CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20375/S007

CHEMISTRY REVIEW(S)

ORIGINAL SEP 12 1997

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS

REVIEW OF CHEMISTRY MANUFACTURING AND CONTROLS
CHEMIST'S REVIEW

1. NDA NUMBER: 20-375

2. NAME AND ADDRESS OF APPLICANT
Berlex Laboratories, Inc.
300 Fairfield Road
Wayne, NJ 07470

3. SUPPLEMENT NUMBER/DATE/DATE ASSIGNED
SCS-007/10-18-96/2-11-97

Amendment to SCS-007/8-13-97/8-20/97

4. NAME OF THE DRUG:Climara ^{R} (estradiol transdermal system)
5. NONPROPRIETARY NAME: Estradiol Transdermal System
6. SUPPLEMENT PROVIDES FOR: An alternate manufacturing process for drug substance to meet tighter specifications of related substances.
7. AMENDMENTS/REPORTS/ DATE: Amendment to SCS-007, dated 8-20-97
8. PHARMACOLOGICAL CATEGORY
Estrogen

9. HOW DISPENSED
Prescription

10. RELATED IND/NDA/DMF/SUPPLEMENT
DMF
11. DOSAGE FORM : Transdermal
12. POTENCY
0.05 mg and 0.1 mg/day

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-3,17β-diol, hemi hydrate

14. COMMENTS

NDA 20-375 was approved for marketing 12.5 and 25 Cm^2 patches of estradiol. The drug substance used in the patches were prepared using a synthetic scheme described in DMF The new synthetic scheme described in the DMF provides further purification of crude estradiol to meet the EP specifications. However, the DMF was considered inadequate in conjunction with ANDA 40-212. The deficiencies were corrected on 2-10-97 and considered adequate

The following changes were made:

The amendment refers to the changes in DMF to address the deficiencies.

15. CONCLUSIONS AND RECOMMENDATIONS: Since the DMF is now adequate to support this NDA, the supplement can be approved.

/S/

Reviewed By: Amit K. Mitra, Ph.D. 9-12-97

/S/ 9/12/97

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

CC: A. K. MITRA/HFD-580
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NDA 20-375

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4. NAME OF THE DRUG:Climara ^{R} (estradiol transdermal system)
5. NONPROPRIETARY NAME: Estradiol Transdermal System
6. SUPPLEMENT PROVIDES FOR: An alternate manufacturing process for the drug substance to meet tighter specifications of related substances.
7. AMENDMENTS/REPORTS/ DATE: None
8. PHARMACOLOGICAL CATEGORY
Estrogen

9. HOW DISPENSED
Prescription

10. RELATED IND/NDA/DMF/SUPPLEMENT
DMF
11. DOSAGE FORM : Transdermal
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Estra-1,3,5(10)-triene-3,17β-diol, hemi hydrate

14. COMMENTS

NDA 20-375 was approved for marketing 12.5 and 25 Cm^2 patches of estradiol. The drug substance used in the patches were prepared using a synthetic scheme described in DMF .. The new synthetic scheme provides further purification of crude estradiol to meet the EP specifications.

The following changes were made:

1. Chemistry, Manufacturing and Controls Information
a. Reference of changes in DMF and authorization to review the DMF
b. Synthetic flow chart of the drug substance production was provided (further purified to meet EP)
c. Supplier's and Manufacturer's certificate of analyses were provided.
d. 18 months stability data on 3 lots manufactured in pilot scale were provided. The surface area for two lots was 12.5 Cm^2 . One lot had a surface area of 25.0 Cm^2 (same formulation different surface area) . This was done because of changes in the drug substance.
e. Since changes were made in the drug substance manufacture, stability commitment was made that following the approval first three commercial lots of each patch size will be placed on a stability program.

15. CONCLUSIONS AND RECOMMENDATIONS: Since the DMF is deficient, the supplement can not be approved until all the deficiencies listed in the DMF review are corrected.

Reviewed By: Amit K. Mitra, Ph.D, ~~3-31-97~~ /S/ 3-31-97

R/D INIT BY: Moo-Jhong Rhee, Ph.D /S/ 4/2/97

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NDA 20-489