

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: 020994, 020375/S011**

**CHEMISTRY REVIEW(S)**

**DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG  
PRODUCTS**

**REVIEW OF CHEMISTRY MANUFACTURING AND CONTROLS  
CHEMIST'S REVIEW**

1. NDA NUMBER: 20-994
2. NAME AND ADDRESS OF APPLICANT  
Berlex Laboratories, Inc.  
340 Changebridge Road  
P.O Box 1000  
Montville, NJ 07045-1000
3. NDA NUMBER/DATE/DATE ASSIGNED  
NDA 20-994/5-1-98/5-5-98
4. NAME OF THE DRUG: Climara<sup>®</sup> (estradiol transdermal system)
5. NONPROPRIETARY NAME: Estradiol Transdermal System
6. NDA PROVIDES FOR: A new indication (osteoporosis) with the addition of a new patch size of 6.5 cm<sup>2</sup>.
7. AMENDMENTS/REPORTS/ DATE: None
8. PHARMACOLOGICAL CATEGORY  
Estrogen
9. HOW DISPENSED  
Prescription
10. RELATED IND/NDA/DMF/SUPPLEMENT  
DMF /NDA 20-375
11. DOSAGE FORM : Transdermal
12. POTENCY  
2.04, 3.9, 5.85, 7.8 mg per patch delivering  
0.025, 0.05, 0.075 and 0.1 mg/day (6.5, 12.5, 18.75, and 25 cm<sup>2</sup>) respectively
13. CHEMICAL NAME AND STRUCTURE  
 $C_{18}H_{24}O_2 \cdot \frac{1}{2} H_2O$   
MW = 281.4

***Estra-1,3,5(10)-triene-3,17 $\beta$ -diol, hemi hydrate***

14. COMMENTS

NDA 20-375 was approved for marketing 12.5, 18.75, and 25 cm<sup>2</sup> patches of estradiol. The NDA 20-994 asks for approval of those three strengths and an additional strength (6.5 cm<sup>2</sup>) for osteoporosis indication. The drug product is manufactured under DMF by [redacted]. The DMF [redacted] was amended to reflect requested change and it was cross referenced [redacted]. The DMF amendment was reviewed separately [redacted]. The DMF is adequate to support the changes requested in the NDA. The labeling portion of the NDA is reviewed here. An inspection of the manufacturing site was requested. The inspection report is satisfactory.

The clinical and Biopharm sections of this supplement for the osteoporosis indication was reviewed by HFD-510 under NDA 20-994.

**The following changes were made:**

New patch size of 6.5 cm<sup>2</sup> was added to the existing sizes (12.5 cm<sup>2</sup>, 18.75 cm<sup>2</sup>, and 25 cm<sup>2</sup>) for osteoporosis indication.

**15. CONCLUSIONS AND RECOMMENDATIONS:** The NDA can be approved with respect to CMC.

/S/

Reviewed By: Amit K. Mitra, Ph.D, 3-5-99

/S/

3/5/99

R/D INIT BY: Moo-Jhong Rhee, Ph.D

APPEARS THIS WAY  
ON ORIGINAL

CC: A. K. MITRA/HFD-580  
M.J.RHEE/HFD-580  
D. Moore/HFD-580  
NDA 20-994

APPEARS THIS WAY  
ON ORIGINAL

CHEMIST'S REVIEW NOTES