DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-994

MAY 26 1998

Berlex Laboratories
Attention: Geoffrey Millington
340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000

Dear Mr. Millington:

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

Name of Drug Product: Climara II (estradiol transdermal system), 6.5 cm^2

Therapeutic Classification: Standard

Date of Application: May 1, 1998

Date of Receipt: May 5, 1998

Our Reference Number: NDA 20-994

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 July 4, 1998, in accordance with 21 CFR 314.101(a).

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

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

/S/

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

BERLEX

UPS OVERNIGHT
FACSIMILE

Berlex Laboratories
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 964-3566

March 4, 1999

Solomon Sobel, M.D., Director
Division of Metabolic and Endocrine Drug Products, HFD-510
Document Control Room 14B-19
Office of Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA 20-994 Climara® (estradiol transdermal system)
RESPONSE TO A REQUEST FOR INFORMATION

Dear Dr. Sobel:

Reference is made to our NDA 20-994 for Climara® (estradiol transdermal system) which was submitted on May 1, 1998 and which provided information to support an additional indication, prevention of osteoporosis, for Climara® (NDA 20-375).

Reference is also made to a March 4, 1999 phone conversation with Mr. Randy Hedin from your Division wherein we were asked to provide our final package insert.

Attached are the final physician and patient package inserts. Please note the following:

- Physician insert: All Division changes have been accepted. Below Figure 1 (Page 3) we have noted that we will be revising Figures 1 and 2 such that the ordinate scales will be the same for both figures and will range from +6 to -6.

- Patient insert: Only 2 changes were made: In line 5 of the Introduction the word "four" replaced "three" regarding patch sizes. In the last sentence of the Information About Climara section we have substituted the word "may" in place of "will not" so that the patient insert is in agreement with the Division change to the physician insert.

Please contact the undersigned at (973) 276-2254 if you have any additional requests.

Sincerely,

BERLEX LABORATORIES

Geoffrey P. Millington
Manager, Drug Regulatory Affairs

GPM/clima044

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BERLEX

Drug Development & Technology
Division of Berlex Laboratories, Inc.

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February 24, 1999

Solomon Sobel, M.D., Director
Division of Metabolic and Endocrine Drug Products, HFD-510
Document Control Room 14B-19
Office of Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA 20-994 Climara® (estradiol transdermal system)
RESPONSE TO A REQUEST FOR INFORMATION

Dear Dr. Sobel:

Reference is made to our NDA 20-994 for Climara® (estradiol transdermal system) which was submitted on May 1, 1998 and which provided information to support an additional indication, prevention of osteoporosis, for Climara® (NDA 20-375).

Reference is also made to a February 24, 1999 phone call from Mr. Randy Hedin wherein he requested a revised Debarment Certification.

Attached is the requested revised Debarment Certification for NDA 20-375 for Climara® .

Please contact the undersigned at (973) 276-2254 if you have any additional requests.

Sincerely,

BERLEX LABORATORIES

Geoffrey Millington

Geoffrey Millington
Manager, Drug Regulatory Affairs

GPM/clima033

BERLEX

UPS OVERNIGHT
TELEFAXED

Drug Development & Technology
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February 16, 1999

Dr. H. W. Ju
Division of Scientific Investigation
HFD 344, Room 125
Food and Drug Administration
7520 Standish Place
Rockville, Maryland 20855

Dear Dr. Ju: **RE: NDA 20-994**
Climara® (Estradiol Transdermal System)
Response to Request for Information

Reference is made to our submission of May 1, 1998 of a New Drug Application (20-994) for an additional indication, prevention of osteoporosis, for Climara® .

Reference is also made to our phone conversations of today (February 16, 1999) wherein you requested input concerning discrepancies in information from the Daniel Henry, MD clinical site. In response we are providing the explanatory statement below:

Berlex protocol 308-03 attempted prospectively to define compliance in the subjects enrolled in this trial. The definition chosen was patch use for > 75% of the time of the study. Additional patches were dispensed to be used if a patch fell off so compliance could theoretically be 100% even if unused patches were returned. The purpose of assessing compliance was to define a secondary population subset for efficacy analysis. The primary analysis was intended to be, and was, carried out on the intent-to-treat population which was all women randomized to treatment who wore at least 1 patch. It was anticipated that all patches which were dispensed would be returned, either used (in which case only the empty, opened pouch was likely to returned) or unused and calculation of compliance would be "simple." In spite of instruction from site coordinators, many women did not return some pouches. In the case of "missing" pouches, we made the following decision regarding use: if the subjects attested that they had used the patches, these patches were counted as used; in all other cases of missing patches, we made the assumption in the NDA database that patches had been used. This data management operation should have been described in the statistical methods section of the report.

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February 9, 1999

Solomon Sobel, M.D., Director
Division of Metabolic and Endocrine Drug Products, HFD-510
Document Control Room 14B-19
Office of Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA 20-994 Climara® (estradiol transdermal system)
RESPONSE TO A REQUEST FOR INFORMATION

Dear Dr. Sobel:

Reference is made to our NDA 20-994 for Climara® (estradiol transdermal system) which was submitted on May 1, 1998 and which provided information to support an additional indication, prevention of osteoporosis, for Climara® (NDA 20-375).

Reference is also made to a February 9, 1999 telefax from Dr. Gloria Troendle which provided a question to which our response is given below. For convenience, the Division question is repeated in bold type.

The protocol describes a 2-4 week screening period to assess tolerability of patch use before the enrollment process. How many subjects were screened and excluded from participation in the study because of application site reactions in order to enroll the n of 175 subjects?

Although at the time of recruitment we did not prospectively track screen failures, a review of our reimbursement records indicates that there were a total of 184 screen failures, 5 of which were due to application site reactions.

Please contact the undersigned at (973) 276-2254 if you have any additional requests.

Sincerely,

BERLEX LABORATORIES

Geoffrey P. Millington
Manager, Drug Regulatory Affairs

GPM/clima025

BERLEX

UPS OVERNIGHT
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February 4, 1999

Solomon Sobel, M.D., Director
Division of Metabolic and Endocrine Drug Products, HFD-510
Document Control Room 14B-19
Office of Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA 20-994 Climara® (estradiol transdermal system) - Efficacy Supplement (prevention of osteoporosis) to NDA 20-375
RESPONSE TO A REQUEST FOR INFORMATION

Dear Dr. Sobel:

Reference is made to our NDA 20-994 for Climara® (estradiol transdermal system) which was submitted on May 1, 1998 and which provided information to support an additional indication, prevention of osteoporosis, for Climara® (NDA 20-375).

Reference is also made to a telefax from Dr. Gloria Troendle of February 1, 1999 wherein your Division provided 3 requests for information. Responses to these requests are provided below. For convenience, the Division requests are repeated in bold type and are followed by our response.

1) The data analysis for the lumbar spine BMD in the NDA uses an n of 175. However, the disc provided by you has a baseline lumbar spine BMD for only 172 subjects. Please clarify this discrepancy.

The data analysis for lumbar spine BMD in the NDA uses an n of 172 not 175. This is presented in the study report Text Table 11 (NDA page 8 00081/ Report page 47 of 582). In addition, statistical Table 10 (NDA pages 8 00160-8 00161/Report pages 126 and 127 of 582) reflects that data analysis for lumbar spine BMD uses an n of 172 (baseline). Thus, the disc provided to the Division is consistent with the data presented in the NDA.

Although the overall subject population for this study is 175, 3 subjects had lumbar spine data excluded from the database for the following reason:

We contracted with the _____ as a central reading and quality assurance center for the BMD analyses from this study.

The protocol required that sites do an initial BMD assessment to screen for eligibility. (Most centers used a Lunar Densitometer and looked for readings about 0.9 gm/cm2.) If a subject appeared to be qualified the subject was enrolled. The initial reading was sent on diskette to Portland where it was rescanned and this repeat reading became the baseline to which subsequent BMD measurements were compared.

Subjects were scanned 4 times post-baseline at approximately 6 month intervals for 2 years. None of the results of these repeat scans were reported back to the sites or to Berlex unless they revealed a safety problem (i.e., the BMD was below 0.9 gm/cm2 or decreasing at an annualized rate of 6% or more).

When the study was completed and after the database was locked, the complete BMD datasets were sent from Portland to our statistical consultant _____ for analysis. The tabulations of the analyses were then forwarded to us.

It was always apparent to Berlex that there were missing data at some timepoints for some patients. This was assumed to represent, and usually did represent, missed visits. After the study report was completed we became aware that for three subjects, lumbar spine BMD values were missing although BMD of hip and forearm were available. Our investigation of this fact led to the following determination:

The Portland QA site had determined that in three subjects the baseline lumbar spine scan was not interpretable for technical reasons. Reading our protocol perhaps too literally, these subjects were not excluded from the study (the BMD was not below 0.9 gm/cm2) and neither the study sites nor Berlex were informed of the decision to exclude these subjects. As a result, the subjects continued in the study, receiving study medication and undergoing all the study procedures, including repeat lumbar spine scans. In fact, these subjects should have been excluded from participation in the trial because they were not going to contribute data toward the primary efficacy endpoint.

When the study was concluded, none of the lumbar spine scan data from any of these subjects was sent to our statistical consultants and, as a result, the efficacy database does not include their BMD values. Of course, the safety data base includes data from these subjects. The primary dilemma is that because there is no baseline lumbar spine BMD data, these patients cannot be included in an ITT analysis (as we did with subjects who discontinued after baseline but before 6 months).

2) The investigators listed in the NDA for the randomized clinical trial (Sponsor Study 97034) are Henry, Schoenberger, Bath, Funk, Schumacher, Graham, Riffer, Weiss, Soltes, Lenihan. The investigators listed on the Berlex disc are Henry, Hooper, Bath, Gordon, Smucker, Graham, Trop, Weiss, Soltes, Lenihan. Please clarify the discrepancies in names and identify which investigators are from the same centers.

The following Principal Investigator changes were made during the course of the trial:

- Dr. Hooper was replaced by Dr. Schoenberger at Redwood Medical Clinic, Redwood City, CA
- Dr. Gordon was replaced by Dr. Funk at Hill Top Research, Atlanta, GA
- Dr. Smucker was replaced by Dr. Schumacher at Hill Top Research, Columbus, OH
- Dr. Trop (St. Luke's Health Centers, Phoenix, AZ) was replaced by Dr. Riffer (Central Phoenix Medical Clinic, Phoenix, AZ)

3) The 0.075 mg estradiol (Climara) patch is listed as 15 cm^2 containing 4.68 mg of estradiol in the protocol (Appendix 16.1.1, p. 12 of 54) and 18.75 cm^2 containing 5.85 estradiol in the prescribing information. Please clarify which dose was studied and for which dose you are seeking an indication for osteoporosis.

Pivotal study 308-03 used the following patch sizes:
6.5 cm^2 (2.04 mg), 12.5 cm^2 (3.9 mg), **15 cm^2 (4.68 mg)**, 25 cm^2 (7.8 mg).

The 15 cm^2 patch was a clinical trial formulation only and will not be marketed.

The patch sizes for which we are seeking the osteoporosis indication are:
6.5 cm^2, 12.5 cm^2, **18.75 cm^2** and 25 cm^2.

The 18.75 cm^2 patch was approved March 23, 1998 for relief of post-menopausal vasomotor symptoms. The approval was based solely on CMC and in vitro information. The 18.75 cm^2 patch is intermediate in size to the 12.5 cm^2 and 25 cm^2 patches but otherwise identical since all patch sizes are cut from the same rollstock. Therefore, it is our assumption that the approval of the 18.75 cm^2 patch size for prevention of osteoporosis would be based on demonstration of efficacy for the 12.5 cm^2 and 25 cm^2 sizes.

Please contact the undersigned at (973) 276-2254 if you have any additional requests.

Sincerely,

BERLEX LABORATORIES

APPEARS THIS WAY
ON ORIGINAL

Geoffrey P. Millington
Manager, Drug Regulatory Affairs

GPM/clima021

BERLEX

UPS OVERNIGHT

Drug Development & Technology
Division of Berlex Laboratories, Inc.

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February 2, 1999

Solomon Sobel, M.D., Director
Division of Metabolic and Endocrine Drug Products, HFD-510
Document Control Room 14B-19
Office of Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA 20-994 Climara® (estradiol transdermal system)
- Efficacy Supplement (prevention of osteoporosis) to NDA 20-375
RESPONSE TO A REQUEST FOR INFORMATION

Dear Dr. Sobel:

Reference is made to our NDA 20-994 for Climara® (estradiol transdermal system) which was submitted on May 1, 1998 and which provided information to support an additional indication, prevention of osteoporosis, for Climara® (NDA 20-375). Reference is also made to our submission of January 5, 1999 wherein we provided a copy of the validation report pertaining to Item 6 of NDA 20-994 as requested by your representative, Randy Hedin.

Reference is also made to Mr. Hedin's voicemail request of today for 2 additional desk copies of the L.A.B. GC/MS validation report.

Enclosed are 2 copies of the above referenced report.

Please contact the undersigned at (973) 276-2254 if you have any additional requests.

Sincerely,

BERLEX LABORATORIES

Geoffrey P. Millington
Manager, Drug Regulatory Affairs

GPM/clima019

cc: **RANDY HEDIN – 2 DESK COPIES**

UPS OVERNIGHT

BERLEX

Drug Development & Technology
Division of Berlex Laboratories, Inc.

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January 25, 1999

Solomon Sobel, M.D., Director
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA 20-994 Climara® (estradiol transdermal system)
- Efficacy Supplement (prevention of osteoporosis) to NDA 20-375
RESPONSE TO A REQUEST FOR INFORMATION

Dear Dr. Sobel:

Reference is made to our NDA 20-994 for Climara® (estradiol transdermal system) which was submitted on May 1, 1998 and which provided information to support an additional indication, prevention of osteoporosis, for Climara® (NDA 20-375).

Reference is also made to a telefax from Dr. Gloria Troendle of January 22, 1999 wherein your Division provided 5 requests for information. Responses to these requests are provided below. For convenience, the Division requests are repeated in bold type and are followed by our response.

1) Please provide a timeline as to when you plan on responding to our January 8, 1999 fax.

A written response to the January 8, 1999 fax was sent to the Division on January 21, 1999.

2) Please provide or indicate where in the NDA is the listing of subjects, identifying which ones underwent oophorectomy?

The listing of subjects identifying those who underwent oophorectomy can be found in the NDA Item 8 pages 8 01323 through 8 01372. These pages are located in Volume 9 and are within Appendix 16.2.1 of Report 97034.

3) Please provide or indicate where in the NDA is the list of SHBG and FSH levels?

SHBG levels can be found in Volume 15, pages 8 03673 through 8 03731. These pages make up Appendix 16.2.2 of Report 97034. Please note that the header for this Appendix erroneously refers to Report 97043 rather than 97034.
FSH levels can be found in Volume 9 pages 8 01323 through 8 01372.

4) Please provide or indicate where in the NDA is the actual amount of calcium subjects were taking at Visit 5? Was vitamin D prescribed as well?

Information regarding calcium intake for Visit 5 can be found in Volume_10, pages 8 01761 through 8 01811. No vitamin D was prescribed.

5) Please indicate if the BMD assessments by DEXA were made with the same equipment ( ) for each patient? Was the variability the same with both sets of equipment, at different sites, and in comparison to the central readings?

The BMD assessments by DEXA were made with the same equipment for each patient i.e. patients were scanned either with equipment or with equipment but not with both.

According to QA Center, the variability between equipment is the same.

No comparisons were performed between the sites and the central reading since all readings were performed by the QA Center.

Please contact the undersigned at (973) 276-2254 if you have any additional requests.

Sincerely,

BERLEX LABORATORIES

Geoffrey P. Millington
Manager, Drug Regulatory Affairs

GPM/letter/clima016

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

January 21, 1999

Solomon Sobel, M.D., Director
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA 20-994 Climara® (estradiol transdermal system) - Efficacy Supplement (prevention of osteoporosis) to NDA 20-375
RESPONSE TO A REQUEST FOR INFORMATION

Dear Dr. Sobel:

Reference is made to our NDA 20-994 for Climara® (estradiol transdermal system) which was submitted on May 1, 1998 and which provided information to support an additional indication, prevention of osteoporosis, for Climara® (NDA 20-375).

Reference is also made to a telefax from Dr. Gloria Troendle of January 8, 1999 wherein your Division provided 6 requests for information. Responses to these requests are provided below. For convenience, the Division requests are repeated in bold type and are followed by our response.

1) In Section 8, Volume 1.5, Page 00012, text Table 3, 19 out of 175 patients were randomized and then excluded from the study for failing to sign a consent. Please explain why the consent was not signed before randomization.

We apologize for a typographical error. In the referenced table, the term "withheld" is an error. The correct term is "withdrew." Please refer to the end of study page of the CRF (Volume 7, page 800766) and to the listings (Volume 5, page 800151) for subject withdrawal. These 19 subjects gave their consent and were randomized to the study. At a later time, the 19 withdrew their consent to participate, and were discontinued from the study. No subject was randomized to or continued in the study if she withheld consent to participate. All subjects' data have remained in the intent to treat analysis.

2) Also in Text Table 3 mentioned above; submit a breakdown of specific reasons why the patients dropped out in the "other" category.

Attached to this letter is a table listing each subject who had dropped out for "other" reasons with a specific explanation for "other" in each case.

3) Please clarify if the placebo patches contained vehicle or not.

Placebo patches were identical to active patches in every way except for the absence of active substance, estradiol. Therefore, they did contain vehicle.

4) Was BMD calculated both at the study site and centrally? If so, which data is in the NDA? What was the range of difference in results between the central reading and each site?

BMD was calculated by the QA Center. The NDA contains data only from the QA Center. Therefore, there is no comparison of data between the Center and the sites.

Sites scanned patients at baseline and obtained a value to determine if the subject met the entry criteria for the study. This information was not included in the NDA.

5) In what percentage of patients did the 6.5 cm^2 dose alleviate vasomotor symptoms?

We did not assess baseline vasomotor symptoms nor did we follow these symptoms in this study. We have two ongoing studies designed specifically to address this issue for the 6.5 cm^2 patch. These studies are being conducted under IND [redacted] with the Division of Reproductive and Urologic Drug Products.

6) Please inform us when we will receive the intent to treat analysis requested by Dr. Ma (statistical reviewer) in December.

Berlex has provided all analyses requested by Dr. Ma as follows:

- Correspondence of January 15, 1999 provided electronic files via diskettes.
- Facsimiles of January 11 and 15, 1999 provided hardcopies of analyses.

Please contact the undersigned at (973) 276-2254 if you have any additional requests.

Sincerely,

BERLEX LABORATORIES

Geoffrey P. Millington
Manager, Drug Regulatory Affairs

GPM/letter/clima015

NDA 20-994 - Climara - Study 308-03 - Subjects Discontinued for Reason "Other"

TREATMENT: 2.04mg (6.5cm2)

Subject	Investigator	Medication Discontinued?	Date of Last Visit	Study Discontinued?	Primary Reason for Discontinuation - Study Medication
301013	D. Henry	Yes	9/19/96	Yes	Other: Lost to Follow Up
306004	J. Smucker	Yes	5/3/95	Yes	Other: Pt Lost to Follow Up
306005	J. Smucker	Yes	5/13/96	Yes	Other: Pt moved out of State
307008	R. Graham	Yes	3/29/95	Yes	Other: Lost to Follow Up
307015	R. Graham	Yes	Unknown	Yes	Other: Lost to Follow Up
308014	H. Trop	Yes	6/16/97	Yes	Other: Pt stopped - Didn't Think Could Make Follow Up Appt
309009	S. Weiss	Yes	11/29/94	Yes	Other: Relocated
311011	J. Lenihan	Yes	1/11/96	Yes	Other: High Triglycerides

TREATMENT: 3.9mg (12.5cm2)

Subject	Investigator	Medication Discontinued?	Date of Last Visit	Study Discontinued?	Primary Reason for Discontinuation - Study Medication
305001	S. Gordon	Yes	8/2/94	Yes	Other: Lost to Follow Up
306007	J. Smucker	Yes	9/18/95	Yes	Other: Lost to Follow Up
309010	S. Weiss	Yes	Unknown	Yes	Other: Lost to Follow Up
309014	S. Weiss	Yes	12/30/94	Yes	Other: Lost to Follow Up
309026	S. Weiss	Yes	3/22/95	Yes	Other: Lost to Follow Up
309029	S. Weiss	Yes	3/7/95	Yes	Other: Job Travel Out of State 6 Months

TREATMENT: 4.68mg (15cm2)

Subject	Investigator	Medication Discontinued?	Date of Last Visit	Study Discontinued?	Primary Reason for Discontinuation - Study Medication
309003	S. Weiss	Yes	12/5/95	Yes	Other: Lost to Follow Up

NDA 20-994 - Climara - Study 308-03 - Subjects Discontinued for Reason "Other" (page 2)

TREATMENT: 7.8mg (25cm2)

Subject	Investigator	Medication Discontinued?	Date of Last Visit	Study Discontinued?	Primary Reason for Discontinuation - Study Medication
302013	G. Hooper	Yes	4/10/97	Yes	Other: Lost to Follow Up
305012	S. Gordon	Yes	12/1/94	Yes	Other: Lost to Follow Up
306008	J. Smucker	Yes	6/15/95	Yes	Other: Pt Lost to Follow Up
308006	H. Trop	Yes	1/18/95	Yes	Other: Relocation of Patient
309028	S. Weiss	Yes	12/9/96	Yes	Other: Lost to Follow Up
309036	S. Weiss	Yes	2/13/96	Yes	Other: Enrolled in Another Investigational Trial
311010	J. Lenihan	Yes	12/7/95	Yes	Other: Takes Melatonin and Investigator Disontinued Her

TREATMENT: Placebo

Subject	Investigator	Medication Discontinued?	Date of Last Visit	Study Discontinued?	Primary Reason for Discontinuation - Study Medication
301022	D. Henry	Yes	6/17/97	Yes	Other: Pt Lost Patches
304001	R. Bath	Yes	9/26/94	Yes	Other: Lost to Follow Up
304010	R. Bath	Yes	8/5/96	Yes	Other: Lost to F/U
305004	S. Gordon	Yes	8/15/94	Yes	Other: Lost to Follow Up
306006	J. Smucker	Yes	6/9/95	Yes	Other: Lost to Follow Up
307001	R. Graham	Yes	9/26/95	Yes	Other: Unstable Health Conditions
308013	H. Trop	Yes	3/29/95	Yes	Other: Relocation
309007	S. Weiss	Yes	11/24/94	Yes	Other: Relocated
309017	S. Weiss	Yes	8/8/95	Yes	Other: Relocation
309020	S. Weiss	Yes	6/27/95	Yes	Other: Lost to Follow Up
309025	S. Weiss	Yes	Unknown	Yes	Other: Lost to Follow Up
311002	J. Lenihan	Yes	3/27/96	Yes	Other: Lost to Follow Up

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January 15, 1999

Dr. Jonathan Ma
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA 20-994 Climara® (estradiol transdermal system) - Efficacy Supplement (prevention of osteoporosis) to NDA 20-375
RESPONSE TO A REQUEST FOR INFORMATION

Dear Dr. Ma:

Reference is made to our NDA 20-994 for Climara® (estradiol transdermal system) which was submitted on May 1, 1998 and which provided information to support an additional indication, prevention of osteoporosis, for Climara® (NDA 20-375).

Reference is also made to our telephone conversations of January 8 and 14 and our telefaxes of January 11 and 15 regarding reanalysis and provision of additional Bone Mineral Density (BMD) data.

Enclosed are two, 3.5 inch diskettes containing the requested data files. The information is provided as follows:

Disk 1 - Contains a last observation carried forward, intent to treat analysis of BMD percent change from baseline for spine and total hip where data for patients dropping out at baseline is replaced by the actual baseline value. In percent change analysis, this means that data for baseline dropouts is replaced by zero. Contents:

- README.TXT (provided for convenience)
- OUTPUT.PDF (contains tables, figures and SAS log files)
  SAS Program Files provided:
- EVISTA.SAS (Formerly LOCF.SAS, Percent change from baseline BMD on observed data - perform ANOVAs Tables 1,2)
- LOCF.SAS (Generate descriptive statistics for percent change from baseline BMD parameters on observed data - perform ANOVAs - Tables 3,4)

- BMDGRPH4.SAS (Generate graphs of LOCF %chg from B/L for Spine and Total Hip modified per FDA req)
- GSFGEN.SAS (Create GSF output files from catalog BMDGRPH4)
- SDB_MA.SAS (Transform existing analysis dataset for BMD for FDA requests by J. Ma)
- BMDX.SAS (Special analysis dataset w/baseline carried fwd in archive format)

Initialization & setup programs provided:

- INIT.SAS (Standard initialization of librefs, formats, and titles for SAS programs)
- GSETUP.SAS (Establish graphics environment for Postscript, MS-WORD/WordPerfect, or GIF files)

Disk 2: Contains an intent to treat analysis of BMD percent change from baseline for spine and total hip where missing data is replaced by the previous datapoint plus the difference in average placebo response for the corresponding datapoints.
Contents:

- README.TXT (provided for convenience)
- FDA2.PDF (contains tables, figures and SAS log files)

Analysis programs:

- SDB_MA2.SAS (Formerly SDB_MA.SAS, Transform existing analysis dataset for BMD)
- AVG_PLA.SAS (Descriptive statistics for percent change from baseline BMD parameters on imputed data using method provided by Jonathan Ma of FDA)
- BMDGRPH5.SAS (Formerly BMDGRPH3.SAS, Generate graphs of %chg from B/L for Spine and Total Hip modified per FDA req)
- GSFGEN.SAS (Create GSF output files from catalog BMDGRPH5)
- BMDZ.SAS (Special analysis dataset w/baseline carried fwd in archive format)

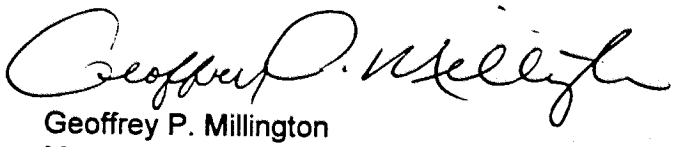
Setup, Initialization, and Utility Programs

- INIT.SAS (Standard initialization of librefs, formats, and titles for SAS programs)
- GSETUP.SAS (Establish graphics environment for Postscript, MS-WORD/WordPerfect, or GIF files)

Please contact the undersigned at (973) 276-2254 if you have any additional requests.

Sincerely,

BERLEX LABORATORIES



Geoffrey P. Millington
Manager, Drug Regulatory Affairs

GPM/letter/clima014

ORIGINAL

BERLEX

UPS OVERNIGHT

ORIG AMENDMENT
BM

Drug Development & Technology
Division of Berlex Laboratories, Inc.

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

January 12, 1999

1/21/99
Received
NAI. /S/

Randy Hedin
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA 20-994 Climara® (estradiol transdermal system) - Efficacy Supplement (prevention of osteoporosis) to NDA 20-375
RESPONSE TO A REQUEST FOR INFORMATION

Dear Mr. Hedin:

Reference is made to our NDA 20-994 for Climara® (estradiol transdermal system) which was submitted on May 1, 1998 and which provided information to support an additional indication, prevention of osteoporosis, for Climara® (NDA 20-375).

Reference is also made to your telephone request for a spreadsheet of Bone Mineral Density (BMD) data from the lumbar spine for all of the 175 subjects treated in the pivotal clinical study.

Enclosed are two, 3.5 inch floppy disks each containing the requested spreadsheet which is named **berlxbmd.xls**. The spreadsheet format is 176 rows (header row followed by 175 subjects) and 12 columns. The columns are arranged, per your request, as follows: Subject, Investigator, Treatment, Baseline BMD value, 6 Month BMD value, 12 month BMD value, 18 month BMD value, 24 month BMD value, 6 month % change from baseline, 12 month % change from baseline, 18 month % change from baseline and 24 month % change from baseline. All data are from readings of lumbar spine.

Please contact the undersigned at (973) 276-2254 if you have any additional requests.

Sincerely,

BERLEX LABORATORIES
Geoffrey P. Millington
Manager, Drug Regulatory Affairs

GPM/letter/clima008

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

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

January 5, 1999

Randy Hedin
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA 20-994 Climara® (estradiol transdermal system)
- Efficacy Supplement (prevention of osteoporosis) to
NDA 20-375
RESPONSE TO A REQUEST FOR INFORMATION

Dear Mr. Hedin:

Reference is made to our NDA 20-994 for Climara® (estradiol transdermal system) which was submitted on May 1, 1998 and which provided information to support an additional indication, prevention of osteoporosis, for Climara® (NDA 20-375).

Reference is also made to your voicemail request for a copy of the L.A.B. GC/MS validation report pertaining to Item 6 of NDA 20-994.

Enclosed is a copy of the above referenced report.

Please contact the undersigned at (973) 276-2254 if you have any additional requests.

Sincerely,

BERLEX LABORATORIES

Geoffrey P. Millington
Manager, Drug Regulatory Affairs

GPM/letter/clima001

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

December 7, 1998

Randy Hedin
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA 20-994 Climara® (estradiol transdermal system)
- Efficacy Supplement (prevention of osteoporosis) to NDA 20-375
RESPONSE TO A REQUEST FOR INFORMATION

Dear Mr. Hedin:

Reference is made to our NDA 20-994 for Climara® (estradiol transdermal system) which was submitted on May 1, 1998 and which provided information to support an additional indication, prevention of osteoporosis, for Climara® (NDA 20-375).

Reference is also made to our phone conversation of December 4, 1998 wherein you requested an additional copy of Volume 1 and of the bioavailability section of NDA 20-994.

Enclosed is a copy of Volume 1, and Volumes 3 and 4 which contain bioavailability information.

Please contact the undersigned at (973) 276-2254 if you have any additional requests.

Sincerely,

BERLEX LABORATORIES

Geoffrey P. Millington
Manager, Drug Regulatory Affairs

GPM/letter/clima096

BERLEX

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Drug Development & Technology
Division of Berlex Laboratories, Inc.

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

July 16, 1998

NEW CORRESP

Dr. H. W. Ju
Division of Scientific Investigation
HFD 344, Room 125
Food and Drug Administration
7520 Standish Place
Rockville, Maryland 20855

ORIGINAL

Dear Dr. Ju:

RE: NDA 20-994
Climara® (Estradiol Transdermal System)
Response to Request for Information

Reference is made to our submission of May 1, 1998 of a New Drug Application (20-994) for an additional indication, prevention of osteoporosis, for Climara® (Estradiol Transdermal System).

Reference is also made to our phone conversation of July 2, 1998 wherein you requested information to be used in preparation for clinical site audits.

The information which you requested is provided in the attached 6 volumes as follows:

- One volume labeled "D. Henry, MD" contains signed 1572 forms, the total number of patients entered and completed, the number of dropouts and the reason for each, the individual data listings for dropouts due to adverse events, and a list of protocol violators. It also contains case report forms for patients 1, 10, 15 and 23.

- One volume labeled "S. Weiss, MD" contains signed 1572 forms, the total number of patients entered and completed, the number of dropouts and the reason for each, the individual data listings for dropouts due to adverse events, and a list of protocol violators. It also contains case report forms for patients 1, 10, 20 and 39.

- Two copies of a volume labeled "Monitor Survey - D. Henry, MD" contain a table of information as you requested plus the Berlex monitoring SOP.

- Two copies of a volume labeled "Monitor Survey - S. Weiss, MD" contain a table of information as you requested plus the Berlex monitoring SOP.

As you requested, a copy of this letter is being forwarded to the reviewing Division (Metabolism and Endocrine Drug Products).

Please contact the undersigned at (973) 276-2254 if you have any questions or require additional information.

Sincerely,

BERLEX LABORATORIES, INC.

Geoffrey P. Millington
Manager
Drug Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

GPM/letter/clima068

cc:

Solomon Sobel, M.D., Director
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

APPEARS THIS WAY
ON ORIGINAL

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

NDA 20-994

BERLEX

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Drug Development & Technology
Division of Berlex Laboratories, Inc.
340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 276-2000

May 1, 1998

Solomon Sobel, M.D., Director
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA 20-375 Climara® (estradiol transdermal system)
- Efficacy Supplement (prevention of osteoporosis)
- Chemistry, Manufacturing & Controls Supplement (additional patch size of 6.5 cm^2)

Dear Dr. Sobel:

Reference is made to our NDA 20-375 for Climara® (estradiol transdermal system) which was approved on December 22, 1994 and was transferred to Berlex Laboratories, Inc. from 3M Pharmaceuticals on November 2, 1995. The approved patch sizes are 12.5 cm^2, 18.75 cm^2 and 25 cm^2.

Reference is also made to the following communications between Berlex and FDA:

- August 13, 1997 - Letter from Ms. Sharon Brown to Dr. Lisa Rarick (HFD 580) outlining discussions concerning the complexities of a multi-faceted submission for a new indication, a bioavailability study and CMC information. The type of application (NDA or Supplement) and destination of application (HFD 580 or HFD 510, the Division of Metabolism and Endocrine Drug Products) were considered.

- September 4, 1997 - Telephone conversation between Ms. Sharon Brown of Berlex and Ms. Diane Moore, CSO, HFD 580, wherein it was confirmed that this application would be a Type 6 NDA submitted to HFD 510.

- January 8, 1998 - Telephone conversation between the undersigned and Mr. Randy Hedin, CSO, HFD 510, wherein general discussion took place concerning submission of a Type 6 NDA which would include a new indication (prevention of osteoporosis), a new patch size and bioavailability data. Also discussed was the submission of SAS datasets electronically. As a result, the enclosed application contains these data on CD-Rom, inserted into the Statistical Item 10, Volume 20, in both the Review and Archival copies.

- January 15, 1998 - Letter from the undersigned to Dr. Lisa Rarick informing HFD 580 of agreements regarding the Type 6 NDA which were reached on January 8, 1998.

- March 26 & 27, 1998 - Telephone conversation between Ms. Geri Besta of Berlex and Ms. Beverly Friedman and Ms. Joslyn Swann of FDA, CDER, User Fee Team (HFD-005/007), wherein FDA concluded that the Climara® Transdermal submission providing for the osteoporosis indication will be considered an Efficacy Supplement to the approved NDA 20-375 rather than a Type 6 NDA.

- March 27, 1998 - Telephone conversation between Ms. Sharon Brown of Berlex and Ms. Lana Pauls, Supervisory, CSO, HFD 580 wherein Ms. Pauls agreed with the Users Fee department that Berlex should submit the application as a single supplement.

Therefore, attached is a 53 volume supplemental application which provides for a new indication, prevention of osteoporosis, for all approved Climara® patch sizes, the addition of a new patch size of 6.5 cm^2, and bioavailability data to support the new patch size.

User Fee I.D. Number, _____ was assigned to this supplement by FDA, Central Documents and Records on _____.

Please note that Chemistry, Manufacturing and Controls information for the new 6.5 cm^2 patch is provided in _____ Drug Master File _____. The DMF was amended by ___ on _____ and a letter authorizing FDA to refer to the DMF in regard to this NDA supplement is provided in the application.

Please contact the undersigned at (973) 276-2254 if you have any questions concerning this supplement.

Sincerely,

BERLEX LABORATORIES

Geoffrey P. Millington
Manager
Drug Regulatory Affairs

cc: Ms. Lana Pauls, Supervisor Consumer Safety Officer
Desk Copy: Randy Hedin, CSO

GPM/letter/clima036