sites of application for Climara®.*

*The adhesion assessment was done visually on days 2, 4, 5, 6, 7 of each week of transdermal system wear. A total of 1654 adhesion observations were conducted for 333 transdermal systems of each size.*

*Of these observations, approximately 90% showed essentially no lift for both the 6.5 $cm^2$ and 12.5 $cm^2$ transdermal systems. Of the total number of transdermal systems applied, approximately 5% showed complete detachment for each size.*

*Adhesion potentials of the 18.75 $cm^2$ and 25.0 $cm^2$ sizes of transdermal systems (0.075 mg/day and 0.1 mg/day) have not been studied.*

The above proposed labeling has been accepted by the sponsor and the final labeling as of the date of this memo is acceptable.

/s/
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Venkateswar Jarugula
4/5/01 01:06:41 PM
BIOPHARMACEUTICS

Ameeta Parekh
4/5/01 01:48:08 PM
BIOPHARMACEUTICS
I concur

NDA 20-375
Climara® (estradiol transdermal system) 0.025, 0.05, 0.075 and 0.1 mg/day
Berlex Pharmaceuticals, Inc.

## Abuse Liability review

There is no abuse liability potential for this approved drug product. No abuse liability review was performed for this supplemental application.

NDA 20-375
Climara® (estradiol transdermal system) 0.025, 0.05, 0.075 and 0.1 mg/day
Berlex Pharmaceuticals, Inc.

## Microbiology Review

No microbiology review was performed for this supplemental efficacy application because microbiology efficacy does not pertain to this product. No preservative challenge is conducted for these (transdermal) products. Microbial limit test and absence of objectionable organisms are conducted for transdermal products. The 0.025 mg strength was approved in an earlier application (supplement 011).

NDA 20-375
Climara® (estradiol transdermal system) 0.025, 0.05, 0.075 and 0.1 mg/day
Berlex Pharmaceuticals, Inc.

**DSI Audit of Clinical Studies**

It was determined at the filing meeting that a DSI inspection was not warranted for this supplement because the drug is already approved for higher dosages.

# FDA CDER EES
# ESTABLISHMENT EVALUATION REQUEST
# SUMMARY REPORT

Application: NDA 20375/016
Stamp: 05-JUN-2000 Regulatory Due: 05-APR-2001
Applicant: BERLEX LABS
340 CHANGEBRIDGE RD
MONTVILLE, NJ 070451000

Priority: 5S Org Code: 580
Action Goal: District Goal: 01-MAR-2001
Brand Name: CLIMARA (ESTRADIOL TRANSDERMAL SYSTEM)
Established Name:
Generic Name: ESTRADIOL TRANSDERMAL SYSTEM
Dosage Form: TDP (TRANSDERMAL PATCH)
Strength: 0.025 MG/DAY, 6.5 CM2

FDA Contacts: A. MITRA (HFD-580) 301-827-4238 , Review Chemist

Overall Recommendation:

**ACCEPTABLE on 29-JAN-2001 by J. D AMBROGIO (HFD-324) 301-827-0062**

Establishment: 2010441
3M PHARMACEUTICALS INC
19901 NORDHOFF ST
NORTHRIDGE, CA 91328

DMF No:
AADA No:

Profile: TDP OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 29-JAN-2001
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: FINISHED DOSAGE MANUFACTURER

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 20375/016
Stamp: 05-JUN-2000
Regulatory Due: 05-APR-2001
Applicant: BERLEX LABS
340 CHANGEBRIDGE RD
MONTVILLE, NJ 070451000
Priority: 5S
Org Code: 580

Action Goal:
District Goal: 01-MAR-2001
Brand Name: CLIMARA (ESTRADIOL TRANSDERMAL SYSTEM)
Estab. Name:
Generic Name: ESTRADIOL TRANSDERMAL SYSTEM

Dosage Form: (TRANSDERMAL PATCH)
Strength: 0.025 MG/DAY, 6.5 CM2

Application Comment: THE DOSAGE FORM AND STRENGTH ARE APPROVED FOR ANOTHER INDICATION (on 13-JAN-2001 by A. MITRA (HFD-580) 301-827-4238)
FDA Contacts: A. MITRA (HFD-580) 301-827-4238 , Review Chemist

Overall Recommendation: ACCEPTABLE on 29-JAN-2001 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: 2010441
3M PHARMACEUTICALS INC
19901 NORDHOFF ST
NORTHRIDGE, CA 91328

DMF No: —
AADA:
Responsibilities: FINISHED DOSAGE MANUFACTURER
Profile: TDP
OAI Status: NONE
Estab. Comment: 3M PHARMACEUTICALS MANUFACTURES AND RELEASES THE PRODUCT (on 13-JAN-2001 by A. MITRA (HFD-580) 301-827-4238)

| Milestone Name | Date | Req. Type | Insp. Date | Decision & Reason | Creator |
|---|---|---|---|---|---|
| SUBMITTED TO OC | 13-JAN-2001 | | | | MITRAA |
| SUBMITTED TO DO | 16-JAN-2001 | 10D | | | FERGUSONS |
| DO RECOMMENDATION | 29-JAN-2001 | | | ACCEPTABLE<br>BASED ON FILE REVIEW | CEVERLY |
| FIRM WAS INSPECTED 12/4-13/00. PROFILE CLASS TDP WAS ACCEPTABLE. | | | | | |
| CARYN EVERLY | | | | | |
| OC RECOMMENDATION | 29-JAN-2001 | | | ACCEPTABLE<br>DISTRICT RECOMMENDATION | DAMBROGIOJ |

/s/
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Amit K. Mitra
2/21/01 05:17:05 PM
CHEMIST
Chemistry Review: The supplement can be approved with respect to CMC

Moo-Jhong Rhee
2/22/01 09:37:55 AM
CHEMIST
I concur

NDA 20-375
Climara® (estradiol transdermal system) 0.025, 0.05, 0.075 and 0.1 mg/day
Berlex Pharmaceuticals, Inc.

**Statistical Review Regarding Dissolution and/or Stability**

No statistical review was performed regarding dissolution and/or stability because the product was previously approved at all dosage strengths and specificity and stability of the product have not changed.

NDA 20-375
Climara® (estradiol transdermal system) 0.025, 0.05, 0.075 and 0.1 mg/day
Berlex Pharmaceuticals, Inc.

**DMF review**

No Drug Master File (DMF) reviews were needed for this efficacy supplement because all strengths of the drug product has been previously approved and no revisions to the associated DMFs have been made.

NDA 20-375
Climara® (estradiol transdermal system) 0.025, 0.05, 0.075 and 0.1 mg/day
Berlex Pharmaceuticals, Inc.

**Environmental Assessment review/FONSI/Categorical exemption.**

The sponsor requested a categorical exclusion on August 18, 2000 based on an EIC less than 1 ppb. The exclusion can be granted (see Chemistry, Manufacturing and Quality Control review dated February 22, 2001).

NDA 20-375/S-016
Climara® (estradiol transdermal system) 0.025 mg/day
Berlex Laboratories, Inc.

**Method Validation**

No new methods validation is needed because the 0.025 mg/day strength is an approved strength.

NDA 20-375
Climara® (estradiol transdermal system) 0.025, 0.05, 0.075 and 0.1 mg/day
Berlex Pharmaceuticals, Inc.

## Micro (validation of sterilization) review

A microbiology validation review is not required for transdermal systems.

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 20375/016
Stamp: 05-JUN-2000
Regulatory Due: 05-APR-2001
Applicant: BERLEX LABS
340 CHANGEBRIDGE RD
MONTVILLE, NJ 070451000
Priority: 5S
Org Code: 580

Action Goal:
District Goal: 01-MAR-2001
Brand Name: CLIMARA (ESTRADIOL TRANSDERMAL SYSTEM)
Estab. Name:
Generic Name: ESTRADIOL TRANSDERMAL SYSTEM

Dosage Form: (TRANSDERMAL PATCH)
Strength: 0.025 MG/DAY, 6.5 CM2

Application Comment: THE DOSAGE FORM AND STRENGTH ARE APPROVED FOR ANOTHER INDICATION (on 13-JAN-2001 by A. MITRA (HFD-580) 301-827-4238)
FDA Contacts: A. MITRA (HFD-580) 301-827-4238 , Review Chemist

Overall Recommendation: ACCEPTABLE on 29-JAN-2001 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: 2010441
3M PHARMACEUTICALS INC
19901 NORDHOFF ST
NORTHRIDGE, CA 91328

DMF No:
AADA:
Responsibilities: FINISHED DOSAGE MANUFACTURER
Profile: TDP
OAI Status: NONE
Estab. Comment: 3M PHARMACEUTICALS MANUFACTURES AND RELEASES THE PRODUCT (on 13-JAN-2001 by A. MITRA (HFD-580) 301-827-4238)

| Milestone Name | Date | Req. Type | Insp. Date | Decision & Reason | Creator |
|---|---|---|---|---|---|
| SUBMITTED TO OC | 13-JAN-2001 | | | | MITRAA |
| SUBMITTED TO DO | 16-JAN-2001 | 10D | | | FERGUSONS |
| DO RECOMMENDATION | 29-JAN-2001 | | | ACCEPTABLE BASED ON FILE REVIEW | CEVERLY |
| FIRM WAS INSPECTED 12/4-13/00. PROFILE CLASS TDP WAS ACCEPTABLE. | | | | | |
| CARYN EVERLY | | | | | |
| OC RECOMMENDATION | 29-JAN-2001 | | | ACCEPTABLE DISTRICT RECOMMENDATION | DAMBROGIOJ |

NDA 20-375
Climara® (estradiol transdermal system) 0.025, 0.05, 0.075 and 0.1 mg/day
Berlex Pharmaceuticals, Inc.

## DSI memo regarding GLP inspection

No GLP inspection was required for this efficacy supplemental application because this is all dosage strengths of this product have previously been approved.

NDA 20-375
Climara® (estradiol transdermal system) 0.025, 0.05, 0.075 and 0.1 mg/day
Berlex Pharmaceuticals, Inc.

**Statistical Review of Carcinogenicity Studies**

No statistical review was performed because all dosage strengths have been previously approved.

NDA 20-375
Climara® (estradiol transdermal system) 0.025, 0.05, 0.075 and 0.1 mg/day
Berlex Pharmaceuticals, Inc.

## CAC/ECAC report

No CAC/ECAC report was made for this efficacy supplemental application because all dosage strengths have previously been approved.

NDA 20-375
Climara® (estradiol transdermal system) 0.025, 0.05, 0.075 and 0.1 mg/day
Berlex Pharmaceuticals, Inc.

## Cartons and Immediate Container labeling

No revisions to the cartons or immediate container labeling has been proposed. The 0.025 mg dosage strength labeling was approved in Supplement 011 on March 5, 1999.

NDA 20-375/S-016
Climara® (estradiol transdermal system) 0.025 mg/day
Berlex Laboratories, Inc.

**DDMAC Labeling Review**

Labeling comments from the Division of Drug Marketing, Advertising and Communications (DDMAC) are incorporated in the meeting minutes dated March 20, 2001.

NDA 20-375
Climara® (estradiol transdermal system) 0.025, 0.05, 0.075 and 0.1 mg/day
Berlex Pharmaceuticals, Inc.

**Status of Advertising**

No advertising material has been submitted. It is requested in the approval letter.

NDA 20-375
Climara® (estradiol transdermal system) 0.025, 0.05, 0.075 and 0.1 mg/day
Berlex Pharmaceuticals, Inc.

## Post-Marketing Commitments

No post-marketing commitments were made for this Supplement.