CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-375/S-016

CHEMISTRY REVIEW

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.
340 Changebridge Road
P.O Box 1000
Montville, NJ 07045-1000

3. NDA NUMBER/DATE/DATE ASSIGNED
NDA 20-375-SE1-016/6-2-00/6-5-00

4. NAME OF THE DRUG:Climara ^{R} (estradiol transdermal system)

5. NONPROPRIETARY NAME: Estradiol-Transdermal System

6. SUPPLEMENT PROVIDES FOR: treatment of vasomotor symptoms associated with menopause for the lowest patch strength (6.5 cm^2 patch, delivering 0.025 mg of estradiol/day)

7. AMENDMENTS/REPORTS/ DATE: SE1-016BZ/7-31-00; SE1-016BC/ 8-18-00

8. PHARMACOLOGICAL CATEGORY
Estrogen

9. HOW DISPENSED
Prescription

10.RELATED IND/NDA/DMF/SUPPLEMENT
DMF — NDA 20-994

11. DOSAGE FORM : Transdermal

12. POTENCY
2.0, 3.8, 5.7, 7.6 mg of estradiol, anhydrous per patch delivering
0.025, 0.05 , 0.075 and 0.1 mg/day (6.5, 12.5, 18.75, and 25 cm^2) respectively

13. CHEMICAL NAME AND STRUCTURE
$C_{18}H_{24}O_2 . \frac{1}{2} H_2O$
MW = 281.4

Estra-1,3,5(10)-triene-3,17β-diol, hemi hydrate

14. COMMENTS

NDA 20-375/SCF-011 was approved for manufacture of 6.5 Cm^2 patch on 3-5-1999 for postmenopausal osteoporosis indication. Later, the NDA # was changed to NDA 20-994 because the new indication review resides within HFD-510. NDA 20-994 was approved on 3-5-99. The NDA 20-994 and NDA 20-375/SCF-011 both referenced DMF — for the CMC information of the 6.5 Cm^2 patch. The DMF was reviewed on 3-3-99 by Dr. A. K. Mitra, and found adequate to support NDA 20-994.

The sponsor is seeking for the new indication of treatment of moderate to severe vasomotor symptoms associated with menopause for the 6.5 Cm^2 patch via this application.

The amendment dated 7-31-00 is a communication for answering an enquiry on the formulation change reported in NDA 20-375. — The communication states that the formulation change reported in the — does not apply to that reported in the NDA 20-375/SE1-016. The sponsor also stated that the formulation reported in the NDA 20-3[illegible] was not used in the clinical studies reported in 20-375/SE1-016. The NDA 20-375[illegible] was deemed not approvable on 10-18-00.

All approved and marketed Climara patch sizes are manufactured from a common laminate, and all have the same formulation composition (%). They differ only in patch sizes. The proposed formulation is die cut to 6.5 cm^2 from the common laminate, and have the same formulation composition (%) to that of the other marketed patch sizes.

The communication, dated 8-18-00 provides the categorical exclusion request based on an EIC less than 1 ppb.

Reviewer's comment: The categorical exclusion can be granted.

An inspection request for the drug product manufacturing site was made. The inspection report is satisfactory (see attached).

The following changes were made:

New patch size of 6.5 cm^2 was added to the existing sizes (12.5 cm^2, 18.75 cm^2, and 25 cm^2) for the indication of treatment of vasomotor symptoms associated with menopause.

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

Reviewed By: Amit K. Mitra, Ph.D, 2-21-01

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

CC: A. K. MITRA/HFD-580
M.J.RHEE/HFD-580
D. Moore/HFD-580
NDA 20-375

Summary of Chemistry Review of NDA 20-375/SE1-016

This NDA was approved in 1994 under the sponsorship of 3M Pharmaceuticals with two strengths, 12.5cm^2 and 25cm^2 to treat moderate to severe vasomotor symptoms associated with menopause. In 1995, the ownership the NDA was transferred to Berlex and Berlex got approval of additional strength, 18.75cm^2 in 1998 through a supplement (S-009).

In 1999, Berlex introduced another strength, 6.5cm^2, and got approval for a new indication of osteoporosis for all available strengths (S-011).

This supplement was submitted for adding an indication of moderate to severe vasomotor symptom to this 6.5cm^2 patch, thereby making all available patches to have the same indications.

All the patches approved including 6.5cm^2 are die cut to each different size (6.5 cm^2, 12.5 cm^2, 18.5 cm^2, and 25 cm^2) from a common laminate and therefore they all have the same composition.

The manufacturer of the drug product is still the original 3M Pharmaceuticals (DMF ==, and the DMF is deemed adequate to support this NDA.

Berlex and 3M Pharmaceuticals are **in compliance to cGMP**.

Categorical exclusion was requested and granted based on EIC less than 1 ppm.

Conclusion and Recommendation:

From the Chemistry point of view, as the primary reviewer recommends, this efficacy supplement can be approved.

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader
For the Division of reproductive and Urologic Drug Products
DNDC II, Office of New Drug Chemistry

/s/

Moo-Jhong Rhee
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CHEMIST