

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-674**

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

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**OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW**

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<b>NDA</b>	21-674
<b>Submission Date</b>	August 7, 2003
<b>Brand Name</b>	Menostar™
<b>Generic Name</b>	Estradiol (E <sub>2</sub> )
<b>Reviewer</b>	S.W. Johnny Lau
<b>Team Leader</b>	Hae-Young Ahn
<b>OCPB Division</b>	DPE II (HFD-870)
<b>ORM Division</b>	Metabolic and Endocrine (HFD-510)
<b>Sponsor</b>	Berlex Laboratories, Inc.
<b>Relevant IND</b>	40,928
<b>Submission Type; Code</b>	Original; S
<b>Formulation; Strength(s)</b>	Transdermal system (3.25 cm <sup>2</sup> ); 1 mg E <sub>2</sub> /system
<b>Indication</b>	Prevention of postmenopausal osteoporosis in women with or without uteri

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**1 Executive Summary**

The sponsor submitted NDA 21-674 to seek approval for the 3.25 cm<sup>2</sup> E<sub>2</sub> transdermal system, which contains 1 mg E<sub>2</sub> (Menostar™) for the prevention of postmenopausal osteoporosis in women with or without uteri. The sponsor markets 6 strengths of Climara® E<sub>2</sub> transdermal system and the composition of these systems per unit area is identical. The 3.25 cm<sup>2</sup> E<sub>2</sub> transdermal system is identical to the lowest strength of Climara® system (cut from the same rollstock except ½ the size). All 6 marketed Climara® systems have the indication for the prevention of postmenopausal osteoporosis. The sponsor conducted a clinical efficacy and safety study (98188) for the 3.25 cm<sup>2</sup> E<sub>2</sub> transdermal system versus placebo system to prevent postmenopausal osteoporosis in non-hysterectomized women. See medical officer's review for Study 98188.

The sponsor conducted a relative bioavailability (BA) study (305851) between a 3.25 cm<sup>2</sup> and a 6.5 cm<sup>2</sup> (Climara®) transdermal E<sub>2</sub> system to the lower abdomen of 18 postmenopausal women. Administration of the 3.25 cm<sup>2</sup> and 6.5 cm<sup>2</sup> transdermal E<sub>2</sub> systems produce geometric mean average serum E<sub>2</sub> concentration of 13.7 and 24.7 pg/mL, respectfully. The pharmacokinetic (PK) parameters such as E<sub>2</sub> C<sub>max</sub>, C<sub>168 h</sub>, and AUC(0 – t<sub>last</sub>) for the 3.25 cm<sup>2</sup> E<sub>2</sub> transdermal system are about ½ of those for the 6.5 cm<sup>2</sup> E<sub>2</sub> transdermal system. Hence, this observation is consistent with the 3.25 cm<sup>2</sup> E<sub>2</sub> transdermal system being ½ the size for the 6.5 cm<sup>2</sup> E<sub>2</sub> transdermal system. The estimated in vivo and in vitro E<sub>2</sub> daily delivery rate is 0.014 mg/day and 0.017 mg/day, respectively, for the 3.25 cm<sup>2</sup> E<sub>2</sub> transdermal system. Hence, the estimated in vivo and in vitro E<sub>2</sub> daily delivery rates are consistent for the 3.25 cm<sup>2</sup> E<sub>2</sub> transdermal system.

The sponsor also assessed the skin adhesion property of the 3.25 and 6.5 cm<sup>2</sup> E<sub>2</sub> transdermal systems in Study 305851. No subject scored >10% lifting on any observation in all 7-day wear periods for both

3.25 and 6.5 cm<sup>2</sup> E<sub>2</sub> transdermal systems administration. For the 3.25 cm<sup>2</sup> E<sub>2</sub> transdermal system, 83% (15/18) of the subjects scored no lifting and 17% (3/18) of the subjects scored <10% lifting in the 7-day wearing period. For the 6.5 cm<sup>2</sup> E<sub>2</sub> transdermal system, 89% (16/18) of the subjects scored no lifting and 11% (2/18) of the subjects scored <10% lifting in the 7-day wearing period. The 3.25 and 6.5 cm<sup>2</sup> E<sub>2</sub> transdermal systems appear to have good skin adhesion property.

No difference exists between the to-be-marketed formulation and the pivotal clinical study formulation.

The proposed dissolution method and specification are acceptable.

### **1.1 Recommendations**

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) has reviewed the Human Pharmacokinetics and Bioavailability section of NDA 21-674 and finds it acceptable. However, the labeling comments on page 10 of this review should be communicated with the sponsor.

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S.W. Johnny Lau, R.Ph., Ph.D.  
OCPB/DPE2

An Optional Intra-Division Clinical Pharmacology and Biopharmaceutics Briefing for NDA 21-674 was conducted on May 4, 2004, participants included H. Malinowski, B. Stadel, P. Madara, H. Ahn, and J. Lau.

FT signed by Hae-Young Ahn, Ph.D., Team Leader \_\_\_\_\_ 5/ /04

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**Figure 3. Mean baseline uncorrected serum E<sub>1</sub> concentrations vs. – time profiles following application of a 3.25 cm<sup>2</sup> E<sub>2</sub> transdermal system and application of a 6.5 cm<sup>2</sup> Climara<sup>®</sup> system**

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### 3 Question-Based Review

#### 3.1 General Attributes

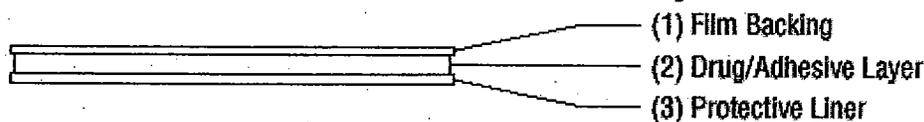
The sponsor seeks approval of the 3.25 cm<sup>2</sup> E<sub>2</sub> transdermal system for the prevention of postmenopausal osteoporosis in women with or without uteri. The sponsor also markets 6 strengths of Climara<sup>®</sup> (25 µg/day, 6.5 cm<sup>2</sup>, 2 mg; 37.5 µg/day, 9.375 cm<sup>2</sup>, 2.85 mg; 50 µg/day, 12.5 cm<sup>2</sup>, 3.8 mg; 60 µg/day, 15 cm<sup>2</sup>, 4.55 mg; 75 µg/day, 18.75 cm<sup>2</sup>, 5.7 mg; and 100 µg/day, 25 cm<sup>2</sup>, 7.6 mg). All 6 marketed Climara<sup>®</sup> systems have the indication for the prevention of postmenopausal osteoporosis.

#### 1. What is the formulation of the to-be-marketed Menostar<sup>™</sup> transdermal system?

Table 1. Composition of the to-be-marketed Menostar<sup>™</sup> transdermal system:

Component	% W/W	Description
		Adhesive
		Excipient
		Excipient
		Excipient
		Active
Ph.Eur.; Estradiol, USP		
Film,		
Film,		
Film,		
Paper/Foil	Pouch	
Polyester/Foil	Pouch	

Menostar<sup>™</sup>'s composition is identical to that of the currently marketed Climara<sup>®</sup> (except ½ the size of the lowest Climara<sup>®</sup> strength). Menostar<sup>™</sup> system has 3 layers, which are: (1) translucent polyethylene film, (2) acrylate adhesive matrix containing E<sub>2</sub>, and (3) protective liner of siliconized or fluoropolymer-coated polyester film that is attached to the adhesive surface and must be removed before the system can be used. Figure 1. Cross-sectional view of the 3.25 cm<sup>2</sup> E<sub>2</sub> transdermal system:



#### 3.2 General Clinical Pharmacology

Public E<sub>2</sub> clinical pharmacology information relevant to Menostar<sup>™</sup> is available in:

- Climara<sup>®</sup>'s product labeling
- N. Poola et al. Pharmacokinetics and bioavailability of an ultra low dose estradiol transdermal system in healthy postmenopausal women. *Clin Pharmacol Ther* 75:P58 (2004)

**1. What is the relative BA between the 3.25 cm<sup>2</sup> and 6.5 cm<sup>2</sup> E<sub>2</sub> transdermal systems?**

The sponsor conducted a relative BA study (Study 305851/Report A08736) for the 3.25 cm<sup>2</sup> (test) and 6.5 cm<sup>2</sup> (reference; Climara<sup>®</sup>) E<sub>2</sub> transdermal systems in 18 healthy postmenopausal women. An E<sub>2</sub> transdermal system (patch) was applied for 7 days to the lower abdomen of each subject per a 2-period crossover randomization schedule. A 3-week washout separated the 2-study periods. Serial blood samples during and after application were collected for serum E<sub>2</sub>, estrone (E<sub>1</sub>), and estrone sulfate (E<sub>1</sub>S) concentrations determination.

The sponsor estimated the mean in vivo E<sub>2</sub> daily delivery rate for the 3.25 cm<sup>2</sup> E<sub>2</sub> transdermal system via:

$$D_{ave} = \frac{AUC(0 - t_{last})}{DoseInterval} \times CL_{ref} \quad \text{and} \quad CL_{ref} = \frac{D_{ref}}{AUC(0 - t_{last})_{ref}}$$

The sponsor's approach to estimate the in vivo E<sub>2</sub> daily delivery rate has 2 assumptions: (1) CL<sub>test</sub> = CL<sub>ref</sub>, (2) AUC(0 - t<sub>last</sub>)<sub>ref</sub> ≅ AUC(0 - infinity)<sub>ref</sub>. Since this is a 2-period crossover study, the assumption of CL<sub>test</sub> = CL<sub>ref</sub> is valid. The assumption of AUC(0 - t<sub>last</sub>)<sub>ref</sub> ≅ AUC(0 - infinity)<sub>ref</sub> is valid since the contribution of AUC (t<sub>last</sub> - infinity)<sub>ref</sub> to AUC(0 - infinity)<sub>ref</sub> is not significant. The sponsor also determined the residual E<sub>2</sub> from the used patches and wipes after application and used this information to estimate the in vitro E<sub>2</sub> delivery rate ((initial amount - total residual amount in used patches and wipes)/7 days).

The estimated in vivo and in vitro E<sub>2</sub> daily delivery rate is 0.014 mg/day (0.012 - 0.016, 95% CI) and 0.017 (± 0.008) mg/day, respectively, for the 3.25 cm<sup>2</sup> E<sub>2</sub> transdermal system. Hence, the estimated in vivo and in vitro E<sub>2</sub> daily delivery rates are consistent for the 3.25 cm<sup>2</sup> E<sub>2</sub> transdermal system. The in vivo and in vitro E<sub>2</sub> daily delivery rate is 0.025 mg/day (per Climara<sup>®</sup> labeling) and 0.039 (± 0.014) mg/day, respectively, for the 6.5 cm<sup>2</sup> E<sub>2</sub> transdermal system. The estimated in vitro E<sub>2</sub> daily delivery rate is higher than that for the in vivo E<sub>2</sub> daily delivery rate for the 6.5 cm<sup>2</sup> E<sub>2</sub> transdermal system.

Figures 2 and 3. Mean baseline uncorrected serum E<sub>2</sub> concentrations vs. - time (left panel) and mean baseline uncorrected serum E<sub>1</sub> concentrations vs. - time (right panel) profiles following application of a 3.25 cm<sup>2</sup> E<sub>2</sub> transdermal system and application of a 6.5 cm<sup>2</sup> Climara<sup>®</sup> system.

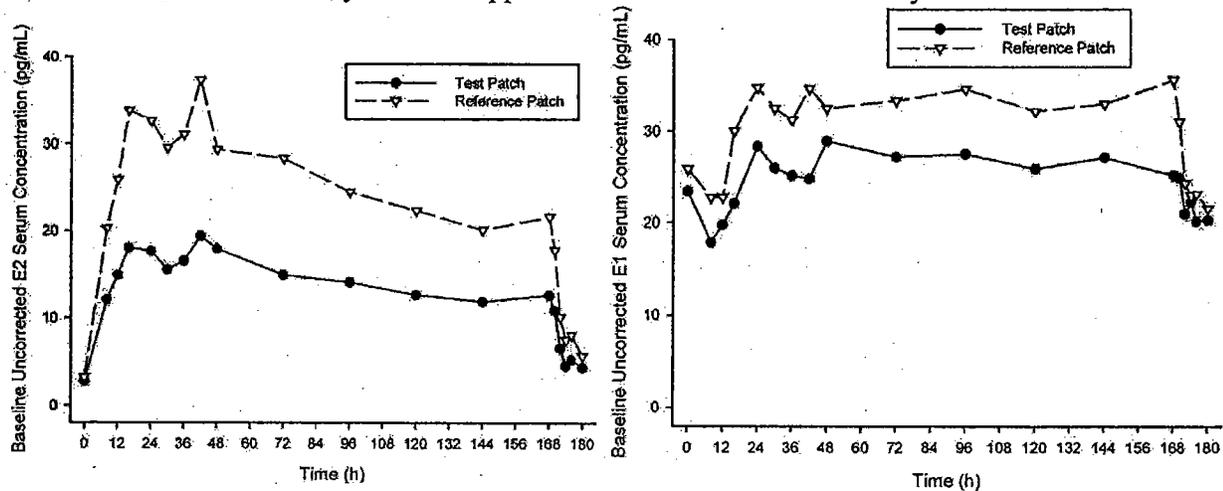


Figure 4. Mean baseline uncorrected serum E<sub>1</sub>S concentrations vs. – time profiles following application of a 3.25 cm<sup>2</sup> E<sub>2</sub> transdermal system and application of a 6.5 cm<sup>2</sup> Climara® system.

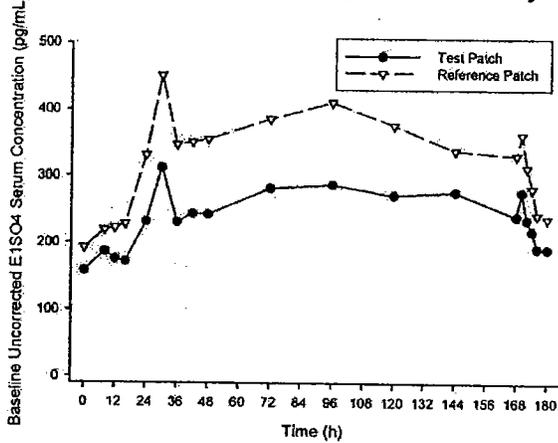


Table 2. Relative BA (baseline uncorrected) following application of a 3.25 cm<sup>2</sup> E<sub>2</sub> transdermal system and application of a 6.5 cm<sup>2</sup> Climara® system (arithmetic mean (%CV) and geometric mean)

Report No. (Study No.)	Number of Subjects	Dosage Form	Dose	Analyte	C <sub>max</sub> pg/mL	C <sub>168h</sub> <sup>a</sup> pg/mL	T <sub>max</sub> <sup>b</sup> h	AUC(0-tlast) pg <sup>h</sup> /mL	C <sub>ave</sub> pg/mL	Average Daily Delivery Rate, µg [95% Confidence Interval]
A08736 (305851)	18	<b>Test</b> Ultra Low Dose Estradiol Transdermal Delivery System (3.25 cm <sup>2</sup> ) 1.0 mg 17β-Estradiol	1 x 3.25 cm <sup>2</sup> patch per week	E <sub>2</sub>	21.7 (32.9) 20.6	12.6 (42.7)	42.0	2462 (37.5) 2296	14.7 (37.5) 13.7	14.3 (24.9) 14 [12 – 16]
				E <sub>1</sub>	38.7 (37.4) 35.9	23.8 (58.9)	39.0	4649 (40.2) 4154	—	—
				E <sub>1</sub> -S	385 (69.6) 326	254 (74.4)	72.0	48481 (76.5) 37121	—	—
		<b>Reference</b> Climara® Estradiol Transdermal Delivery System (6.5 cm <sup>2</sup> ) 2.0 mg 17β-Estradiol	1 x 6.5 cm <sup>2</sup> patch per week	E <sub>2</sub>	39.5 (36.6) 37.2	20.4 (47.7)	42.0	4365 (30.5) 4151	26.0 (30.5) 24.7	25 <sup>c</sup>
				E <sub>1</sub>	45.1 (31.0) 43.0	35.6 (40.4)	45.0	5753 (26.5) 5509	—	—
				E <sub>1</sub> -S	490 (62.9) 415	332 (75.2)	57.0	62590 (68.9) 51807	—	—

AUC(0-tlast) = area under the serum drug concentration-time profile from time zero to last quantifiable concentration; C<sub>max</sub> = maximum serum drug concentration; C<sub>168h</sub> = serum drug concentration at 168 hour post patch application; C<sub>ave</sub> = average serum concentration; E<sub>2</sub> = 17β-estradiol; E<sub>1</sub> = estrone; t<sub>max</sub> = time to achieve maximum serum drug concentration.

<sup>a</sup>Arithmetic mean (%CV)

<sup>b</sup>Median

<sup>c</sup>Nominal delivery rate of Climara® 6.5 cm<sup>2</sup> package insert

The E<sub>2</sub> C<sub>max</sub>, C<sub>168h</sub>, AUC(0 – tlast), and C<sub>ave</sub> for the 3.25 cm<sup>2</sup> E<sub>2</sub> transdermal system are about ½ of those for the 6.5 cm<sup>2</sup> E<sub>2</sub> transdermal system. Hence, this observation is consistent with the 3.25 cm<sup>2</sup> E<sub>2</sub> transdermal system being ½ the size for the 6.5 cm<sup>2</sup> E<sub>2</sub> transdermal system. However, the E<sub>1</sub>S and E<sub>1</sub>'s C<sub>max</sub>, C<sub>168h</sub>, AUC(0 – tlast), and C<sub>ave</sub> did not show the ratio of ½ between the 3.25 cm<sup>2</sup> E<sub>2</sub> transdermal system and the 6.5 cm<sup>2</sup> E<sub>2</sub> transdermal system.

### 3.3 Intrinsic Factors

The sponsor did not conduct any study to evaluate the effect of intrinsic factors on the PK of Menostar™.

### 3.4 Extrinsic Factors

The sponsor did not conduct any study to evaluate the effect of extrinsic factors on the PK of Menostar™.

### 3.5 General Biopharmaceutics

#### 1. Does difference exist between the to-be-marketed formulation and the pivotal clinical study formulation?

No. The Menostar™ formulation used in Study 98188 (pivotal clinical study) is identical to the to-be-marketed Menostar™ formulation, per the sponsor's April 23, 2004 submission to Drug Master File

#### 2. What are the results of the skin adhesion test for Menostar™?

In the relative BA study (Study 305851), the sponsor assessed the skin adhesion properties for the 3.25 cm<sup>2</sup> and 6.5 cm<sup>2</sup> E<sub>2</sub> transdermal systems. The system was pressed firmly and had good skin contact, especially around the edges, on a clean and dry area of the lower abdomen. The application site was alternated from the left lower abdominal area for the 1<sup>st</sup> treatment period, and to the right side for the 2<sup>nd</sup> treatment period. If there was any sign of patch lifting off of the skin, the clinical study staff or the subject (during outpatient period) gently pressed the partially detached patch to the skin with the palm of their hand. If the patch was completely detached, it was not reapplied and the subject was withdrawn from the study. The clinical study staff assessed the patch adhesion daily during the treatment period. Complete attachment was defined as ≥75% of the patch still attached to the skin. A subject was withdrawn from the study if the patch attachment to the skin was <75% after 24 hours. The same applied to premature complete detachment of the patch. A 7-point scale was used throughout each patch-application interval:

1. no lift
2. < 10% lifting (edge lifting)
3. 10 - 25% lifting
4. >25 - 50% lifting
5. >50 - 75% lifting
6. >75% - <100% lifting
7. fall off

Table 3. Comparison of system adhesion by treatment:

Category	Parameter	Test Patch	Reference Patch
		Ultra Low Dose E <sub>2</sub> (3.25 cm <sup>2</sup> )	Climara <sup>®</sup> E <sub>2</sub> (6.5 cm <sup>2</sup> )
Subjects with complete patch adhesion (score ≤ 3) across 7 days	Total	18 (100%)	18 (100%)
	Yes	18 (100%)	18 (100%)
	No	0 (0%)	0 (0%)
Subjects with no patch lifting (score = 1) across 7 days	Total	18 (100%)	18 (100%)
	Yes	15 (83%)	16 (89%)
	No	3 (17%)	2 (11%)
Maximum patch adhesion score across 7 days	Total	18 (100%)	18 (100%)
	Score = 1 (no lifting)	15 (83%)	16 (89%)
	Score = 2 (< 10% lifting)	3 (17%)	2 (11%)
Number of days with complete patch adhesion (score ≤ 3) across all subjects	N	18	18
	Mean	7.00	7.00
	Median	7.00	7.00
	SD	0.00	0.00
	Min	7.00	7.00
	Max	7.00	7.00

No subject scored >10% lifting on any observation in all 7-day wear periods for both 3.25 and 6.5 cm<sup>2</sup> E<sub>2</sub> transdermal systems administration. For the 3.25 cm<sup>2</sup> E<sub>2</sub> transdermal system, 83% (15/18) of the subjects scored no lifting and 17% (3/18) of the subjects scored <10% lifting in the 7-day wearing period. For the 6.5 cm<sup>2</sup> E<sub>2</sub> transdermal system, 89% (16/18) of the subjects scored no lifting and 11% (2/18) of the subjects scored <10% lifting in the 7-day wearing period. See Attachment for detailed adhesion results. The 3.25 and 6.5 cm<sup>2</sup> E<sub>2</sub> transdermal systems appear to have good skin adhesion property.

**3. What is the proposed in vitro dissolution method and specification for Menostar™?**

Table 4. Proposed in vitro dissolution method and specification ( ).

Apparatus		dissolution apparatus
Medium	—	- ethanol/water
Medium volume	—	
Medium temperature	—	
Basket shaft rotating speed	—	rpm
Sampling times		10, 45, 180 minutes
Specifications		

The proposed dissolution method is acceptable, since it is the same as the approved in vitro dissolution method for Climara® except that the medium is — for the 3.25 cm<sup>2</sup> system ( — mL for the 6.5 cm<sup>2</sup> system). Per discussion with Dr. Amit Mitra (reviewing chemist from the Division of Reproductive and Urologic Drug Products), the proposed — dissolution medium is acceptable since it maintains sink condition and more than ½ of — medium may be necessary to account for sampling. The proposed in vitro dissolution specification is acceptable and is identical to that for the 6 marketed Climara® systems. See Attachment for individual in vitro dissolution data.

**3.6 Bioanalytical**

**1. Are the bioanalytical methods properly validated for measuring serum E<sub>2</sub>, E<sub>1</sub> and E<sub>1</sub>S concentrations?**

Yes. Table 5. Validation for the bioanalytical methods for E<sub>2</sub>, E<sub>1</sub> and E<sub>1</sub>S in human serum samples (Study 305851).

	E <sub>2</sub>	E <sub>1</sub>	E <sub>1</sub> S
Method	GC/MS	GC/MS	LC/MS/MS
LLOQ, pg/mL			
Linearity, pg/mL			
Precision (CV%)			
(interassay)	6.2 (10 pg/mL) 3.65 (75 pg/mL) 3.43 (200 pg/mL)	6.86 (20 pg/mL) 4.79 (150 pg/mL) 2.98 (400 pg/mL)	6.28 (100 pg/mL) 5.00 (500 pg/ml) 3.51 (4000 pg/mL)
Accuracy (bias%)			
(interassay)	4.65 (10 pg/mL) 2.88 (75 pg/mL) 0.77 (200 pg/mL)	5.88 (20 pg/mL) 3.89 (150 pg/mL) 2.76 (400 pg/mL)	1.05 (100 pg/mL) 2.09 (500 pg/ml) 1.31 (4000 pg/mL)

GC/MS = gas chromatography/mass spectrometry detection; LC/MS/MS = liquid chromatography/tandem mass spectrometry detection; LLOQ = lower limit of quantitation

#### 4 Labeling Comments

The following comments are based on the proposed labeling (relevant for clinical pharmacology) submitted on August 7, 2003. Strikethrough text means recommended deletion. Single underscore text means recommended addition. Double underscore text means annotation for the recommendation and does not need to be communicated with the sponsor.

#### CLINICAL PHARMACOLOGY

The Menostar™ system provides ultra low estradiol ~~concentrations~~ concentrations by releasing 17β-estradiol, the major estrogenic hormone secreted by the human ovary.

#### PHARMACOKINETICS

~~\_\_\_\_\_~~ The relative bioavailability of estradiol following application of ~~a~~ a Menostar™ system ~~\_\_\_\_\_~~ to that from a Climara® 0.025 mg/day system was investigated in 18 healthy postmenopausal women mean age 66 years (range 60-80 years). The mean serum estradiol concentrations ~~\_\_\_\_\_~~ upon administration of the two patches to the lower abdomen are shown in Figure 1. Transdermal administration of Menostar™ produces geometric mean average serum concentration (C<sub>avg</sub>) of estradiol of 13.7 pg/mL. No patches failed to adhere during the one-week application period of both transdermal systems. Following the application of the Menostar™ system ~~\_\_\_\_\_~~ it is estimated to provide an average nominal in-vivo daily delivery of 0.014 mg estradiol/day. Repositioning for clarity. Adding factual information.

#### Absorption

The Menostar™ transdermal delivery system continuously releases estradiol which is transported across intact skin leading to sustained circulating levels of estradiol during a 7-day treatment period. The systemic availability of estradiol after transdermal administration is about 20 times higher than that after oral administration. This difference is due to the absence of first pass metabolism when estradiol is given by the transdermal route, ~~\_\_\_\_\_~~

#### Figure 1

Mean ~~\_\_\_\_\_~~ Uncorrected Serum 17 β-Estradiol Concentrations vs. Time Profile Following Application of Menostar™ \_\_\_\_\_ and Climara® 6.5 cm<sup>2</sup>

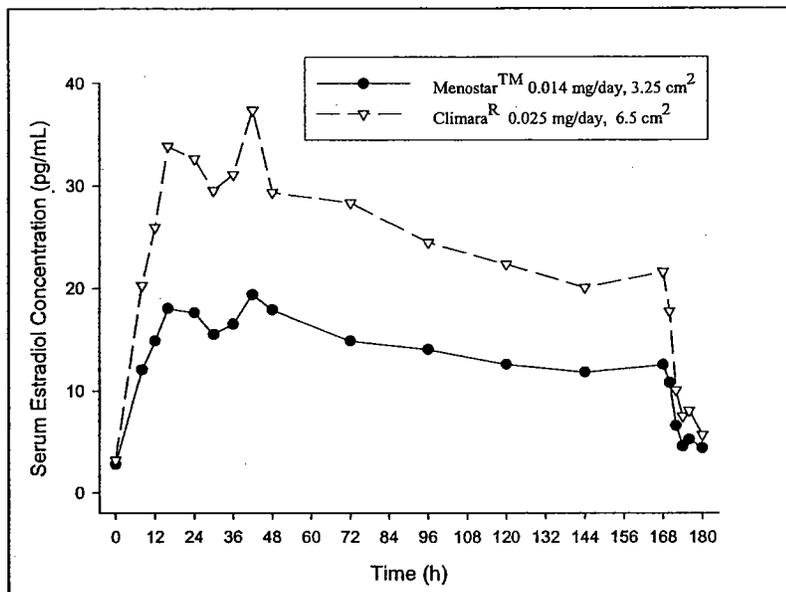


Table 1 provides a summary of estradiol pharmacokinetic parameters determined during evaluation of Menostar™ using baseline uncorrected serum concentrations.

**Table 1**

**Summary of Estradiol Pharmacokinetic Parameters**

Estradiol Transdermal Delivery System	Estimated Estradiol Daily Delivery Rate, mg/day	Application Site	AUC (0-tlast) pg.h/mL	Cmax pg/mL	Cavg pg/mL	Tmax h	Cmin pg/mL
Menostar™ 3.25 cm <sup>2</sup>	0.014	Lower Abdomen	2296	20.6	13.7	42	12.6
Climara® 6.5 cm <sup>2</sup>	0.025	Lower Abdomen	4151	37.2	24.7	42	20.4

Pharmacokinetic parameters are expressed in geometric means except for the tmax which represents the median estimate and the Cmin which is expressed as the arithmetic mean. The Estimated Estradiol Daily Delivery Rate for Climara® 6.5 cm<sup>2</sup> is quoted from the Climara® labeling. Adding factual information.

**Distribution**

The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone

target organs. Estrogens circulate in the blood largely bound to sex hormone binding globulin (SHBG) and albumin.

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### **Metabolism**

Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is the major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the gut followed by reabsorption. In postmenopausal women, a significant proportion of the circulating estrogens exist as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens.

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### **Excretion**

Estradiol, estrone, and estriol are excreted in the urine along with glucuronide and sulfate conjugates.

### **Special Populations:**

*Pediatric:* No pharmacokinetic studies have been conducted for Menostar™ in children.

*Gender:* Menostar™ is indicated for use in women only.

*Race:* No studies were done to determine the effect of race on the pharmacokinetics of Menostar™.

*Patients with Renal Impairment:* Total estradiol serum levels are higher in postmenopausal women with end stage renal disease (ESRD) receiving maintenance hemodialysis than in normal subjects at baseline and following oral doses of estradiol. Therefore, conventional transdermal estradiol doses used in individuals with normal renal function may be excessive for postmenopausal women with ESRD receiving maintenance hemodialysis.

*Patients with Hepatic Impairment:* Estrogens may be poorly metabolized in patients with impaired liver function and should be administered with caution.

## **Drug Interactions**

No drug interaction studies have been conducted for Menostar™.

In vitro and in vivo studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's Wort preparations (Hypericum perforatum), phenobarbital, carbamazepine, and rifampin may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects.



# Attachment

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**Text Table 10: Statistical Comparison of Dose-Normalized Estradiol Pharmacokinetic Parameters for Baseline Uncorrected Serum Concentrations.**

Parameter	Test Patch	Reference Patch
	Ultra Low Dose E2 (3.25 cm <sup>2</sup> ) N = 18	Climara <sup>®</sup> E2 (6.5 cm <sup>2</sup> ) N = 18
<b>AUC(0-last) (pg*h/mL)</b>		
Geometric Mean	4591	4151
Ratio (Ultra Low Dose / Climara <sup>®</sup> )		1.106
p-value		0.1700
90% Confidence Limits		0.979, 1.250
<b>Cmax (pg/mL)</b>		
Geometric Mean	41.2	37.2
Ratio (Ultra Low Dose / Climara <sup>®</sup> )		1.108
p-value		0.1049
90% Confidence Limits		0.998, 1.230

REF: Section 14, Tables 33.1 and 33.2



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Table 7: Summary of Patch Adhesion (Safety Analysis Set)

Period	Treatment	Day	Patch Adhesion Score							TOTAL	
			1 No lift	2 Edge lifting < 10%	3 10 - 25% lifting	4 >25 - 50% lifting	5 >50 - 75% lifting	6 >75 - <100% lifting	7 Fall Off		
PERIOD 1	Climara E2 (6.5 cm2)	DAY 1	9(100.0%)	0(0.0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	9	
		DAY 2	9(100.0%)	0(0.0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	9	
		DAY 3	9(100.0%)	0(0.0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	9	
		DAY 4	9(100.0%)	0(0.0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	9	
		DAY 5	9(100.0%)	0(0.0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	9	
		DAY 6	9(100.0%)	0(0.0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	9	
		DAY 7	9(100.0%)	0(0.0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	9	
		MAXIMUM*	9(100.0%)	0(0.0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	9	
		Ultra Low Dose E2 (3.25 cm2)	DAY 1	9(100.0%)	0(0.0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	9
			DAY 2	9(100.0%)	0(0.0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	9
			DAY 3	9(100.0%)	0(0.0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	9
			DAY 4	8(88.9%)	1(11.1%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	9
			DAY 5	7(77.8%)	2(22.2%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	9
			DAY 6	8(88.9%)	1(11.1%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	9
	DAY 7		8(88.9%)	1(11.1%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	9	
	MAXIMUM*	7(77.8%)	2(22.2%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	9		

Patch adhesion status was scored as follows:  
 1= no lift, 2= edge lifting < 10%, 3= 10-25% lifting, 4= >25-50% lifting, 5= >50-75% lifting, 6= >75- <100% lifting, 7=fall off  
 Cell frequencies are numbers(%) of subjects  
 Total = Number of Subjects with an evaluation at the time point (does not include missing values)  
 \*Number of subjects assessed to have the indicated score as the maximum score for that time period.



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Table 7: Summary of Patch Adhesion (Safety Analysis Set)

Period	Treatment	Day	Patch Adhesion Score							TOTAL	
			1 No. lift	2 Edge lifting < 10%	3 10 - 25% lifting	4 >25 - 50% lifting	5 >50 - 75% lifting	6 >75 - <100% lifting	7 Fall Off		
PERIOD 2	Climara E2 (6.5 cm <sup>2</sup> )	DAY 1	9(100.0%)	0(0.0%)	0(%)	0(%)	0(%)	0(%)	0(%)	9	
		DAY 2	9(100.0%)	0(0.0%)	0(%)	0(%)	0(%)	0(%)	0(%)	9	
		DAY 3	9(100.0%)	0(0.0%)	0(%)	0(%)	0(%)	0(%)	0(%)	9	
		DAY 4	9(100.0%)	0(0.0%)	0(%)	0(%)	0(%)	0(%)	0(%)	9	
		DAY 5	9(100.0%)	0(0.0%)	0(%)	0(%)	0(%)	0(%)	0(%)	9	
		DAY 6	8(88.9%)	1(11.1%)	0(%)	0(%)	0(%)	0(%)	0(%)	9	
		DAY 7	7(77.8%)	2(22.2%)	0(%)	0(%)	0(%)	0(%)	0(%)	9	
		MAXIMUM*	7(77.8%)	2(22.2%)	0(%)	0(%)	0(%)	0(%)	0(%)	9	
		Ultra Low Dose E2 (3.25 cm <sup>2</sup> )	DAY 1	9(100.0%)	0(0.0%)	0(%)	0(%)	0(%)	0(%)	0(%)	9
			DAY 2	9(100.0%)	0(0.0%)	0(%)	0(%)	0(%)	0(%)	0(%)	9
DAY 3	9(100.0%)		0(0.0%)	0(%)	0(%)	0(%)	0(%)	0(%)	9		
DAY 4	9(100.0%)		0(0.0%)	0(%)	0(%)	0(%)	0(%)	0(%)	9		
DAY 5	9(100.0%)		0(0.0%)	0(%)	0(%)	0(%)	0(%)	0(%)	9		
DAY 6	8(88.9%)		1(11.1%)	0(%)	0(%)	0(%)	0(%)	0(%)	9		
DAY 7	8(88.9%)		1(11.1%)	0(%)	0(%)	0(%)	0(%)	0(%)	9		
MAXIMUM*	8(88.9%)		1(11.1%)	0(%)	0(%)	0(%)	0(%)	0(%)	9		

Patch adhesion status was scored as follows:

1= no lift, 2= edge lifting < 10%, 3= 10-25% lifting, 4= >25-50% lifting, 5= >50-75% lifting, 6= >75- <100% lifting, 7=fall off

Cell frequencies are numbers(%) of subjects

Total = Number of Subjects with an evaluation at the time point (does not include missing values)

\*Number of subjects assessed to have the indicated score as the maximum score for that time period.

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Table 8: Treatment Comparisons for Patch Adhesion (Safety Analysis Set)

CATEGORY	TREATMENT	STATISTIC	Patch Adhesion Score							TOTAL
			1	2	3	4	5	6	7	
Maximum Patch Adhesion Scores Across All Subjects	Climara E2 (6.5 cm2)		16(88.89%)	2(11.11%)	0(%)	0(%)	0(%)	0(%)	0(%)	18(100%)
	Ultra Low Dose E2 (3.25cm2)		15(83.33%)	3(16.67%)	0(%)	0(%)	0(%)	0(%)	0(%)	18(100%)
Number of days with Complete Patch Adhesion (<= 25% lifting)	Climara E2 (6.5 cm2)	N	18.00							
		MEAN	7.00							
		MEDIAN	7.00							
		SD	0.00							
		MIN	7.00							
	Ultra Low Dose E2 (3.25cm2)	N	18.00							
		MEAN	7.00							
		MEDIAN	7.00							
		SD	0.00							
		MIN	7.00							

Patch adhesion status was scored as follows:  
 1= no lift, 2= edge lifting < 10%, 3= 10-25% lifting, 4= >25-50% lifting, 5= >50-75% lifting, 6= >75- <100% lifting, 7=fall off  
 A maximum score across 7 days was calculated for each subject within each study period.  
 Total = Number of Subjects with an evaluation at the time point (does not include missing values)



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Table 8: Treatment Comparisons for Patch Adhesion (Safety Analysis Set), cont'd

CATEGORY	TREATMENT	NO	YES	TOTAL
Subjects with Patch Adhesion Score=1 (No lift)	Climara E2 (6.5 cm <sup>2</sup> )	2 (11.11%)	16 (88.89%)	18 (100.00%)
	Ultra Low Dose E2 (3.25cm <sup>2</sup> )	3 (16.67%)	15 (83.33%)	18 (100.00%)
Subjects with Patch Adhesion <= 25% lifting	Climara E2 (6.5 cm <sup>2</sup> )	0 (0%)	18 (100.00%)	18 (100.00%)
	Ultra Low Dose E2 (3.25cm <sup>2</sup> )	0 (0%)	18 (100.00%)	18 (100.00%)

Patch adhesion status was scored as follows:  
1= no lift, 2= edge lifting < 10%, 3= 10-25% lifting, 4= >25-50% lifting, 5= >50-75% lifting, 6= >75- <100% lifting, 7=fall off  
A maximum score across 7 days was calculated for each subject within each study period.  
Total = Number of Subjects with an evaluation at the time point (does not include missing values)

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