CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-258

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

6 Sept. 2002

Review for HFD 580

NDA:	21-258
Drug Product Name	
Proprietary:	Climara-Pro
Non-proprietary:	Estradiol/levorgestrel
Drug Product Classification:	
Review Number:	2
Subject of this Review	
Submission Date:	June 22, 2002
Receipt Date:	
Consult Date:	August 20, 2002
Date Assigned for Review:	August 23,. 2002
Submission History (for amendments only)	
Date(s) of Previous Submission(s):	June 16, 2000
Date(s) of Previous Micro Review(s):	May 14, 2001
Applicant/Sponsor	
Name:	Berlex Laboratories Inc.
Address:	P.O. Box 1000 Montville, NJ 07450-1000
Representative:	Geoffery Millington
Telephone:	
Name of Reviewer:	Stephen E. Langille, Ph.D.
Conclusion:	Approvable pending revision of DMF

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUPPLEMENT: N/A

2. SUPPLEMENT PROVIDES FOR: N/A

3. MANUFACTURING SITE: 3M Pharmaceuticals
19901 Nordhoff
Northridge, CA 91328

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:
Transdermal Patch
22 cm^2 or 30 cm^2

5. METHOD(S) OF STERILIZATION: Non-sterile drug product

6. PHARMACOLOGICAL CATEGORY: treatment of vasomotor symptoms

B. SUPPORTING/RELATED DOCUMENTS: DMF —

C. REMARKS: DMF — contains the CMC information for this drug product and has been found to be deficient. The DMF holder will be informed of the microbiological deficiencies to the DMF.

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Executive Summary

I. Recommendations

A. Recommendation on Approvability -
NDA 21-258 is approvable pending revision of DMF

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable -

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology -
Refer to the review of DMF

B. Brief Description of Microbiology Deficiencies -
Refer to the review of DMF

C. Assessment of Risk Due to Microbiology Deficiencies -
Refer to the review of DMF

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block
In DFS

C. CC Block
In DFS

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

/s/

Stephen Langille
9/6/02 02:57:21 PM
MICROBIOLOGIST

Peter Cooney
9/6/02 03:13:46 PM
MICROBIOLOGIST

REVIEW TO HFD 580
OFFICE OF NEW DRUG CHEMISTRY
Microbiology Staff, HFD-805
Microbiologist's Review #1 of NDA
April 25, 2001

A. 1. NDA — **21-258**

2. APPLICANT/SPONSOR: — **Berlex Laboratories and**
3M Laboratories
3M Center
Building 270-3A-08
St. Paul, MN 55144-1000

Contact for — DMF: —

3. MANUFACTURING SITE: — **3M Pharmaceuticals**
19901 Nordhoff
Northridge, CA 91328

4. DRUG PRODUCT NAME
Proprietary: — **ClimaraPro**
Nonproprietary: — **estradiol/levonorgestrel transdermal system**
Drug Priority Classification: — **Standard**

5. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:

- **Transdermal patch**
- **22 cm^2 and 30 cm^2**

6. METHOD(S) OF STERILIZATION: — **Non-Sterile Drug Product**

7. PHARMACOLOGICAL CATEGORY AND/OR PRINCIPLE INDICATION:
Treatment of vasomotor symptoms

B. 1. DOCUMENT/LETTER DATE: — **June 16, 2000**
2. RECEIPT DATE: — **June 19, 2000**
3. CONSULT DATE: — **February 12, 2000**
4. DATE OF AMMENDMENT:
5. ASSIGNED FOR REVIEW: — **February 2, 2000**
6. SUPPORTING/RELATED DOCUMENTS:
— **has submitted a Type II Drug Master File in support of NDA 21-258.**

C. REMARKS: **Berlex Laboratories has outsourced the production of Climarapro to 3M laboratories. — submitted a DMF describing the manufacture of this drug product. The patch is applied to the skin of the abdomen for a period of seven days.**

D. CONCLUSIONS: **The submission is approvable pending resolution of microbiological deficiencies. Specific comments regarding the — tests are provided in "E. Review Notes" and "List of Microbiology Deficiencies and Comments" of DMF**

Stephen E. Langille, Ph. D.

cc: Original **NDA 21-258**
HFD-580/Division File
HFD-580/Diane Moore
HFD 805/Consult File/Langille
Drafted by S. Langille c:reviews/21-258
Initialed by P. Cooney

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

/s/

Stephen Langille
5/14/01 01:19:53 PM
MICROBIOLOGIST

Peter Cooney
5/14/01 02:11:08 PM
MICROBIOLOGIST

NDA 21-258
Climara Pro™ transdermal system
(estradiol/levonorgestrel) 0.045/0.015, 0.045/0.030, and 0.045/0.040 mg/day
Berlex laboratories, Inc.

Facilities Inspection

No facilities were inspected for this review cycle 2.

NDA 21-258
Climara Pro™ transdermal system
(estradiol/levonorgestrel) 0.045/0.015, 0.045/0.030, and 0.045/0.040 mg/day
Berlex laboratories, Inc.

Methods Validation

Methods validation is pending forthis review cycle 2.

NDA 21-258
Climarapro™ (estradiol transdermal system) estradiol/levonorgestrel 0.045/0.015, 0.045/0.030 and 0.045/0.040 mg per day
Berlex laboratories, Inc.

Methods Validation

Methods validation are pending.

Diane Moore 6/11/01

14 Page(s) Withheld

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

____ § 552(b)(5) Deliberative Process

____ § 552(b)(4) Draft Labeling