

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-674**

**CHEMISTRY REVIEW(S)**

**NDA 21-674**

**Menostar**

**Berlex Laboratories**

**Amit K. Mitra, Ph.D**  
**Reproductive and Urologic Drug Products**



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# Chemistry Review Data Sheet

1. NDA 21-674
2. REVIEW # 1
3. REVIEW DATE: 14-MAY-2004
4. REVIEWER: Amit K. Mitra, Ph.D

5. PREVIOUS DOCUMENTS:

Previous Documents

None

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original  
Amendment  
Amendment

Document Date

7-AUG-2003  
7-OCT-2003  
14-May-2004

7. NAME & ADDRESS OF APPLICANT:

Name: Berlex Laboratories  
Address: 340 Changebridge Rd. PO Box 1000, Montville,  
NJ 07450-1000  
Representative: Mr. Geoffrey Millington, Manager Regulatory  
Affairs  
Telephone: 973-487-2254

# CHEMISTRY REVIEW

## Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Menostar
- b) Non-Proprietary Name (USAN): Estradiol transdermal system
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 6
  - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: NA

10. PHARMACOL. CATEGORY: Estrogen/Hormone replacement therapy

11. DOSAGE FORM: Estradiol transdermal system

12. STRENGTH/POTENCY: 0.99 mg estradiol/3.25 Cm<sup>2</sup> delivering 0.014 mg estradiol per day

13. ROUTE OF ADMINISTRATION: Transdermal

14. Rx/OTC DISPENSED:  Rx  OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

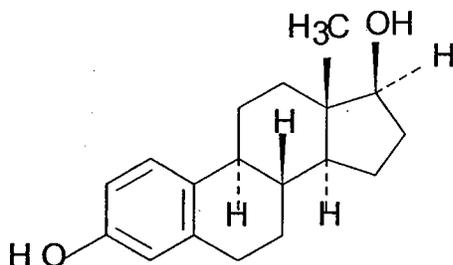
Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

# CHEMISTRY REVIEW

## Chemistry Review Data Sheet

Estradiol, Estra-1,3,5(10)-triene-3,17-diol (17 $\beta$ ), C<sub>18</sub>H<sub>24</sub>O<sub>2</sub> · ½ H<sub>2</sub>O, 281.4



### 17. RELATED/SUPPORTING DOCUMENTS:

#### A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
—	II	—	CMC for drug substance and drug product	1	Adequate	30-JAN-2004	See Chemistry Review #1 for DMF — by Dr. A. K. Mitra, dated 5-MAY-2004

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**CHEMISTRY REVIEW**

## Chemistry Review Data Sheet

## 18. STATUS:

<b>CONSULTS/ CMC RELATED REVIEWS</b>	<b>RECOMMENDATION</b>	<b>DATE</b>	<b>REVIEWER</b>
Biometrics	NA		
EES	Acceptable	30-APR-2004	Ms. S. Adams
Pharm/Tox	NA		
Biopharm	NA		
LNC	NA		
Methods Validation	Not needed		
DMETS <sup>1</sup>	See below		
EA	Categorical exclusion granted (see Chemistry Review #1 for DMF	5-MAY-2004	Dr. A. K. Mitra
Microbiology	NA		

1. DMETS recommended not to have a separate trademark "Menostar" for the "Climara" drug product. The division (HFD-510) disagreed with the recommendation of DMETS and determined that the trademark "Menostar" is appropriate (see Memo to File by Dr. B V. Stadel, dated 11-May-2004).

# The Chemistry Review for NDA 21-674

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The CMC information for this NDA is documented in DMF — The DMF — is adequate to support the NDA 21-674. The “Description” and “How Supplied” sections of the label were reviewed here and those are satisfactory. Therefore, the application can be approved with respect to CMC.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

NA

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

*(The following information is based on DMF — (3M Pharmaceuticals) and it is proprietary. This information should not be released to the sponsor of the NDA).*

The drug product is an oval shaped transdermal drug delivery system containing estradiol and it is proposed to be marketed in one strength only. The transdermal system contains 0.99 mg of estradiol per 3.25 Cm<sup>2</sup> delivering 0.014 mg estradiol per day.

The drug product is composed of a polyethylene backing film, estradiol in a pressure sensitive adhesive matrix, and a protective release liner. The estradiol in the drug product is moisture sensitive; therefore, a desiccant system is used to maintain low moisture content within the foil pouch. Based on the Agency's request, the sponsor of the DMF provided various in-process controls including the pouching operation. The sponsor's proposal to use alternate pouches based on a comparability protocol was deemed unacceptable and the sponsor of the DMF withdrew the comparability protocol. The sponsor requested a shelf life of 3 years based on 3 years long term stability data. Based on 3 years satisfactory stability data at 30°C/70%RH, a 3 year shelf life for the drug product can be granted.

#### B. Description of How the Drug Product is Intended to be Used

Menostar is proposed to be marketed in one strength only. The transdermal system contains 0.99 mg estradiol in a 3.25 Cm<sup>2</sup> system delivering 0.014 mg estradiol per day for prevention of postmenopausal osteoporosis in women with or without uterus. Each transdermal system is individually packaged in a foil pouch containing a desiccant

**Executive Summary Section**

system. The shelf pack carton consists of 6 individual cartons of 4 foil pouches, each containing one transdermal system. The adhesive side of the Menostar transdermal system should be placed on a clean, dry area of lower abdomen after removing the release liner from the transdermal system. A single transdermal system should be worn for one week and should be changed every week.

The drug product is to be stored at 86°F (30 °C). The sponsor provided long term stability data at 30 °C to support this claim.

**C. Basis for Approvability or Not-Approval Recommendation**

The DMF contains all the CMC information for Menostar drug product and it is adequate to support the Chemistry, Manufacturing and Controls section of the NDA. The labeling information is provided by the NDA sponsor and the labeling information is satisfactory. The NDA can be approved with respect to CMC.

**III. Administrative****A. Reviewer's Signature****B. Endorsement Block**

Amit K. Mitra, Ph.D/HFD-580  
Moo-Jhong Rhee, Ph.D/HFD-580  
P. Madara/HFD-510

**C. CC Block**

2 Page(s) Withheld

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

       § 552(b)(5) Deliberative Process

       § 552(b)(5) Draft Labeling

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

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Amit K. Mitra  
5/21/04 08:33:28 AM  
CHEMIST

Moo-Jhong Rhee  
5/21/04 02:58:30 PM  
CHEMIST  
I concur