CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020994, 020375/S011

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

14. PATENT CERTIFICATION

Paragraph III Certification

Pursuant to 21 CFR 314.50(i)(1)(i)(A)(3), the undersigned declares that Patent No. 5,223,261 covers the composition and method of use of Climara® (estradiol transdermal system), in a 6.5 cm^2 system for the prevention of osteoporosis in postmenopausal hysterectomized women, which is the subject of this supplemental application for which approval is being sought, and certifies that the patent will expire on June 29, 2010.

BERLEX LABORATORIES, INC.

Ted Ikeda

Ted Ikeda
General Counsel Intellectual Properties

April 21, 1998
Date

GAB/patcrt/023b

13. PATENT INFORMATION

Pursuant to 21 CFR 314.50(h) and 21 CFR 314.53(d)(2)(i)(B) and (C), the undersigned declares that the following United States patent, owned by 3M Pharmaceuticals, and its associated original expiration date apply to Climara® (estradiol transdermal system).

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

BERLEX LABORATORIES, INC.

Ted Ikeda

Ted Ikeda
General Counsel Intellectual Properties

April 21, 1998
Date

GAB/patcrt/023a
clmsmpat.doc

EXCLUSIVITY SUMMARY FOR NDA # 20-994 SUPPL # _____

Trade Name Climara Generic Name estradiol TDS

Applicant Name Berlex HFD # 510

Approval Date If Known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it an original NDA?

YES /✓/ NO /___/ Type 6

b) Is it an effectiveness supplement?

YES /___/ NO /✓/

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

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

YES /✓/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /✓/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request? Didn't state years requested. but cited 21 CFR 314.108(b)(5) = 3 years

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

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

YES /___/ NO /✓/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active

moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /✓/ NO /___/

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

NDA# 20-375 Climara

NDA# 19-081 Estraderm

NDA# _____ _____

2. Combination product. N/A

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

YES /___/ NO /___/

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

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

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

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

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

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

YES /✓/ NO /___/

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

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

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

YES /✓/ NO /___/

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

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

YES /✓/ NO /___/

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

YES /___/ NO /✓/

If yes, explain: _____

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

YES /___/ NO /___/

If yes, explain: _____

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

_____

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

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

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

Investigation #1 YES /___/ NO /✓/

Investigation #2 YES /___/ NO /___/

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

_____ _____

_____ _____

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

Investigation #1 YES /___/ NO /✓/

Investigation #2 YES /___/ NO /___/

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

_____ _____

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

Study 308-036

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

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

Investigation #1	
IND # YES /✓/	NO /___/ Explain: _____
Investigation #2	
IND # _____ YES /___/	NO /___/ Explain: _____

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

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

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

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

YES /___/ NO /✓/

If yes, explain: _____

_____

/S/

Signature

Title: CSO

3/4/99

Date

/S/

Signature of Division Director

3/5/99

Date

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

Statement of Claimed Exclusivity

Pursuant to 21 CFR 314.50(j) and with reference to 21 CFR 314.108(b)(5), Berlex Laboratories, Inc. hereby submits this statement of claimed marketing exclusivity.

1. Berlex claims exclusivity under 21 CFR 314.108(b)(5);

2. 21 CFR 314.108(b)(5)(i) and (ii) support this claim;

3. Pursuant to 21 CFR 314.50(j)(4), this supplemental application contains a "new clinical investigation" that is "essential to approval" and was "conducted or sponsored by" Berlex Laboratories, Inc. under IND 40,928 for Estradiol Transdermal Drug Delivery System.

GAB/patcrt/023c

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20994	**Trade Name:**	CLIMARA(ESTRADIOL TRANSDERMAL SYS)0.025/
Supplement Number:		**Generic Name:**	ESTRADIOL TRANSDERMAL SYS
Supplement Type:		**Dosage Form:**	
Regulatory Action:	AP	**Proposed Indication:**	Prevention of Postmenopausal Osteoporosis (loss of bone mass).

IS THERE PEDIATRIC CONTENT IN THIS SUBMISSION? No

What are the INTENDED Pediatric Age Groups for this submission? No-1

____NeoNates (0-30 Days)____Children (25 Months-12 years)
____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Status -
Formulation Status -
Studies Needed -
Study Status -

APPEARS THIS WAY
ON ORIGINAL

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:
The indication is for use in postmenopausal women; therefore, it is not indicated for pediatric patients.

The indication is for the prevention of osteoporosis in postmenopausal women and therefore the drug is not used in pediatric patients

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, RANDY HEDIN

/S/

Signature

3/5/99

Date

APPEARS THIS WAY
ON ORIGINAL

BERLEX Laboratories, Inc.

NDA 20-375
Climara® (estradiol transdermal system)

"DEBARMENT" CERTIFICATION

CERTIFICATION UNDER SECTION 306(k)(1) OF THE FD & C ACT

This is to certify that neither Berlex Laboratories, Inc. ("Berlex"), nor any person employed by Berlex in connection with the New Drug Application for Climara® (estradiol transdermal system), NDA 20-375, has been debarred under Section 306(a) or (b) of the Federal Food Drug and Cosmetic Act, and that Berlex will not employ any debarred person in connection with the New Drug Application for Climara® (estradiol transdermal system).

APPEARS THIS WAY
ON ORIGINAL

BERLEX LABORATORIES, INC.

Joan Mutascio
Regulatory Submissions &
Information Associate

2/24/99
Date

jm\clmdebr5

NDA20994, Berlex Labs Inc.
Climara, Estradiol Transdermal System
For Postmenopausal Osteoporosis
Submitted 5/5/98
Review Completed February 25, 1999

Team Leader's Review of Original New Drug Application

This application is for an estradiol patch to prevent bone loss in postmenopausal women. The proposed label, as modified at a Division meeting on the label, says," (first 4 indications shortened, because they are concerns of HFD-580 and not of 510),
"Climara is indicated in the:"

1. Treatment of ...vasomotor symptoms...
2. Treatment of vulval and vaginal atrophy.
3. Treatment of hypoestrogenism due to hypogonadism...
4. Treatment of abnormal uterine bleeding.
5. "Prevention of Osteoporosis (loss of bone mass). The mainstays of prevention of osteoporosis are estrogen, an adequate lifetime calcium intake, and exercise."

One study was conducted for demonstration of efficacy in prevention of osteoporosis. The primary endpoint for this study was measurement (DEXA) of bone mineral density of the lumbar spine. Other efficacy endpoints were: per cent change in BMD (DEXA) of the femoral neck, radius, and total hip, and per cent change in the biochemical bone markers osteocalcin (in serum), and pyridinoline/deoxypyridinoline/creatinine ratios, in urine. The usual safety endpoints were determined, plus breast and pelvic exams, vaginal Pap smears, spine x-rays, mammograms. Five groups of women were treated with placebo patches, or with patches of four different sizes: 6.5 cm^2, 12.5 cm^2, 15 cm^2, and 25 cm^2 calculated to deliver 0.025, 0.05, 0.06 (approximately), 0.075, and 0.1 mg/d estradiol. Blinding was assured by using two patches for each patient each week. The five groups had 46, 32, 31, 31 and 35 subjects at randomization, and 21, 16, 20, 22, and 22 at 24 months (after twenty-six 28-day cycles).

The change in BMD of the lumbosacral spine is significantly greater in each of the drug groups than in the placebo group, but the smallest patch results in less change in BMD, appears to be less effective than the other drug patches. There is an implication that the patch is superior to oral dosing forms, because it does not get metabolized in a first pass through the liver. This might be true if inadequate estradiol reached bone, but effective estrogen levels are achieved in blood and in bone. We accept that ethinyl estradiol is effective for prevention of PMO, but safety and efficacy of the different doses must be established.

Recommendation: Approve. AP

Several issues have come to my attention regarding this drug. Possibly some of them could be addressed in labeling; others are related to design and would have required earlier attention. The issues are as follows:

1. A most important and frequent reason that postmenopausal women choose not to use estrogen replacement therapy or that they discontinue such therapy is vaginal bleeding. Because the population studied is hysterectomized women, there are no data on which to estimate the incidence of bleeding when taking Climara.

2. The population that is selected for this study is a much healthier one than will ordinarily be using this drug, so the subjects are much less likely to experience adverse events, giving a false impression that Climara is less prone to adverse events than are other estrogen products.

3. In this study, there were numerous entry exclusions that I doubt the Sponsor expects to exclude from the population for which the drug is indicated. It may not be reasonable to put into the label that patients with the following conditions were excluded from the study, and there is, therefore, inadequate information on which to recommend use of Climara in these conditions: osteoporosis, hypo or hypercalcemia, vitamin D deficiency, fracture within 6 months, immobilization for more than 2 of the last 6 months, MI within 6 months, CHD requiring anti-anginal drugs, thrombophlebitis within 3 years, CHF, disturbances of cardiac rhythm requiring anti-arrhythmic drugs, uncontrolled hypertension, uncontrolled thyroid disease, insulin-dependent diabetes, or treatment with heparin, warfarin, or chronic corticosteroids. Also excluded were patients with a history of any of the following: premalignant disease, stroke, TIA, depression, severe headaches during estrogen therapy, skin irritation or allergy due to tape or any transdermal products.

4. Many of the patients screened for entry were not entered because of irritation at the last-screening patch application, and, even so, there were twice the number of site reactions with Climara as with estraderm. The sponsor has not determined whether the patches containing estrogen were more irritating than the placebo patches, which all patients used. This might easily be done because all patients used two patches at least one of which was placebo.

5. No restrictions on women for whom the drug should be prescribed are mentioned in the Indications section of the Climara label. This drug is studied in a population designed to minimize reports of adverse events by admitting only healthy women, and women in whom the primary target for adverse effects (the uterus) is not present.

6. Women with osteoporosis were excluded from the study. There should be instructions in the label for selecting women who do not have fractures or do not have (by BMD) T score<-2.5. However, the indication does not mention

bone density or risk factors for osteoporosis. It seems that all women, regardless of age and bone density and postmenopausal status and risk factors for osteoporosis qualify for treatment with Climara. I believe this is also true of the Premarin label. The Premarin label should also give suggestions for choosing women who are in need of estrogen replacement.

7. In the Indications section, both labels go on to discuss treatment of osteoporosis and effects of estrogen on bone. This general discussion does not belong in Indications, but should be moved to the "clinical pharmacology section.

8. Osteoporosis was among the exclusion criteria, and lumbar spine x-rays were made at screening to exclude women who had fractures, but no subsequent x-rays were made to detect incidental fractures.

9. Height was measured only at baseline, so it is not possible to examine any changes in height for evidence of efficacy.

10. Dietary calcium was assessed, and supplements provided if necessary. In spite of this provision, intake of calcium was less than 1000 mg/d. Vitamin D sufficiency was neither evaluated nor was vitamin D provided if there was insufficient intake.

11. No attempt has been made in the label to suggest an appropriate starting dose. The label does say that dose can be adjusted using biochemical markers and BMD and that the lowest effective dose is the 6.5cm^2 patch. However, instructions for postmenopausal symptoms say to start at a higher dose and attempt to reduce the dose periodically. That method is likely to be used for dosing in prevention of osteoporosis, unless the label says to start with the lowest dose and increase as needed. Of course, titration using biochemical markers has not been studied.

Recommendation: Approve

AP

Gloria Troendle /S/

2/21/97 Concur /S/

cc: HFD-580
NDA 20375
HFD-510
HFD-510/Troendle/Zawadzki/Hedin

NDA 20-994
Climara (estradiol transdermal system)

Dear Mr. Millington:

Please refer to your pending May 1, 1998 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Climara (estradiol transdermal system).

We are reviewing the clinical section of your submission and have the following comment and information request:

1. In reviewing the pharmacokinetic data, the following question was raised:

   Are the patches, particularly the 6.5 cm^2 patch, equally effective in obese women in the prevention of postmenopausal osteoporosis?

   To help us answer this question, please provide the following data and analyses:

   A. The relationship of lumbosacral spine bone mineral density percent change and baseline weight.

   B. The relationship of total hip bone mineral density percent change and baseline weight.

   C. The relationship of percent change in lumbosacral spine bone mineral density to estradiol concentrations for a subset of subjects (87 at visit 1; 69 at visit 3; 57 at visit 5) for whom hormonal concentrations are available.

   D. An electronic file with the following parameters:

      - subject #
      - patch size
      - age
      - years between menopause and enrollment in study
      - oophorectomy done (yes or no)
      - race
      - height
      - baseline weight
      - lumbosacral baseline BMD
      - total hip BMD

- percent change in lumbosacral baseline BMD
- percent change in total hip BMD
- The following should be reported for baseline visit, visit 1, 3 and 5.

  - estradiol – unconjugated
  - estradiol – conjugated
  - estrone – unconjugated
  - estrone – conjugated
  - SHBG

2. Please clarify how many subjects had natural versus surgical menopause (i.e., underwent oophorectomy), the duration between menopause and enrollment in study (range, SD), and whether these factors affected the percent change in lumbosacral or total hip BMD.

3. The summary regarding abnormal liver function tests lists abnormal tests that were thought to be clinically significant according to the investigators. Please submit a listing of all abnormal liver function tests at baseline and during the study, by treatment group.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.
If you have any questions, contact Randy Hedin, R.Ph., Senior Regulatory Management Officer, at (301) 827-6392.

Sincerely,

/S/

Dr. Gloria Troendle
Deputy Division Director
Division of Metabolic and
Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

N20994_FAX5.doc

NDA 20-994
Climara (estradiol transdermal system)

Dear Mr. Millington:

Please refer to your pending May 1, 1998 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Climara (estradiol transdermal system).

We are reviewing the clinical section of your submission and have the following comment and information request:

> 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?

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.
If you have any questions, contact Randy Hedin, R.Ph., Senior Regulatory Management Officer, at (301) 827-6392.

Sincerely,

/S/

Dr. Gloria Troendle
Deputy Division Director
Division of Metabolic and
Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

N20994_FAX4.doc

NDA 20-994
Climara (estradiol transdermal system)

Dear Mr. Millington:

Please refer to your pending May 1, 1998 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Climara (estradiol transdermal system).

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

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.

3. The 0.075 mg estradiol (Climara) patch is listed as 15 cm2 containing 4.68 mg of estradiol in the protocol (Appendix 16.1.1, p. 12 of 54) and 18.75 cm2 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.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

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

Sincerely,

/S/

Dr. Gloria Troendle
Deputy Division Director
Division of Metabolic and
Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

N20994_FAX3.doc

NDA 20-994
Climara (estradiol transdermal system)

Dear Mr. Millington:

Please refer to your pending May 1, 1998 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Climara (estradiol transdermal system).

We are reviewing the clinical section of your submission and have the following comments and information requests:

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

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

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

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?

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?

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

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

Sincerely,

/S/

Dr. Gloria Troendle
Deputy Division Director
Division of Metabolic and
Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

N20994_FAX.doc

NDA 20-994
Climara (estradiol transdermal system)

Dear Mr. Millington:

Please refer to your pending May 1, 1998 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Climara (estradiol transdermal system).

We are reviewing the clinical and statistical section of your submission and have the following comments and information requests:

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.

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

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

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?

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

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

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

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

Sincerely,

/S/

Dr. Gloria Troendle
Deputy Division Director
Division of Metabolic and
Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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