

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: NDA 20-375/S-009**

**CHEMISTRY REVIEW(S)**

ORIGINAL

MAR 16 1993

**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. SUPPLEMENT NUMBER/DATE/DATE ASSIGNED  
SCS-009/9-19-97/9-24-97
4. NAME OF THE DRUG: Climara<sup>®</sup> (estradiol transdermal system)
5. NONPROPRIETARY NAME: Estradiol Transdermal System
6. SUPPLEMENT PROVIDES FOR: An addition of an intermediate patch size of 18.75 cm<sup>2</sup>
7. AMENDMENTS/REPORTS/ DATE: None
8. PHARMACOLOGICAL CATEGORY  
Estrogen
9. HOW DISPENSED  
Prescription
10. RELATED IND/NDA/DMF/SUPPLEMENT  
DMF
11. DOSAGE FORM : Transdermal
12. POTENCY  
0.075 cm<sup>2</sup>
13. CHEMICAL NAME AND STRUCTURE  
C<sub>18</sub>H<sub>24</sub>O<sub>2</sub> · ½ H<sub>2</sub>O  
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<sup>2</sup> patches of estradiol. The drug product is manufactured under DMF                      See the DMF review. The DMF                      has been updated to provide CMC information on the drug product.

**The following changes were made:**

An approval to market an intermediate size (18.75 cm<sup>2</sup>) has been requested.

**15. CONCLUSIONS AND RECOMMENDATIONS:** This supplement can be approved. However, the followings should be conveyed to the sponsor:

1. An extension of shelf life to 36 months as reported in DMF                      is not acceptable. The expiration date should be 24 months until real time stability data from 3 commercial lots of each strength are available. The bracketing and matrixing is acceptable. In future the stability studies of the new commercial lots including the 18.75 cm<sup>2</sup> strength should be studied under ICH conditions, unless justified.
2. Biopharm's recommendation
3. The standard statement on submission of Final Printed Label

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Reviewed By: Amit K. Mitra, Ph.D, 3-16-98

R/D INIT BY: Moo-Jhong Rhee, Ph.D                      */S/*                      *3/16/98*

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

**CENTER FOR DRUG EVALUATION AND RESEARCH**

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**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

FEB 23 1998

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**CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW**  
**Division of Pharmaceutical Evaluation II**

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**NDA 20-375**  
Supplement No. S-009

**SUBMISSION DATE:** September 19, 1997  
December 19, 1997

Climara® (Estradiol Transdermal System)  
Berlex Laboratories, Inc.  
Wayne, NJ

**REVIEWER:** Angelica Dorantes, Ph.D.

**TYPE OF SUBMISSION:** Addition of an Intermediate Patch Size 18.75 cm<sup>2</sup>

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**SYNOPSIS:**

Reference is made to NDA 20-375 for Climara® (estradiol transdermal system) which was approved by FDA on December 22, 1994. It should be noted that on November 2, 1995, 3M transferred this NDA to Berlex Laboratories, Inc.

In supplement S-009 to NDA 20-375 dated September 19, 1997 the sponsor is providing for the addition of an intermediate patch size of 18.75 cm<sup>2</sup>. The proposed intermediate size patch is identical in all respects to the approved 12.5 cm<sup>2</sup> and 25 cm<sup>2</sup> patch sizes. The only difference is the surface area of the patch which is cut with a different size die. The roll stock for the 3 patch sizes is the same. Also, this supplement includes a revised labeling including the newly proposed patch size.

In supplement S-009 dated December 19, 1997, the sponsor is requesting a waiver for the requirement of the submission of bioavailability data for the newly proposed intermediate 18.75 cm<sup>2</sup> size. To support the bio-waiver, the sponsor is providing comparative *in vitro* release data for the 12.5 cm<sup>2</sup>, 18.75 cm<sup>2</sup>, and 25 cm<sup>2</sup> patch sizes and dose proportionality data for estradiol for the 12.5 cm<sup>2</sup> and 25 cm<sup>2</sup> patch sizes

**RECOMMENDATION:**

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) has reviewed the information included in the supplements (S-009) to NDA 20-375 dated September 19 and December 19, 1997. OCPB/DPEII is of the opinion that the overall information provided to support the bio-waiver request is appropriate and the proposed addition of an intermediate patch size of 18.75 cm<sup>2</sup> for Climara is acceptable. With respect to the proposed

**ATTACHMENT I**

**NDA 20-375**

**Includes;**

**Supportive Information**

**Dissolution Data**

The DMF contains dissolution data on three lots of 18.75 cm<sup>2</sup> patches on May 6, 1997. These data are summarized Table 1:

**Table 1**

Lot No.	Units Tested	Mean % Dissolved (Range)		
		10 minutes	45 minutes	180 minutes
PD4575	6	24.4%	64.1% <sup>l</sup>	99.0%
PD4576	6	23.5% <sup>l</sup>	62.2% <sup>l</sup>	98.3%
PD4577	6	24.0%	63.0%	96.5% <sup>l</sup>

Product specifications: 10 minutes %; 45 minutes % and 180 minutes NLT %

Comparative data for the approved 12.5 cm<sup>2</sup> and 25 cm<sup>2</sup> patches are given in the attachment which is from NDA 20-375, volume 1, page 0279. The dissolution profiles of the three patch sizes are similar.

**Dose Proportionality**

Dose proportionality of estradiol from the formulation was shown in NDA 20-375. In Study R-838T-017-01 (Volumes 9-15 of NDA 20-375), 54 post-menopausal women received application of a 12.5 cm<sup>2</sup> patch and Climara 25 cm<sup>2</sup> patches from 2 different sites of manufacture, according to a randomized, 3-way cross-over design. The mean data follow in Table 2 and are derived from NDA 20-375: Volume 9, Abstract Table B, P. 0010; Volume 9, Table 19, p. 0091.

**Table 2 - Pharmacokinetic Parameters**

**Study Report R-838T-017-01 Comparative absorption study of 3M Pharmaceuticals' Transdermal Estradiol Drug Delivery System from two manufacturing sites and from two patch sizes (NDA 20-135: Volumes 9-15)**

	25 cm <sup>2</sup> Patch	12.5 cm <sup>2</sup> Patch	Ratio*
C <sub>max</sub> (pg/mL)	144	74	1.94
AUC(0-168) (pgxh/mL)	13370	7000	1.91
AUC(0-192) (pgxh/mL)	13780	7240	1.90

\*25 cm<sup>2</sup>/12.5 cm<sup>2</sup>

Firm 3M Pharmaceuticals  
 Drug Estradiol Transdermal Drug Delivery System  
 NDA/ANDA NDA

ATTACHMENT E

DRUG PRODUCT DISSOLUTION TESTING

Date	Patch Size/Strength	Lot No.	Units Tested	Dissolution Test		
				10 minutes	180 minutes	
				Mean X Dissolved	RSD (Range)	
10/25/89	20 cm <sup>2</sup> /6.2 mg	89-076	6	17.4±4.6%	54.8±5.0%	85.5±4.2%
7/24/90	12.5 cm <sup>2</sup> /3.9 mg	90-040	6	17.7±3.0%	55.6±2.4%	91.1±2.8%
8/09/90	25 cm <sup>2</sup> /7.8 mg	90-041	6	20.3±2.8%	58.7±1.3%	97.3±0.7%
2/13/90	20 cm <sup>2</sup> /6.2 mg	90-004	6	18.9±4.4%	57.5±1.2%	89.9±0.2%
2/13/90	25 cm <sup>2</sup> /7.8 mg	90-005	6	21.0±2.9%	58.7±1.8%	86.2±2.0%
8/03/92	25 cm <sup>2</sup> /7.8 mg	P03204	12	22.1±5.4%	62.4±1.8%	103.3±3.0%
8/03/92	25 cm <sup>2</sup> /7.8 mg	P03205	12	20.5±5.9%	61.0±1.6%	100.2±1.1%
7/31/92	12.5 cm <sup>2</sup> /3.9 mg	P03206	12	21.5±7.4%	60.7±2.0%	98.2±1.9%
8/03/92	25 cm <sup>2</sup> /7.8 mg	P03224	12	20.4±6.4%	59.1±2.2%	96.8±1.3%

a: Dissolution Test Description:  
 - USP Type Dissolution Apparatus (Modified, Vessel Capacity 150 mL).  
 - Media Temperature:  
 - Speed of Rotation:  
 - Collection Times: