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RESEARCH**

*APPLICATION NUMBER:*

**21-885**

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

## OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

<b>NDA Submission Dates</b>	21-885 February 28, 2005 (original); August 19, 2005 (N-000-BL); December 1, 2005 (N-000-BB)
<b>Brand Name</b>	Climara Pro <sup>®</sup>
<b>Generic Names</b>	Estradiol (E <sub>2</sub> ) and levonorgestrel (LNG)
<b>Reviewer</b>	S.W. Johnny Lau
<b>Team Leader</b>	Hae-Young Ahn
<b>OCPB Division</b>	CPB2
<b>ORM Division</b>	Metabolic and Endocrine Products
<b>Sponsor</b>	Berlex, Inc.
<b>Relevant IND</b>	69.721
<b>Submission Type: Code</b>	Type 6 NDA: S
<b>Formulation; Strength(s)</b>	Transdermal system; (4.4 mg E <sub>2</sub> and 1.39 mg LNG)/22 cm <sup>2</sup>
<b>Indication</b>	To prevent postmenopausal osteoporosis in women

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### 1 Executive Summary

The sponsor submitted NDA 21-885 to seek approval for the 22 cm<sup>2</sup> transdermal system (Climara Pro<sup>®</sup>), which nominally delivers 0.045 mg E<sub>2</sub>/day and 0.015 mg LNG/day, for the prevention of postmenopausal osteoporosis (PMO) in women. Climara Pro<sup>®</sup> is approved for the relief of menopausal vasomotor symptoms under NDA 21-258 with the Division of Reproductive and Urologic Products. There is no change to Climara Pro<sup>®</sup> for seeking the additional indication's approval.

The sponsor conducted 2 clinical efficacy and safety studies (96041B/A09585 as pivotal and 12226/A10079 as supportive) with lumbar spine bone mineral density (BMD) changes as the primary efficacy variable. See Dr. Bruce Stadel's medical review for details. The sponsor cross-referred NDA 21-885's clinical pharmacology and biopharmaceutics information to that of NDA 21-258's.

### 1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Clinical Pharmacology and Biopharmaceutics 2 (OCPB/DCPB2) has reviewed NDA 21-885's clinical pharmacology and biopharmaceutics information and finds it acceptable.

### 1.2 Phase IV Commitments

None

### 1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The sponsor conducted a pivotal clinical efficacy and safety study with the 22 cm<sup>2</sup> transdermal system containing 4.40 mg E<sub>2</sub> without LNG and conducted a supportive clinical efficacy and safety study with the 22 cm<sup>2</sup> transdermal system containing 4.40 mg E<sub>2</sub> + 2.75 mg LNG. The clinically-tested E<sub>2</sub> dose was the same as that of the to-be-marketed Climara Pro<sup>®</sup> and E<sub>2</sub> is the drug of interest for this NDA. The to-be-marketed Climara Pro<sup>®</sup> is different from the clinically-tested transdermal systems. However, in vivo E<sub>2</sub> bioequivalence study between the clinically-tested and the to-be-marketed transdermal systems has not been conducted but is justified because:

- The clinically tested 4.4 mg E<sub>2</sub> + 2.75 mg LNG transdermal systems showed slightly better efficacy results than that for the 4.4 mg E<sub>2</sub> only system ( ). The 2 PMO clinical studies did not reveal any new or unexpected safety concerns beyond those already noted in the Climara Pro<sup>®</sup> labeling approved for the vasomotor symptom indication. The currently approved Climara Pro<sup>®</sup> labeling has extensive safety data from the Women's Health Initiative studies regarding the long term use of estrogen and estrogen combined with a progestin.
- The to-be-marketed Climara Pro<sup>®</sup> contains the same amount of E<sub>2</sub> as those clinically-tested systems and the 1.39 mg LNG is between those that were clinically tested.
- The major difference between the clinically-tested systems and to-be-marketed Climara Pro<sup>®</sup> is the absence of presence of LNG, which is correspondingly adjusted with the adhesive.
- Hence, the efficacy information for the to-be-marketed Climara Pro<sup>®</sup>'s prevention of PMO indication may be inferred from the clinically-tested formulations via the approach.
- E<sub>2</sub> is bioequivalent between Climara Pro<sup>®</sup> and the 4.4 mg E<sub>2</sub> + 2.75 mg LNG transdermal system as shown in the approved NDA 21-258.

Furthermore, the f<sub>2</sub> (similarity) values between the clinically-tested E<sub>2</sub> alone transdermal system and 5 Climara Pro<sup>®</sup> lots are all above 50 and the f<sub>2</sub> values between the clinically-tested E<sub>2</sub> + 2.75 mg LNG transdermal system and 5 Climara Pro<sup>®</sup> lots are also all above 50. Hence, the in vitro dissolution profiles for the E<sub>2</sub> only transdermal system and the E<sub>2</sub> + 2.75 mg LNG transdermal system are all similar to those of Climara Pro<sup>®</sup>.

S.W. Johnny Lau, R.Ph., Ph.D.  
OCPB/DCPB2

FT signed by Hae-Young Ahn, Ph.D., Team Leader \_\_\_\_\_ 11/ /05

An Optional Intra-Division Clinical Pharmacology and Biopharmaceutics Briefing for NDA 21-885 was conducted on November 18, 2005, participants included H. Malinowski, B. Gierhart, J. Mele, P. Madara, H. Ahn, and J. Lau.

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Moreover, the sponsor markets 3 lower strengths of Climara<sup>®</sup> (2, 2.85, and 3.8 mg E<sub>2</sub> only systems) and also Menostar<sup>™</sup> (1 mg E<sub>2</sub> only system). These transdermal systems all have the indication to prevent PMO in women.

The consensus based on the Medical Staff's opinions was that this proposal would not be included in the final labeling because of the following reasons:

- no new safety concerns for the proposed 4.4 mg E<sub>2</sub> + 1.39 mg LNG besides the safety issues that are already known for the relief of menopausal vasomotor symptoms and the Women's Health Initiative studies
- If a patient with uterus needs lower doses of E<sub>2</sub>, she has the option to receive the lower strengths of Climara<sup>®</sup> with an oral progestin.
- Climara Pro<sup>®</sup> with the proposed prevention of postmenopausal osteoporosis indication primarily serves as a convenient package for the medium strength Climara<sup>®</sup> and a progestin.

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## 2 Question-Based Review

### 2.1 General Attributes

The sponsor seeks approval for the 22 cm<sup>2</sup> E<sub>2</sub> and LNG transdermal system for the prevention of PMO in women. The sponsor markets the same transdermal system (Climara Pro<sup>®</sup>) to treat moderate and severe menopausal vasomotor symptoms.

#### 2.1.1 What is the formulation of the to-be-marketed Climara Pro<sup>®</sup> transdermal system?

See question 2.3.1 below for the to-be-marketed Climara Pro<sup>®</sup> formulation. There is no change in Climara Pro<sup>®</sup> formulation for the approved indication and this NDA's proposed indication.

Climara Pro<sup>®</sup>'s transdermal system (22 cm<sup>2</sup>) has 3 layers and they are (Figure 1 below):

- a translucent polyethylene backing film
- an acrylate adhesive matrix containing E<sub>2</sub> and LNG
- A protective liner of either siliconized or fluoropolymer coated polyester film.



### 2.2 General Clinical Pharmacology

E<sub>2</sub> and LNG clinical pharmacology information is available in:

- Dollery C. Oestradiol. *Therapeutic Drugs* 04 – 09 1991 ed.
- Fotherby K. Levonorgestrel: clinical pharmacokinetics. *Clin Pharmacokinet* 28:203-15 (1995)
- NDA 21-258's clinical pharmacology and biopharmaceutics review

### 2.3 General Biopharmaceutics

#### 2.3.1 Does difference exist between the to-be-marketed formulation and the clinically-tested formulations? If so, is the difference adequately addressed?

Yes to both questions. The sponsor used the 4.4 mg E<sub>2</sub> only transdermal system of 22 cm<sup>2</sup> in the pivotal study (96041B/A09585) and the 4.4 mg E<sub>2</sub> + 2.75 mg LNG transdermal system of 22 cm<sup>2</sup> in the supportive study (12226/A10079). Hence, the clinically-tested formulations are different from the to-be-marketed Climara Pro<sup>®</sup> formulation. Table 1 below details the difference between the 2 clinically-tested formulations and the to-be-marketed Climara Pro<sup>®</sup> formulation:

Ingredient	4.40 mg E <sub>2</sub> -only patch (22 cm <sup>2</sup> )	Climara Pro <sup>®</sup> (4.40 mg E <sub>2</sub> + 1.39 mg LNG) (22 cm <sup>2</sup> )	4.40 mg E <sub>2</sub> + 2.75 mg LNG patch (22 cm <sup>2</sup> )
E <sub>2</sub> (%)			
LNG (%w/w)	0		
Patch Size (cm <sup>2</sup> )	22	22	22

E<sub>2</sub> = 17β-estradiol; LNG = levonorgestrel.

The major difference between the above 3 transdermal systems is the absence or presence of LNG, which is correspondingly deleted or replaced with the ██████████ adhesive per weight. An in vivo E<sub>2</sub> bioequivalence study between the clinically-tested formulations and the to-be-marketed Climara Pro<sup>®</sup> has not been conducted but is justified because:

- The 6% increase in lumbar spine BMD from baseline (primary efficacy variable) is slightly higher for the 4.4 mg E<sub>2</sub> + 2.75 mg LNG transdermal system in the supportive study than that for the 4.4 mg E<sub>2</sub> only transdermal system in the pivotal study (>3.7%). Table 2 below (from page 10 of Ms. Joy Mele's statistical review) shows the lumbar spine BMD changes for the 2 studies.

	estradiol arms	estradiol	placebo	Trt Effect
<b>Study A09585</b> hyster. (reviewer's numbers)	0.0225 mg/day	+0.4%	-2.9%	+3.2%
	<b>0.045 mg/day</b>	+1.7%		<b>+4.9%</b>
	baseline estradiol <5	+2.9%	-3.4%	<b>+6.3%</b>
	≥5	+1.5%	-2.2%	<b>+3.7%</b>
	POM >1 to 3 yrs	+1.1%	-2.6%	<b>+3.7%</b>
	POM >3 to 10 yrs	+1.4%	-2.8%	<b>+4.2%</b>
<b>Study A10079</b> post meno with intact uteri	<b>0.045 mg/day+LNG.3</b>			
	POM >1 to 3 yrs	+3.8%	-2.6%	+6.4%
	POM >3 to 10 yrs	+4.6%	-1.6%	+6.2%
	<b>0.045 mg/day+LNG.4</b>			
POM >1 to 3 yrs	+4.2%	-2.6%	+6.8%	
POM >3 to 10 yrs	+5.2%	-1.6%	+6.8%	

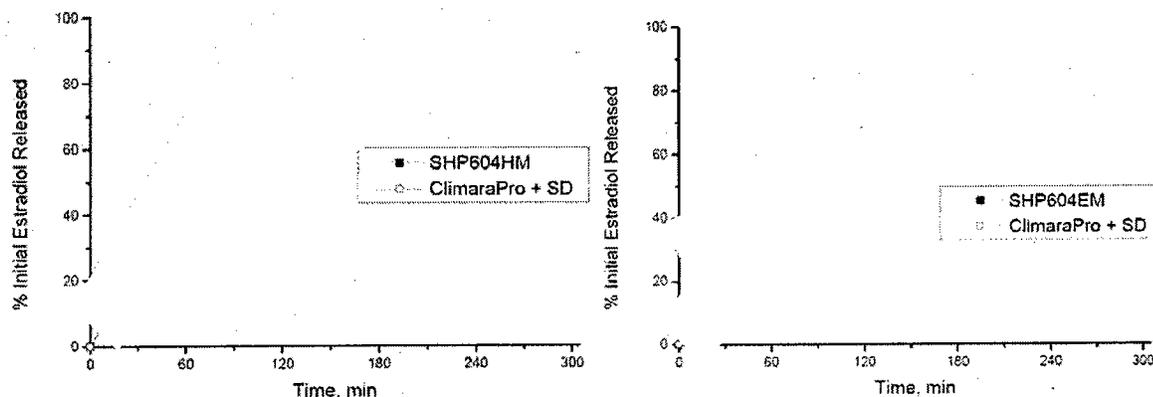
Hence, twice the LNG dose in Climara Pro<sup>®</sup> (2 x 1.39 mg) does not appear to decrease the efficacy of E<sub>2</sub>.

- The 2 osteoporosis clinical studies did not reveal any new or unexpected safety concerns beyond those already noted in the Climara Pro<sup>®</sup> labeling approved for the vasomotor symptom indication. The currently approved Climara Pro<sup>®</sup> labeling contains extensive safety data from the Women's Health Initiative (WHI) studies regarding the long term use of estrogen and estrogen combined with a progestin.
- The to-be-marketed Climara Pro<sup>®</sup> for the prevention of PMO indication contains the same amount of E<sub>2</sub> as those clinically-tested systems and its 1.39 mg LNG is between those that were clinically tested.
- Hence, the efficacy information for the to-be-marketed Climara Pro<sup>®</sup>'s prevention of osteoporosis indication may be inferred from the clinically-tested formulations via the ██████████ approach.
- E<sub>2</sub> is bioequivalent between Climara Pro<sup>®</sup> and the 4.4 mg E<sub>2</sub> + 2.75 mg LNG transdermal system in Study 304180, which was reviewed by Dr. Ronald Kavanagh for NDA 21-258.

The sponsor also substantiated the similarity of E<sub>2</sub> in vitro dissolution data between the clinically-tested formulations and the to-be-marketed Climara Pro<sup>®</sup> via Release Method 3314. Although Method 3314 is not the approved regulatory in vitro dissolution method for Climara Pro<sup>®</sup>, the approved Method 3557 for NDA 21-258 is modified from Method 3314. The only differences between the 2 methods were the mounting surface and securing method (see Section 4.2 for details). Modification to Method 3557 results in less variability between individual dissolution tests. The sponsor's use of Method 3314 to study the similarity of different transdermal systems' in vitro dissolution is justified,

because Method 3314 and Method 3557 are basically the same except the mounting surface and securing method.

Figure 2 below (left) shows mean  $E_2$  in vitro dissolution data for the 4.40 mg  $E_2$  only system (SHP604HM; 22 cm<sup>2</sup>) used in the pivotal study vs. Climara Pro<sup>®</sup>. Figure 3 below (right) shows mean  $E_2$  in vitro dissolution data for the 4.40 mg  $E_2$  + 2.75 mg LNG system (SHP604EM; 22 cm<sup>2</sup>) used in the supportive study vs. Climara Pro<sup>®</sup>. Only 1 lot each for SHP604HM and SHP604EM but 5 lots of Climara Pro<sup>®</sup> were tested.



This reviewer calculated the  $f_2$  values between the clinically-tested  $E_2$  alone transdermal system and 5 Climara Pro<sup>®</sup> lots as 74.72, 86.32, 90.47, 91.27, and 96.74. All of these  $f_2$  values are above 50. Hence, the in vitro dissolution profile for the  $E_2$  only transdermal system is similar to those of Climara Pro<sup>®</sup>.

This reviewer calculated the  $f_2$  values between the clinically-tested  $E_2$  + 2.75 mg LNG transdermal system and 5 Climara Pro<sup>®</sup> lots as 62.19, 70.87, 72.1, 81.7, and 89.86. All of these  $f_2$  values are above 50. Hence, the in vitro dissolution profile for the  $E_2$  + 2.75 mg LNG transdermal system is similar to those of Climara Pro<sup>®</sup>.

All clinical lots were manufactured on a production scale, including the  $E_2$  only transdermal system.

## 2.4 Analytical

### 2.4.1 Are the $E_2$ and LNG bioanalytical methods properly validated?

Not applicable since the sponsor did not conduct new clinical pharmacology study.

27 Page(s) Withheld

       Trade Secret / Confidential

✓ Draft Labeling

       Deliberative Process

## 4.2 In Vitro Dissolution Method and Individual Data

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Per submission NDA 21-885 on November , 2005:

You have indicated in NDA 21-885's Human Pharmacokinetics and Bioavailability section (page 9 of 18) that you used "Release Rate Method 3314" to conduct the in vitro estradiol dissolution tests for the clinically-tested transdermal system and the to-be-marketed Climara Pro<sup>®</sup>.

To complete our review, we need to confirm the following:

- 1) Is "Release Rate Method 3314" the approved regulatory in vitro dissolution method to study estradiol release from Climara Pro<sup>®</sup>?

Although Method 3314 is not our approved regulatory method, we feel that it is the correct method for the release rate  $f_1/f_2$  analysis of estradiol delivery from the clinical lots. Please see our attached rationale.

- 2) Is "Release Rate Method 3314" cited in page 9 of 18 the same as "Release Rate Method 3314/3305" cited in pages 13, 15, and 16 of 18 in NDA 21-885's Human Pharmacokinetics and Bioavailability section?

There is only one release rate Method 3314 so all citations refer to the same method. The reference to release rate method 3314/3305 is a more complete method description that is actually referring to two methods: Method 3314 is the release rate procedure, and Method 3305 is the HPLC assay method. Although only Method 3314 was cited on page 9, Method 3305 was also used for the HPLC assay.

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The method comparison data that was submitted and found to allow the method switch in NDA 21-258 consisted of 9 analysis dates (0, 1, 2, 3, 6, 9, 12, 18, and 24 months) conducted over a 2-year interval as part of the stability program on the 3 NDA lots. A summary of the initial method comparison data is given in Table 2. The data showed that Method 3557 gave consistent and only slightly higher release rate values than did Method 3314. Table 3 shows that, as desired, less variability was seen with Method 3557. These findings, in general, are representative of the findings at the other analysis dates, under both ambient and accelerated conditions.

**Table 2. Mean % Initial Estradiol Content for Release Rate Methods 3314 and 3557; Data given for time 0 from the stability analyses of the three NDA lots [a]**

Lot	Mean % Initial Estradiol Content for Release Rate using Method:							
	3314	3557	3314	3557	3314	3557	3314	3557
PD-99-10605	24	26	40	43	64	67	95	96
PD-99-10606	25	26	41	43	65	68	94	95
PD-99-10607	24	27	40	43	61	67	89	95

[a] Note that these mean values are different from those submitted as part of the January 22, 2002 Stability Update/Amendment to DMF [redacted] as the latter values were reported as % Label Claim

n = 6

**Table 3. Range of % Initial Estradiol Content for Release Rate Methods 3314 and 3557 and % CV; Data given for time 0 from the stability analyses of the three NDA lots**

Lot	Range of % Initial Estradiol Content for Release Rate using Method:							
	(%CV)							
Lot	3314	3557	3314	3557	3314	3557	3314	3557
PD-99-10605								
PD-99-10606								
PD-99-10607								
<b>Mean % CV</b>	2.8	1.3	2.5	1.3	1.3	0.92	1.2	1.2

n = 6

### **1.3 Appropriateness of Method 3314 for Difference Factor ( $f_1$ ) and Similarity Factor ( $f_2$ ) Analysis of Estradiol Delivery from Clinical Lots**

The drug release rate tests for the clinical lots used in all the clinical studies in NDA 21-885 were done with Method 3314. All clinical lots were manufactured on a production scale, including the estrogen only reference patch. When the decision was made to switch release rate methods to Method 3557, there was no plan to remanufacture a production lot of the estrogen only reference patch for the sole purpose of repeating the release rate test. [Note that the estrogen only reference patch in NDA 21-885 is different from the Climara patch.] Given the similarities of the two release rate methods and the fact that the method switch validation had been reviewed by the FDA as part of NDA 21-258, it was assumed that Method 3314 would be sufficient for the difference factor and similarity factor analysis of estradiol delivery from the clinical lots<sup>1</sup>.

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1. Retesting the release rates with Method 3557 with laboratory lots made by hand was considered, but our experience is that release rates from hand-spread laboratory lots can be appreciably different than production lots.



Text Table 5: Individual Release-Rate Results for the Test and Reference Product Lots

Release Rate Method 3314/3305	% Initial Estradiol			
PD-10057 SHP604HM 22cm2 (2%Estradiol/0% Levonorgestrel)				
mean	25.5	40.3	62.8	91.7
sd	0.516	1.86	3.43	2.66
CV%	2	5	5	3
PD-10054 Climara Pro 22cm2 (2%Estradiol/0.63% Levonorgestrel)				
mean	23.0	37.0	59.5	88.7
sd	1.10	1.79	1.76	2.50
CV%	5	5	3	3
PD-99-10605 Climara Pro 22cm2 (2%Estradiol/0.63% Levonorgestrel)				
mean	24.2	38.7	61.7	91.3
sd	0.753	0.816	0.816	0.816
CV%	3	2	1	1
PD-99-10606 Climara Pro 22cm2 (2%Estradiol/0.63% Levonorgestrel)				
mean	25.5	40.5	63.8	92.3
sd	0.516	0.837	0.408	1.03
CV%	2	2	1	1



Text Table 5: Individual Release-Rate Results for the Test and Reference Product Lots (continued)

Release Rate Method 3314/3305	% Initial Estradiol			
	PD-99-10607 Climara Pro 22cm2 (2%Estradiol/0.63% Levonorgestrel)			
mean	24.2	40.3	62.2	90.0
sd	0.753	1.37	1.33	1.41
CV%	3	3	2	2
PD-99-10449 Climara Pro 22cm2 (2%Estradiol/0.63% Levonorgestrel)				
mean	25.7	41.2	65.0	93.8
sd	0.816	1.33	1.10	1.33
CV%	3	2	2	1
PD-10056 SHP604EM 22cm2 (2%Estradiol/1.25% Levonorgestrel)				
mean	26.7	42.7	66.7	94.0
sd	2.25	2.80	4.63	4.34
CV%	8	7	7	5



**Text Table 6: Calculation of Difference factor ( $f_1$ ) for the Release-Rate Profiles of Two Test Products compared with the Reference Product: Calculation of key terms in Equation (1)**

Time (t min)	$R_t$ R = Climara Pro	$ R_t - T_t $ T = SHP604HM	$ R_t - T_t $ T = SHP604EM
$\Sigma$	217.6	2.7	12.33

**Text Table 7: Calculation of Similarity factor ( $f_2$ ) for the Release-Rate Profiles of Two Test Products compared with the Reference Product: Calculation of key terms in Equation (2)**

Time (t min)	$R_t$ R = Climara Pro	$(R_t - T_t)^2$ T = SHP604HM	$(R_t - T_t)^2$ T = SHP604EM
$\Sigma$	217.6	2.05	40.20

### 1.1.3.3 In vivo bioequivalence data

In addition, *in vivo* clinical bioequivalence data show that the LNG content of the patch has no effect on either E2 transdermal absorption or E2 pharmacokinetics from these patches. This protocol presents the bioequivalence results for E2 delivery from this 2-way, 4-week multiple-dose, crossover study in 44 postmenopausal women (Protocol 304180, submitted as part of NDA 21-258). One test patch was Climara Pro<sup>®</sup> and the other patch was essentially the same formulation as that of Climara Pro<sup>®</sup> except that the LNG delivery was doubled (Text table 8). Both the C<sub>max</sub> and AUC values of E2 and estrone for these patches met the criteria for bioequivalence at Week 4, despite the difference in LNG content.

### 4.3 Cover Sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics New Drug Application Filing and Review Form				
General Information About the Submission				
Information		Information		
NDA	21-885	Brand Name	Climara Pro <sup>®</sup>	
OCPB Division	II	Generic Name	estradiol + levonorgestrel	
Medical Division	DMEDP, HFD-510	Drug Class	Hormones	
OCPB Reviewer	S.W. Johnny Lau	Indication(s)	Prevention of osteoporosis	
OCPB Team Leader	Hae-Young Ahn	Dosage Form	Transdermal delivery system	
Date of Submission	28-FEB-2005	Dosing Regimen	1 system once weekly	
Estimated Due Date of OCPB Review	7-NOV-2005	Route of Administration	Transdermal	
PDUFA Due Date	15-DEC-2005	Sponsor	Berlex Laboratories, Inc.	
Division Due Date	21-NOV-2005	Priority Classification	Standard	
Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments if any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies				
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods				
<b>I. Clinical Pharmacology</b>				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
<b>II. Biopharmaceutics</b>				
Absolute bioavailability:				
Relative bioavailability -				
alternate formulation as reference:				

<b>Bioequivalence studies -</b>				
traditional design; multi dose:	x	1		Study 304180/6199 in NDA 21-258
replicate design; single / multi dose:				
<b>Food-drug interaction studies:</b>				
Dissolution:	x	1		
(IVIVC):				
Bio-wavler request based on BCS				
BCS class				
<b>III. Other CPB Studies</b>				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
<b>Total Number of Studies</b>		2		
<b>Filability and QBR comments</b>				
	"X" if yes	Comments		
Application filable ?	X			
Comments to-be-sent to firm?				
QBR questions (key issues to be considered)				
Other comments or information not included above				
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

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 S.W. Johnny Lau  
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Hae-Young Ahn  
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## Filing Memo

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### CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

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**NDA:** 21-885  
**Compound:** Estradiol/levonorgestrel (transdermal delivery system; Climara Pro<sup>®</sup>)  
**Sponsor:** Berlex Laboratories, Inc.  
**Submission Date:** February 28, 2005  
**From:** S.W. Johnny Lau, R.Ph., Ph.D.

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#### Background

The sponsor submitted NDA 21-885 to seek approval of the combination estradiol (E<sub>2</sub>) and levonorgestrel (LNG) transdermal delivery system 22 cm<sup>2</sup>, which contains 4.40 mg E<sub>2</sub> and 1.39 mg LNG (Climara Pro<sup>®</sup>) for the prevention of postmenopausal osteoporosis. Climara Pro<sup>®</sup> is approved for the relief of vasomotor symptoms due to menopause under NDA 21-258 with the Division of Reproductive and Urologic Drug Products (HFD-580).

#### Findings

- The sponsor referenced NDA 21-258's clinical pharmacology and biopharmaceutics information (agreed per October 13, 2004's preNDA meeting).
- The sponsor conducted a pivotal clinical safety and efficacy study (96041B/A09585) with the 22 cm<sup>2</sup> transdermal delivery system containing 4.40 mg E<sub>2</sub> without LNG (E<sub>2</sub> only patch). The E<sub>2</sub> dose was the same as that of the 22 cm<sup>2</sup> Climara Pro<sup>®</sup> patch.
- The sponsor also conducted a supportive clinical safety and efficacy study (12226/A10079) with the 22 cm<sup>2</sup> transdermal delivery system containing 4.40 mg E<sub>2</sub> + 2.75 mg LNG.
- The to-be-marketed formulation is different from the clinically-tested formulations but in vivo bioequivalence study between the clinically-tested and to-be-marketed formulations is not needed because:
  - Pivotal Study 96041B/A09585 provides efficacy and safety data for the E<sub>2</sub> only patch. The supportive Study 12226/A10079 provides safety and efficacy data for E<sub>2</sub> plus higher LNG delivery. Hence, this is  approach and the sponsor does not need to do in vivo bioequivalence study.
  - Per October 13, 2004's preNDA meeting, the sponsor provided in vitro dissolution data (individual, mean, SD, %CV) to substantiate the E<sub>2</sub> difference factor (f<sub>1</sub>) and similarity factor (f<sub>2</sub>) for the in vitro release of E<sub>2</sub> from the clinically-tested formulations (E<sub>2</sub> alone and E<sub>2</sub> + LNG) used in the pivotal and supportive studies to the to-be-marketed formulation.
- The sponsor also referenced an in vivo bioequivalence study (304180/6199) between the 4.40 mg E<sub>2</sub> + 1.39 mg LNG and 4.40 mg E<sub>2</sub> + 2.75 mg LNG transdermal delivery systems under NDA 21-258, which was reviewed by Dr. Ron Kavanagh.
- The sponsor provided proposed labeling for review.

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