

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-674

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**

*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER

21-674

NAME OF APPLICANT / NDA HOLDER

Berlex, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

MENOSTAR

ACTIVE INGREDIENT(S)

Estradiol

STRENGTH(S)

0.014 mg estradiol/day

DOSAGE FORM

Transdermal Patch

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number

5,223,261

b. Issue Date of Patent

June 29, 1993

c. Expiration Date of Patent

June 29, 2010

d. Name of Patent Owner

Riker Laboratories, Inc.

Address (of Patent Owner)

City/State

St. Paul, Minnesota

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Tatsuya Ikeda

Address (of agent or representative named in 1.e.)

Berlex, Inc.

City/State

P.O. Box 1000, 340 Changebridge Rd., Montville, NJ

ZIP Code

07045-1000

FAX Number (if available)

(973) 487 - 2712

Telephone Number

(973) 487-2000

E-Mail Address (if available)

ted_ikeda@berlex.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Claim Number (as listed in the patent) 8, 15 Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)
Prevention of postmenopausal osteoporosis in women with or without a uterus.

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6 Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed

Tatsuya Ikeda

December 16, 2003

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Ted Ikeda

Address

Berlex, Inc.

City/State

P.O. Box 1000
340 Changebrige Road
Montville, NJ

ZIP Code

07045-1000

Telephone Number

(973) 487-2024

FAX Number (if available)

(973) 487-2712

E-Mail Address (if available)

ted_ikeda@berlex.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

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.

**PATENT INFORMATION SUBMITTED WITH THE
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MENOSTAR

ACTIVE INGREDIENT(S)
Estradiol

STRENGTH(S)
0.014 mg estradiol/day

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For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

GENERAL

a. United States Patent Number 5,891,868	b. Issue Date of Patent April 6, 1999	c. Expiration Date of Patent Nov. 21, 2017
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d. Name of Patent Owner University of California Berlex Laboratories, Inc. Kaiser Foundation Health Plan	Address (of Patent Owner) Berlex, Inc.	
	City/State P.O. Box 1000, 340 Changebridge Rd., Montville, NJ	
	ZIP Code 07045-1000	FAX Number (if available)
	Telephone Number (973) 487-2000	E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)  Tatsuya Ikeda	Address (of agent or representative named in 1.e.) Berlex, Inc.	
	City/State P.O. Box 1000, 340 Changebridge Rd., Montville, NJ	
	ZIP Code 07045-1000	FAX Number (if available) (973) 487 - 2712
	Telephone Number (973) 487-2000	E-Mail Address (if available) ted_ikeda@berlex.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? Yes No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? Yes No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

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2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

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3.2 Does the patent claim only an intermediate? Yes No

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4. Method of Use

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4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Claim Number (as listed in the patent) 1-3, 5-10, 12-15, 17-19, 20-25, 27-29 Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)
Prevention of postmenopausal osteoporosis in women with or without a uterus.

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

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Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed

Tatsuya Ikeda

December 16, 2003

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Ted Ikeda

Address

Berlex, Inc.

City/State

P.O. Box 1000
340 Changebrige Road
Montville, NJ

ZIP Code

07045-1000

Telephone Number

(973) 487-2024

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Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

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.

d) Did the applicant request exclusivity?

YES /XX/

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

3 years

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

YES /___/ NO /XX/

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

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

NO /XX/

IF THE ANSWER TO QUESTION 2 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.

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 /xx/

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 /xx/

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 /xx/

(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?

NO /XX/

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:

A11926(98188):A phase 3,24-month,randomized,placebo-controlled parallel-group, double-blind, multi-center clinical trial.

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.

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 #40928	YES /XXX/	!	NO /___/ Explain: _____
		!	
Investigation #2	!		
IND # _____	YES /___/	!	NO /___/ Explain: _____

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

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

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

YES /___/ NO /XXX/

If yes, explain: _____

Pat Madara
Regulatory Project Manager
DMEDP

Date

David G. Orloff, M.D.
Division Director

Date

Form OGD-011347 Revised 05/10/2004

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

/s/

Patricia Madara
6/10/04 07:59:08 AM

David Orloff
6/10/04 04:17:05 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

DA/BLA #: 21-674 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: August 8, 2003 Action Date: _____

HFD 510 Trade and generic names/dosage form: Menostar (estradiol transdermal system); 0.014 mg/day

Applicant: Berlex Laboratories Therapeutic Class: 3020425

Indication(s) previously approved: Prevention of osteoporosis in women with and without a uterus

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

Number of indications for this application(s): 1

Indication #1: prevention of osteoporosis

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

XX Yes: Please proceed to Section A.

No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

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

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

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for partial waiver:

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

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is

complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

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

Other: _____

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

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

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

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

This page was completed by:

{See appended electronic signature page}

Pat Madara
Regulatory Project Manager

cc: NDA 21-674
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

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

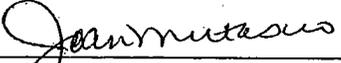
/s/

Patricia Madara
6/15/04 02:59:19 PM

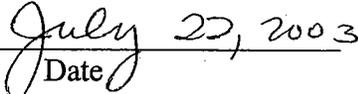
16. DEBARMENT CERTIFICATION**Certification Under Section 306(k)(1) of the FD & C Act**

Berlex Laboratories, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with NDA 21-674 for Menostar™ (estradiol transdermal system).

BERLEX LABORATORIES, INC.



Joan Mutascio
Associate, Regulatory
Submissions & Information



Date

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

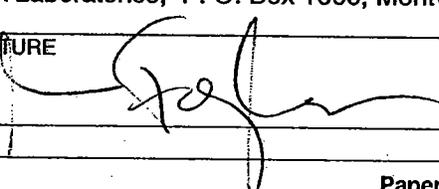
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
------------------------	--	--

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Marie L. Foegh, MD, D. Sc.	TITLE Vice President, Clinical Development Female Health Care
FIRM / ORGANIZATION Berlex Laboratories, P. O. Box 1000, Montville, NJ 07045-1000	
SIGNATURE 	DATE 2/23/03

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Rockville, MD 20857

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

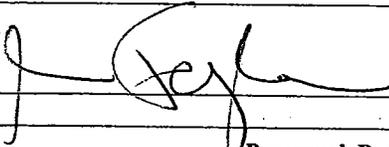
The following information concerning Bruce Ettinger, MD,
Name of clinical investigator

Who participated as a clinical investigator in the submitted study # 98188 – A multicenter, double-blind, randomized, placebo controlled study to evaluate the safety and efficacy of an ultralow dose of estradiol given by continuous transdermal administration in the prevention of osteoporosis in post menopausal women is submitted in accordance with 21 CFR 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

- any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;
- any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;
- any proprietary interest in the product tested in the covered study held by the clinical investigator;
- any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME Marie L. Foegh, MD, D. Sc	TITLE Vice President, Clinical Development Female Health Care
FIRM / ORGANIZATION Berlex Laboratories, P. O. Box 1000, Montville, NJ 07045-1000	
SIGNATURE 	DATE 7/29/03

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Food and Drug Administration
5600 Fishers Lane, Room 14-72
Rockville, MD 20857

CONSULTATION RESPONSE
Division Of Medication Errors And Technical Support
Office of Drug Safety
(DMETS; HFD-420)

Date Received:
September 30, 2003

Desired Completion Date:
November 30, 2003
PDUFA Date: June 8, 2004

ODS CONSULT#: 03-0275

TO:
David Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products
HFD-510

THROUGH:
Patricia Madara
Project Manager, Division of Metabolic and Endocrine Drug Products
HFD-510

PRODUCT NAME:
Menostar
(Ultra-low Dose Estradiol Transdermal System)
0.014 mg/day
NDA#: 21-674

NDA SPONSOR:
Berlex Laboratories, Inc.

SAFETY EVALUATOR: Linda Y. Kim-Jung, R.Ph.

RECOMMENDATIONS:

1. DMETS does not recommend the use of the proprietary name, Menostar. DMETS did not identify any look-alike or sound-alike names, which may result in medication errors. However, DMETS is concerned that the dual trademarks of Menostar and Climara may result in the potential of adverse outcomes due to inadvertent co-administration of these two estradiol containing products.
2. DMETS recommends that "Ultra-low Dose" be deleted from the established name which is consistent with U.S.P. nomenclature practice.
3. DMETS recommends implementation of the insert labeling revisions outlined in section III of this review to minimize potential errors with the use of this product. Please submit container labels and carton labeling when available.
4. DDMAC finds the proprietary name, Menostar, acceptable from a promotional perspective.
5. DMETS recommends the Division of Metabolic and Endocrine Drug Products consult with the CDER Labeling and Nomenclature Committee (LNC) for the proper nomenclature of the established name.

Carol Holquist, RPh
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: 301-827-3242 Fax: 301-443-9664

Jerry Phillips, RPh
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420; Parklawn Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: January 28, 2004
NDA NUMBER: 21-674
NAME OF DRUG: Menostar
(ultra-low dose estradiol transdermal system)
0.014 mg/day
NDA SPONSOR: Berlex Laboratories, Inc.

*****NOTE: This review contains proprietary and confidential information that should not be released to the public.*****

I. INTRODUCTION

This consult was written in response to a request from the Division of Metabolic and Endocrine Drug Products (HFD-510), to review the proprietary name, Menostar, regarding potential name confusion with other proprietary and established drug names. Berlex Laboratories currently manufactures Climara (estradiol transdermal system). Climara was approved on December 22, 1994 under NDA 02-0375. Menostar contains the same active ingredient as Climara but in a lower dose. Climara is available in six different strengths. Climara is indicated for the treatment of:

- moderate to severe vasomotor symptoms associated with the menopause;
- vulval and vaginal atrophy;
- hypoestrogenism due to hypogonadism, castration or primary ovarian failure;
- abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology and only when associated with a hypoplastic or atrophic endometrium; and
- the prevention of postmenopausal osteoporosis (loss of bone mass).

Product Name	Estradiol (delivered over 24 hours)
Climara	0.025 mg
Climara	0.0375 mg
Climara	0.05 mg
Climara	0.06 mg
Climara	0.07 mg
Climara	0.1 mg

Additionally, Climara Pro (by Berlex Laboratories) contains estradiol 0.45 mg and levonorgestrel 0.015 mg combined in a transdermal patch, which is given every 24 hours. Climara Pro is only indicated for the treatment of moderate to severe vasomotor symptoms associated with the menopause.

Menostar provides for a lower strength of estradiol (0.014 mg over 24 hours) and is indicated in the prevention of postmenopausal osteoporosis in women with or without a uterus. Thus, upon approval of this NDA, the sponsor will market three transdermal products containing estradiol under three different proprietary names (Climara, Climara Pro, and Menostar). All three products contain estradiol in varying strengths and share the indication of prevention of postmenopausal osteoporosis. Although, Climara has numerous indications of use and Menostar has only one, the only other difference is the strength of the patch.

Container labels and carton labeling were not submitted for review. However, the sponsor did submit the insert labeling and the patient information for review and comment.

PRODUCT INFORMATION

Menostar (ultra-low dose estradiol transdermal system), is indicated in the prevention of postmenopausal osteoporosis in women with or without a uterus. Menostar delivers 0.014 mg of estradiol per day. The adhesive side of the Menostar system should be placed on a clean, dry area of the lower abdomen and should be applied immediately after opening the pouch and removing the protective liner. The system should be pressed firmly in place with the fingers for about 10 seconds, making sure there is good contact, especially around the edges. Only one system should be worn at any one time during the 7-day dosing interval. Menostar is available in individual carton of 4 systems and a shelf pack carton of 6 individual cartons of 4 systems.

II. RISK ASSESSMENT

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2} as well as several FDA databases³ for existing drug names which sound-alike or look-alike to Menostar to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted⁴. The Saegis⁵ Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

¹ MICROMEDEX Integrated Index, 2004, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems

² Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO

³ AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-04, and the electronic online version of the FDA Orange Book

⁴ WWW location <http://www.uspto.gov/tmdb/index.html>

⁵ Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

A. EXPERT PANEL DISCUSSION (EPD)

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

1. DDMAC finds the proprietary name, Menostar, acceptable from a promotional perspective.
2. The Expert Panel identified one proprietary name, _____ which was thought to have the potential for confusion with Menostar. However, _____ is not marketed in the United States and thus, it will not be discussed in this review. In addition, the Expert Panel was also concerned that the name, Menostar, may lead practitioners to think of the product 'Menotropin' because both names begin with the same letters 'Meno'. However, there are other drug names marketed in the United States which start with the letters, "Meno" (e.g., Menogen) that do not belong to the drug classification of the Menotropins.
3. Through independent review, one additional drug name, Menopur*** was also determined to have potential for confusion with Menostar.

B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Menostar were discussed by the Expert Panel (EPD).

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Menostar with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 127 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Menostar. These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or

verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<p><u>Inpatient Rx sample:</u></p> <p>Continue Menostar as dir.</p>	<p>Menostar</p> <p>Apply as directed for 7 days.</p>
<p><u>Outpatient Rx sample:</u></p> <p>Menostar</p> <p>Apply as dir for 7 days</p> <p>#4</p>	<p>#4</p>

2. Results:

None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed U.S. product. See appendix A for the complete listing of interpretations from the verbal and written studies.

D. SAFETY EVALUATOR RISK ASSESSMENT

1. Look-alike and Sound-alike Names

No proprietary names were identified by the expert panel or via POCA as having the potential to look or sound similar to Menostar. However, Menopur*** was identified through independent review as having potential look-alike and or sound-alike confusion with Menostar (see Table 1). DMETS also conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any existing approved drug products. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Menostar.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual adult dose	Other
Menostar	Ultra-low dose estradiol transdermal system 0.014mg/day each 3.25cm ² patch contains 1mg estradiol	Patch is applied for 7 day intervals	N/A
Menopur***	Menotropins for Injection, USP Injection 75 International Units FSH / 75 International Units LH Vials.	Assisted Reproductive Technology: 225 International Units daily, with subsequent individualized dosing. Not to exceed 450 International Units. Ovulation Induction: initial dose of 75 International Units daily with subsequent individualized dosing.	L/A, S/A

*Frequently used, not all-inclusive.
 **L/A (look-alike), S/A (sound-alike)
 ***Name pending approval. Not FOI releasable.

Menostar may look and sound similar to Menopur***. Menopur is indicated in the prevention of postmenopausal osteoporosis in women with or without a uterus. Both names begin with the same four letters 'meno' and end with letters that may look similar when scripted 'ur versus ar'. However, the downstroke of the 'p' in Menopur and the upstroke of the 't' in Menostar may help differentiate the two names when scripted. The beginnings of both names are the same contributing to the sound-alike similarities. However, the endings (star vs. pur) are phonetically different. Thus the two names may sound different when pronounced. Although, both products are dosed once daily and may have similar prescribers [Women's Health Practitioners, (e.g. obstetricians, gynecologists, etc)] there are product characteristics that will help differentiate the two. These include dose (0.014 mg/day vs. 75 International Units to 225 International Units, with individualized dosing), route of administration (transdermal vs. intramuscular or subcutaneously), strength (1 mg of estradiol per patch vs. 75 International Units), indication of use (prevention of postmenopausal osteoporosis vs. Assisted Reproductive Technology), and length of use (7 days vs. 20 days). Thus, the product characteristics may help minimize the potential for confusion with these two products.

menostar
menopur

MEMUSTAR
MENOPUR

2. Concomitant Drug Usage Concerns

The sponsor proposes to market estradiol transdermal system under two proprietary names (approved NDA #20-375 Climara and the pending application NDA #21-674 with a proposed name Menostar). Both NDAs share the same indication of use and are marketed by the same manufacturer. The only difference between Climara and Menostar is that Menostar will be available in a lower strength of 0.014 mg/day. DMETS is concerned with the potential for concomitant administration of Climara and Menostar resulting in adverse events. DMETS is also concerned that two different products that share the same active ingredient, dosage form, established name and are manufactured by the same company but have two separate proprietary names may be confusing and misleading to practitioners and result in medication errors.

- a. Although Climara and Menostar share an indication of use, Climara has other indications of use (e.g., vulval and vaginal atrophy). Thus, two different practitioners (e.g., gynecologist and primary care physician) could potentially co-prescribe Climara and Menostar for a patient. Since the products have different names and different strengths, the practitioner or patient may not realize that they contain the same active ingredient. A patient may experience estrogen-related adverse effects due to overdosing of the same drug, such as nausea and vomiting, and withdrawal bleeding. DMETS has received postmarketing reports relating to concomitant administration of products with different proprietary names but that share the same active ingredients. Furthermore, due to the nature of this type of error, it is likely that the error could go undetected and may never be spontaneously reported to the sponsor, ISMP, USP or FDA MedWatch.
 - b. Practitioners may think that Menostar is a safer product or has additional characteristics, other than the lower strength, that may be beneficial to patients. For example, a patient who experiences an application site reaction (ASR) with Climara may be prescribed Menostar because the practitioner thinks it is a different product that may not result in the same type of ASR as the patient experienced with Climara.
 - c. Finally, DMETS expects the potential for confusion to be further complicated when the products associated with multiple proprietary names become available as generic drugs. Not only will there be potential for confusion that leads to inadvertent dosing with the generic products themselves, there is also the potential for the generic applications to submit a proprietary name for each indication of use. It becomes a burden to practitioners to determine which branded generic product is equivalent to Climara and which branded generic product is equivalent to Menostar. This is especially a problem when the generic manufacturer chooses not to use a proprietary name because both products will simply be labeled Estradiol Transdermal System.
3. Established Name Safety Concerns

DMETS is concerned with the proposed established name 'Ultra-low Dose Estradiol Transdermal System.' What does the prefix "Ultra-low Dose" represent? What happens if another dose that is lower is approved? This is not an approved dosage form or descriptor. This terminology is also not currently used in conjunction with estradiol for other estrogen containing products. We recommend that "Ultra-low Dose" be deleted from the established name which is consistent with U.S.P. nomenclature practice.

III. COMMENTS TO THE SPONSOR

DMETS does not recommend the use of proprietary name, Menostar. In reviewing the proprietary name, Menostar, the primary concerns related to the safety issues concerning the use of dual trademarks for Berlex's estradiol transdermal systems.

A. Concomitant Drug Usage Concerns

The sponsor proposes to market estradiol transdermal system under two proprietary names (approved NDA #20-375 Climara and the pending application NDA #21-674 with a proposed name Menostar). Both NDAs share the same indication of use and are marketed by the same manufacturer. The only difference between Climara and Menostar is that Menostar will be available in a lower strength of 0.014 mg/day. DMETS is concerned with the potential for concomitant administration of Climara and Menostar resulting in adverse events. DMETS is also concerned that two different products that share the same active ingredient, dosage form, established name and are manufactured by the same company but have two separate proprietary names may be confusing and misleading to practitioners and result in medication errors.

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2. Practitioners may think that Menostar is a safer product or has additional characteristics, other than the lower strength, that may be beneficial to patients. For example, a patient who experiences an application site reaction (ASR) with Climara may be prescribed Menostar because the practitioner thinks it is a different product that may not result in the same type of ASR as the patient experienced with Climara.
3. Finally, DMETS expects the potential for confusion to be further complicated when the products associated with multiple proprietary names become available as generic drugs. Not only will there be potential for confusion that leads to inadvertent dosing with the generic products themselves, there is also the potential for the generic applications to submit a proprietary name for each indication of use. It becomes a burden to practitioners to determine which branded generic product is equivalent to Climara and which branded generic product is equivalent to Menostar. This is especially a problem when the generic manufacturer chooses not to use a proprietary name because both products will simply be labeled Estradiol Transdermal System.

B. Established Name Safety Concerns

DMETS is concerned with the proposed established name 'Ultra-low Dose Estradiol Transdermal System.' What does the prefix "Ultra-low Dose" represent? What happens if another dose that is lower is approved? This is not an approved dosage form or descriptor. This terminology is also not currently used in conjunction with estradiol for other estrogen containing products. We recommend that "Ultra-low Dose" be deleted from the established name which is consistent with U.S.P. nomenclature practice

C. INSERT LABELING COMMENTS

In the review of the insert labeling of Menostar, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified several areas of possible improvement, which might minimize potential user error.

1. GENERAL COMMENT

Include a warning statement in the insert labeling that states that the "Patients should be made aware that Menostar contains the same active ingredient found in Climara and that Menostar should not be used in combination with Climara. This warning statement should be presented in both insert labeling of Menostar and Climara.

2. PRESCRIBING INFORMATION

a. Description Section

When referring to the product strength, dosing recommendations or the size of the product; whole numbers should be expressed without a trailing zero (e.g., 1 mg rather than 1.0 mg). Revise accordingly throughout the text of the insert.

b. Precautions, Information for Patient Section

Give instructions on how to properly discard the transdermal patch (i.e., wrap and discard the patch...keep away from children and pets)

c. Dosage and Administration Section

- i. The statement "if the estrogen dose is increased, a progestin should also be initiated...", does not provide the reader with guidance on when a progestin should be added (e.g., how much of an estrogen increase).
- ii. Additionally, under the Initiation of Therapy subsection, state the usual recommended dosage (i.e., Apply one patch every 7 days).

3. PATIENT INFORMATION

DMETS' comments on the patient information materials were forwarded in a joint review from the Division of Surveillance, Research, and Communication Support on January 30, 2004. Additionally, DMETS recommends that the presentation of the information in the Patient Information for Menostar and Climara be consistent to prevent confusion. Moreover, include a warning statement in the Patient Information that states that "Menostar contains the same active ingredient found in Climara and that Menostar should not be used in combination with Climara. This warning statement should be presented in both Patient Information of Menostar and Climara.

IV. RECOMMENDATIONS:

- A. DMETS does not recommend the use of the proprietary name, Menostar. Although DMETS did not identify any look-alike or sound-alike names which may result in medication errors, DMETS is concerned with the dual trademark issues and the potential of adverse outcomes due to inadvertent co-administration of products containing estradiol.
- B. DMETS recommends that "Ultra-low Dose" be deleted from the established name which is consistent with U.S.P. nomenclature practice.
- C. DMETS recommends implementation of the insert labeling revisions outlined in section III of this review to minimize potential errors with the use of this product. Please submit container labels and carton labeling when available.
- D. DDMAC finds the proprietary name, Menostar, acceptable from a promotional perspective
- E. DMETS recommends the Division of Metabolic and Endocrine Drug Products consult with the CDER Labeling and Nomenclature Committee (LNC) for the proper nomenclature of the established name.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

Linda Y. Kim-Jung, R.Ph. Date
Safety Evaluator
Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety

Concur:

Denise Toyer, PharmD Date
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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 X § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

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/s/

Linda Kim-Jung
4/1/04 11:08:11 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
4/1/04 12:06:49 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
4/1/04 12:20:13 PM
DRUG SAFETY OFFICE REVIEWER

Jerry Phillips
4/1/04 01:07:22 PM
DRUG SAFETY OFFICE REVIEWER

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 § 552(b)(5) Draft Labeling

MEMO

To: David Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products HFD-510

From: Denise P. Toyer, PharmD
Team Leader, Division of Medication Errors and Technical Support, Office of Drug Safety, HFD-420

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

CC: Patricia Madara
Project Manager, Division of Metabolic and Endocrine Drug Products HFD-510

Date: May 25, 2004

Re: ODS Consult 03-0275-2, Menostar (Estradiol Transdermal System) 0.14 mg/day; NDA 21-674

This memorandum is in response to a May 19, 2004 request from your Division for a review of the revised container labels and carton labeling (submission dated May 14, 2004) for Menostar. DMETS previously reviewed the container labels, carton and insert labeling (see DMETS consult dated April 1, 2004), and the patient insert (see DSRCS review dated January 30, 2004) and forwarded comments to the Division. The Division did not submit a revised package insert or patient insert labeling for review and comment.

In the review of the Menostar container labels and carton labeling, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

A. GENERAL COMMENTS

1. Relocate the graphic that covers the beginning letter 'M' of the proprietary name so that it does not interfere with the readability of the proprietary name.
2. Increase the prominence of the established name and strength, so that they are at least one-half the size of the proprietary name.
3. The terminal zeros listed throughout the container labels and carton labeling should be deleted since they could be misinterpreted (e.g., 1.0 as 10). Revise accordingly.

B. MENOSTAR FOIL LABELS (TRADE AND SAMPLE)

1. See General Comments A-1 through A-3.
2. Include the route of administration on the principal display panel (e.g., For Transdermal Use).

C. MENOSTAR CARTON LABELING (4 systems)

1. See General Comments A-1 through A-3.
2. Increase the prominence of the route of administration statement on the principal display panel. Revise accordingly.
3. Revise the net quantity statement to read '4 Transdermal Systems.'

D. MENOSTAR CARTON LABELING (6 x 4 systems)

1. See General Comments A-1 through A-3.
2. Increase the prominence of the route of administration statement on the main display panel. Revise accordingly.
3. Revise the net quantity statement to read '6 Patient Packs each containing 4 Transdermal Systems.'

E. MENOSTAR CARTON LABELING (Sample Card)

1. See General Comments A-1 through A-3.
2. Increase the prominence of the route of administration statement on the main display panel. Revise accordingly.
3. Revise the net quantity statement so that it reads '1 Transdermal System.'

In summary, DMETS recommends implementation of the label and labeling revisions outlined above that might lead to safer use of Menostar. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer. If you have any questions or need clarification, please contact Sammie Beam at 301-827-2102.

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/s/

Denise Toyer
5/25/04 09:09:12 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
5/26/04 07:41:20 AM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM

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

DATE: May 20, 2004

TO: David Orloff, M.D., Director
Division of Metabolic and Endocrine Drug Products
HFD-510

VIA: Pat Madara, Regulatory Health Project Manager
Division of Metabolic and Endocrine Drug Products
HFD-510

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Gerald Dal Pan, M.D., M.H.S., Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: ODS/DSRCS Review #2 of Patient Labeling for Menostar
(estradiol transdermal system), NDA 21-674

The patient labeling which follows represents the revised risk communication materials of the Patient Labeling for Menostar (estradiol transdermal system), NDA 21-674. It has been reviewed by our office and by DDMAC. We have made it consistent with the revised February 2004, suggested labeling changes for non-contraceptive estrogen containing products, based on findings from the WHI study. The detailed instructions for use of the product were moved to the end of the leaflet to allow for easier readability of important information. These revisions are based on draft labeling submitted by the sponsor on May 12, 2004.

Comments to the review division are bolded, underlined and italicized. We can provide a marked-up copy of the revised document in Word if requested by the review division. Please call us if you have any comments.

6 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

X § 552(b)(5) Draft Labeling

MEMO

To: David Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products HFD-510

From: Denise P. Toyer, PharmD
Team Leader, Division of Medication Errors and Technical Support, Office of Drug Safety, HFD-420

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

CC: Patricia Madara
Project Manager, Division of Metabolic and Endocrine Drug Products HFD-510

Date: May 5, 2004

Re: ODS Consult 03-0275-1, Menostar (Estradiol Transdermal System) 0.14 mg/day; NDA 21-674

This memorandum is in response to an April 19, 2004 request from your Division for a review of the container labels and carton labeling for Menostar. Container labels and carton labeling were submitted for review and comment. The insert labeling and the patient package insert were previously reviewed by DMETS and comments forwarded to the Division. The Division did not submit revised insert labeling or patient insert for review.

In the review of the Menostar container labels and carton labeling, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

A. GENERAL COMMENTS

1. Increase the prominence of the proprietary name, established name and strength, so that they are the most prominent information presented.
2. The terminal zeros listed throughout the container labels and carton labeling should be deleted since they could be misinterpreted (e.g., 3.0 as 30). Revise accordingly.

B. MENOSTAR FOIL LABELS (TRADE AND SAMPLE)

1. See General Comments A-1 and A-2.
2. Revise the net quantity statement to read '4 Transdermal Systems.'
3. Include the route of administration on the principal display panel (e.g., For Transdermal Use).

C. MENOSTAR CARTON LABELING (6X4)

1. See General Comments A-1 and A-2.
2. Revise the net quantity statement to read '4 Transdermal Systems.'

D. MENOSTAR CARTON LABELING (Sample)

1. See General Comments A-1 and A-2.
2. Increase the prominence of the route of administration statement on the main display panel. Revise accordingly.
3. Revise the net quantity statement so that it appears in the lower right corner to read '4 Transdermal Systems.'

E. INSERT LABELING

DMETS' comments on the insert labeling were included in the April 1, 2004 proprietary name review.

F. PATIENT PACKAGE INSERT

DMETS' comments on the patient information materials were forwarded in a joint review from the Division of Surveillance, Research, and Communication Support on January 30, 2004.

In summary, DMETS recommends implementation of the label and labeling revisions outlined above that might lead to safer use of Menostar. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer. If you have any questions or need clarification, please contact Sammie Beam at 301-827-2102.

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/s/

Denise Toyer
5/10/04 01:22:05 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
5/10/04 02:18:00 PM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM

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

DATE: January 30, 2004

TO: David Orloff, M.D., Director
Division of Metabolic and Endocrine Drug Products
HFD-510

VIA: Pat Madara, Regulatory Health Project Manager
Division of Metabolic and Endocrine Drug Products
HFD-510

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Gerald Dal Pan, M.D., M.H.S., Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: ODS/DSRCS Review of Patient Labeling for Menostar (estradiol transdermal system), NDA 21-674

The patient labeling which follows represents the revised risk communication materials of the Patient Labeling for Menostar (estradiol transdermal system), NDA 21-674. It has been reviewed by our office and by DDMAC (see DDMAC consult, January 22, 2004.) We have made it consistent with the January 3, 2003, suggested labeling changes for estrogen containing products, based on findings from the WHI study. The detailed instructions for use of the product were moved to the end of the leaflet to allow for easier readability of important information. These revisions are based on draft labeling submitted by the sponsor on August 7, 2003.

Comments to the review division are bolded, underlined and italicized. We can provide marked-up and clean copies of the revised document in Word if requested by the review division. Please call us if you have any comments.

6 Page(s) Withheld

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_____ § 552(b)(5) Deliberative Process

6 § 552(b)(5) Draft Labeling

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/s/

Jeanine Best
1/30/04 12:47:30 PM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
1/30/04 04:31:45 PM
DRUG SAFETY OFFICE REVIEWER
for Gerald Dal Pan

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-674

Trade Name: Menostar
Generic Name: estradiol transdermal system
Strengths: 0.14 mg/day

Applicant: Berlex Labs

Date of Application: 8/7/03
Date of Receipt: 8/8/03
Date clock started after UN: N/A
Date of Filing Meeting: 9/29/03
Filing Date: 10/7/03
Action Goal Date (optional):

User Fee Goal Date: 6/8/04

Indication(s) requested: prevention of post-menopausal osteoporosis

Type of Original NDA: (b)(1) XX (b)(2) _____
OR

Type of Supplement: (b)(1) _____ (b)(2) _____

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

Therapeutic Classification: S XX P _____
Resubmission after withdrawal? No Resubmission after refuse to file? No
Chemical Classification: (1,2,3 etc.) 6
Other (orphan, OTC, etc.) N/A

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

Form 3397 (User Fee Cover Sheet) submitted: YES
User Fee ID # 4571
Clinical data? YES XX NO, Referenced to NDA # _____

Is there any 5-year or 3-year exclusivity on this active moiety in either a (b)(1) or a (b)(2) application?

NO

If yes, explain:

Does another drug have orphan drug exclusivity for the same indication?

NO

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

N/A

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

If yes, has OC/DMPQ been notified of the submission? N/A

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

Additional comments:

- If in Common Technical Document format, does it follow the guidance? N/A
- Is it an electronic CTD? N/A
If an electronic CTD, all certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format?

Additional comments:

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

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

- Financial Disclosure forms included with authorized signature? YES
 (Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)
- Field Copy Certification (that it is a true copy of the CMC technical section)? YES

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? YES
 If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.
- List referenced IND numbers: 66,714
- End-of-Phase 2 Meeting(s)? NO
 If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) 4/10/03
- If yes, distribute minutes before filing meeting.

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? NO
 PI and PPI only will be consulted (type 6 NDA)
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? YES
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? PPI only YES
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A YES NO
- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

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

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES
 If no, did applicant submit a complete environmental assessment?
 If EA submitted, consulted to Nancy Sager (HFD-357)? N/A

- Establishment Evaluation Request (EER) submitted to DMPQ? YES
- If a parenteral product, consulted to Microbiology Team (HFD-805)? NO

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

- Name of listed drug(s) and NDA/ANDA #:
- Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").
- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs.)
YES NO
- Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 314.101(d)(9).
YES NO
- Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? (See 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9).
YES NO
- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

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

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

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

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

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

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

___ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.

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

• Did the applicant:

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

YES NO

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

YES NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

N/A YES NO

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?)

N/A YES NO

- If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that each of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

YES NO

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

YES NO

- EITHER

The number of the applicant's IND under which the studies essential to approval were conducted.

OR IND # _____ NO

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

N/A YES NO

- Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: September 29, 2003

BACKGROUND: This is a Type 6 NDA – the original NDA (20-375, Climara) resides in HFD 580. This is a transdermal patch for a lower dose of estradiol ONLY for the prevention of post menopausal osteoporosis.

ATTENDEES: Hae Young Ahn, Japo Choudhury, Eric Colman, Kati Johnson, Johnny Lau, Pat Madara, Amit Mitra, Todd Sahlroot

ASSIGNED REVIEWERS:

<u>Discipline</u>	<u>Reviewer</u>
Medical:	Eric Colman
Secondary Medical:	Phil Price (HFD-580, consult)
Statistical:	Japo Choudhury
Pharmacology:	NN
Statistical Pharmacology:	
Chemistry:	Amit Mitra (HFD-580, consult)
Environmental Assessment (if needed):	NN
Biopharmaceutical:	Johnny Lau
Microbiology, sterility:	NN
Microbiology, clinical (for antimicrobial products only):	NN
DSI:	Andrea Slavin
Regulatory Project Management:	Pat Madara
Other Consults:	DMETS, DDMAC, DSRCS

Per reviewers, are all parts in English or English translation? YES
If no, explain:

CLINICAL FILE XX

- Clinical site inspection needed: YES
- Advisory Committee Meeting needed? NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
N/A

CLINICAL MICROBIOLOGY NA XX FILE _____ REFUSE TO FILE _____

STATISTICS FILE XX REFUSE TO FILE _____

BIOPHARMACEUTICS FILE XX REFUSE TO FILE _____

- Biopharm. inspection needed: NO

PHARMACOLOGY NA XX FILE _____ REFUSE TO FILE _____

- GLP inspection needed: YES NO

CHEMISTRY FILE XX REFUSE TO FILE _____

- Establishment(s) ready for inspection? **PM Will request this document** YES NO
- Microbiology NO

ELECTRONIC SUBMISSION:

Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ The application is unsuitable for filing. Explain why:

XX The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

XX No filing issues have been identified.

_____ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. If RTF, notify everybody who already received a consult request of the RTF action. Cancel the EER.
2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. Document filing issues/no filing issues conveyed to applicant by Day 74:

Pat Madara
Regulatory Project Manager, HFD-510

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/s/

Patricia Madara
11/18/03 01:59:11 PM
CSO

Patricia Madara
11/18/03 02:01:25 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING REVIEW LETTER

NDA 21-674

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 August 7, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Menostar (estradiol transdermal system).

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on October 7, 2003, in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call me at (301) 827-6416.

Sincerely,

{See appended electronic signature page}

Pat Madara
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
(HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Patricia Madara
10/9/03 08:36:17 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-674

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

Dear Mr. Millington:

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

Name of Drug Product:	Menostar™ (estradiol transdermal system)
Review Priority Classification:	Standard (S)
Date of Application:	August 7, 2003
Date of Receipt:	August 8, 2003
Our Reference Number:	NDA 21-674

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on October 7, 2003, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be June 8, 2004.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service/Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Fishers Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

NDA 21-674

Page 2

If you have any questions, call Pat Madara, Regulatory Project Manager, at (301) 6416.

Sincerely,

{See appended electronic signature page}

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

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/s/

Patricia Madara
8/21/03 03:17:59 PM

PRESCRIPTION DRUG USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

Completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

1. APPLICANT'S NAME AND ADDRESS

Berlex Laboratories
P.O. Box 1000
Montville, NJ 07045-1000

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
NDA 21-674

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

YES NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

(APPLICATION NO. CONTAINING THE DATA).

2. TELEPHONE NUMBER (Include Area Code)

(973) 487 - 2157

3. PRODUCT NAME

Menostar™ (estradiol transdermal system)

6. USER FEE I.D. NUMBER

4571

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

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

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

THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)

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

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

YES NO

(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
and 12420 Parklawn Drive, Room 3046
Rockville, MD 20852

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.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE



TITLE

Manager, Regulatory Intelligence and
Submission Compliance

DATE

7/15/2003

5 Page(s) Withheld

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8 § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

MEMORANDUM OF MEETING MINUTES

MEETING DATE: April 10, 2003
TIME: 12:00 PM
LOCATION: Parklawn Conference Room B
APPLICATION: PIND 66,714, Estradiol Transdermal System
TYPE OF MEETING: Pre-NDA
MEETING CHAIR: Eric Colman, M.D.
MEETING RECORDER: Pat Madara

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION:

Division of Metabolic and Endocrine Drug Products

<u>Name of FDA Attendee</u>	<u>Title</u>
Eric Colman, M.D.	Medical Officer Team Leader
S.W. Johnny Lau, Ph.D.	Clinical Pharmacology Reviewer
Japobrata Choudhury, Ph.D.	Statistical Reviewer
Kati Johnson Pat Madara	Chief, Regulatory Project Management Staff Regulatory Project Manager

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

<u>External Attendee</u>	<u>Title</u>	<u>Sponsor/Firm Name</u>
Marie Foegh, M.D.	Vice President, Female Health Care Development	Berlex
Lester Harrison, Ph.D., <hr/>	Section Head, Clinical Pharmacology	3M Pharmaceuticals
Adel Karara, Ph.D.	Director of Clinical Pharmacology	Berlex
Geoffrey Millington, M.S., Mino Niknian, Ph.D., <hr/>	Regulatory Affairs Manager Director of Biostatistics	Berlex Berlex
Vladimir Yankov, M.D., B.Lawrence Riggs, M.D., <hr/>	Director of Clinical Research Consultant	Berlex Berlex

BACKGROUND:

Climara ® (Estradiol Transdermal System) is currently regulated by the Division of Reproductive and Urologic Drug Products (DRUDP) under NDA 20-375 for the relief of vasomotor symptoms and prevention of postmenopausal osteoporosis. There are 4 currently approved patch sizes ranging in size from 6.5 to 25 cm², delivering 25 to 100 mcg estradiol per day, respectively.

PIND 66,714 was originally submitted on February 11, 2003 and provides for an ultra low dose estradiol transdermal system for prevention of postmenopausal osteoporosis. The estradiol patch has a surface area of 3.25 cm² and a daily estradiol delivery rate of approximately 12.5 ug/day

The firm has conducted a Phase III study (number 98188), entitled, "A Multicenter, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Safety and Efficacy of an Ultralow Dose of Estradiol Given by Continuous Transdermal Administration in the Prevention of Osteoporosis in Postmenopausal Women." In this study 417 postmenopausal non-hysterectomized women of 60 years and older were randomized to ultralow dose estradiol patch or placebo. The primary efficacy variable was the percentage change of lumbar spine bone mineral density (BMD) from baseline to two years. The primary safety variable was the incidence of endometrial hyperplasia or cancer after two years of treatment. According to the firm, there was a statistically significant increase in percent BMD from baseline in patients on ultralow dose estradiol patch compared to placebo.

A Pre-NDA meeting was requested to discuss specific questions relating to this product.

The Firm presented the following specific questions to the Agency:

Chemistry, Manufacturing and Controls

Does the Division agree with the proposal to provide drug product information via Type II Drug Master File?

Response: Prior to the meeting, the firm was informed that this was acceptable.

Human Pharmacokinetics and Bioavailability

1. Does the Division concur that the Phase I bioavailability study conducted for ultra-low dose estradiol transdermal system is sufficient to support the filing of the supplemental NDA?
 - **Response:** The Agency asked for clarification of several issues. First, where was the site of placement for the patch in the phase III study (98188)? The Firm responded that the site of placement was the lower abdomen. Second, the Firm was asked to clarify how they assessed the average daily estradiol delivery rate. The Sponsor responded that they used the AUC approach to estimate the estradiol delivery rate. Third, the Firm was asked if the 3.25 cm² transdermal estradiol system tested in the phase III study is identical to the formulation in the product to be marketed. The Sponsor asserted that it was the same.

The response to these 3 issues should be stated in the Human Pharmacokinetics and Bioavailability section of future NDAs.

Based on the above clarification of the information provided, the Agency stated that the application would be filable.

In addition, the Agency requested the following items:

- The Firm should develop and submit an *in vitro* dissolution method and include the specifications for this.
 - Provide a bioanalytical and validation report for Study 305851.
2. Does the Division concur that our pivotal phase III study, which was conducted to assess efficacy and safety of ultra-low dose estrogen transdermal system is adequate to support the filing of the supplemental NDA for the indication of prevention of postmenopausal osteoporosis in women with or without a uterus?
 - **Response:** The design of the study appears acceptable to support filing of the application. However, a final determination of filing can only be made once the application is submitted for review.
 3. Does the Division concur that the safety profile proved lack of endometrial stimulation and that the atypical hyperplasia is unlikely related to treatment?
 - **Response:** From the numbers provided (hyperplasia in one woman), it is impossible to say for sure that stimulation is not related to the drug.
 4. Does the Division concur that the statistical methods utilized for the pivotal study are acceptable?
 - **Response:** The Agency responded that no obvious problems had been found during a preliminary review of the abbreviated information provided. The Firm was given a handout of statistical consideration and encouraged to contact the statistical reviewer if they had technical questions.
 5. Does the Division concur that no submission of non clinical information will be necessary for this ultra-low dose of estrogen transdermal system based on the fact that is identical (except for patch size cut from common rollstock) to the approved strengths of the currently marketed product, Climara?
 - **Response:** The Agency concurs.

Other Issues

The firm is considering a different tradename to differentiate this product from the currently approved Climara products. In response to a question from the firm, the Agency stated that as many as three possible choices could be submitted for review. Although the proposed names can be submitted under the IND, any name found acceptable under the IND must be re-reviewed and found acceptable shortly before the expected approval of the NDA.

Minutes Preparer: /s/ Pat Madara, Regulatory Project Manager

Chair Concurrence: /s/ Eric Colman, M.D., Medical Officer Team Leader

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

/s/

Patricia Madara
5/9/03 12:26:55 PM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-764	Efficacy Supplement Type SE-	Supplement Number
Drug: Menostar (estradiol transdermal system)		Applicant: Berlex Laboratories
RPM:	HFD-	Phone #
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name):
❖ Application Classifications:		
<ul style="list-style-type: none"> • Review priority 		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
<ul style="list-style-type: none"> • Chem class (NDAs only) 		
<ul style="list-style-type: none"> • Other (e.g., orphan, OTC) 		
❖ User Fee Goal Dates		
		June 8, 2004
❖ Special programs (indicate all that apply)		
		<input checked="" type="checkbox"/> None <input type="checkbox"/> Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review
❖ User Fee Information		
<ul style="list-style-type: none"> • User Fee 		<input checked="" type="checkbox"/> Paid
<ul style="list-style-type: none"> • User Fee waiver 		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
<ul style="list-style-type: none"> • User Fee exception 		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other
❖ Application Integrity Policy (AIP)		
<ul style="list-style-type: none"> • Applicant is on the AIP 		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP 		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • Exception for review (Center Director's memo) 		
<ul style="list-style-type: none"> • OC clearance for approval 		
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.		
		<input checked="" type="checkbox"/> Verified
❖ Patent		
<ul style="list-style-type: none"> • Information: Verify that patent information was submitted 		<input checked="" type="checkbox"/> Verified
<ul style="list-style-type: none"> • Patent certification [505(b)(2) applications]: Verify type of certifications submitted 		21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> • For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice). 		<input type="checkbox"/> Verified
Exclusivity Summary (approvals only)		
		June 9, 2004
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)		
		November 18, 2003

General Information	
Actions	
• Proposed action	(X) AP () TA () AE () NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	(X) Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	() Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None () Press Release () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling	XX (PI and PPI)
• Original applicant-proposed labeling	XX (pouches, containers, cartons)
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings (<i>indicate dates of reviews and meetings</i>)	DMETS: 4/1/04, 5/10/04, 5/26/04 DDMAC: 1/22/04, 2/12/04 DSRCS: 1/30/04, 5/20/04
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	XX
• Reviews	
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	XX
❖ Memoranda and Telecons	XX
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	
• Pre-NDA meeting (indicate date) 4-10-03	XX
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other	
❖ Advisory Committee Meeting	
• Date of Meeting	
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	NN

Clinical and Summary Information

Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) <i>(indicate date for each review)</i>	DD = 6/8/04; MTL = 6/8/04
❖ Clinical review(s) <i>(indicate date for each review)</i>	May 13, 2004
❖ Microbiology (efficacy) review(s) <i>(indicate date for each review)</i>	NN
❖ Safety Update review(s) <i>(indicate date or location if incorporated in another review)</i>	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	XX
❖ Statistical review(s) <i>(indicate date for each review)</i>	5/21/04, 5/58/04
❖ Biopharmaceutical review(s) <i>(indicate date for each review)</i>	May 5, 2004
❖ Controlled Substance Staff review(s) and recommendation for scheduling <i>(indicate date for each review)</i>	N/A
❖ Clinical Inspection Review Summary (DSI)	May 1, 2004
• Clinical studies	XX
• Bioequivalence studies	

CMC Information

❖ CMC review(s) <i>(indicate date for each review)</i>	May 21, 2004
❖ Environmental Assessment	
• Categorical Exclusion <i>(indicate review date)</i>	XX May 21, 2004
• Review & FONSI <i>(indicate date of review)</i>	
• Review & Environmental Impact Statement <i>(indicate date of each review)</i>	acceptable
Micro (validation of sterilization & product sterility) review(s) <i>(indicate date for each review)</i>	NN
❖ Facilities inspection (provide EER report)	Date completed: April 30, 2004 (X) Acceptable () Withhold recommendation
❖ Methods validation	() Completed () Requested () Not yet requested

Nonclinical Pharm/Tox Information

❖ Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	NN
❖ Nonclinical inspection review summary	
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	
❖ CAC/ECAC report	