

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-258**

**STATISTICAL REVIEW(S)**

## Statistical Consultation

Date: September 25, 2002

NDA #: 21-258

Applicant: BERLEX Laboratories, Inc.

Name of Drug: Climarapro (estradiol/levonorgestrel transdermal delivery system)

Indication: treatment of vasomotor symptoms associated with menopause

Document Reviewed: Response to non-approval letter

Statistical Reviewer: Kate Meaker, M.S. (HFD-715)

Medical Input: Phill Price, M.D. (HFD-580)

NDA 21-258 received a non-approval letter on June 27, 2001. One of the reasons was that DSI was not able to audit the eligibility criteria or the efficacy results because the source documents had not been retained at the sites. In this submission, Berlex provided information on the training of participants and validation of the phone data collection process (IVRS) used in the clinical trials. The purpose of this statistical consult is to provide feedback to the Medical Officers on the ability of this new submission to address the original concerns.

The first topic addressed by the sponsor is proof that subjects were able to use the IVRS system prior to study initiation to report the frequency and severity of vasomotor symptoms. Berlex covers the training of study site staff, and subjects using the system to create a PIN number. However, this does not provide evidence that, prior to starting the baseline recording period, subjects were able to accurately record and report their vasomotor symptoms. The baseline vasomotor symptoms were part of the entry criteria which could not be audited. Therefore this response does not adequately address that concern.

The other issue addressed in this submission is the attempts by Berlex to find any available daily diary sheets used by the subjects to record vasomotor symptoms prior to reporting the data using the IVRS system. Berlex submitted a total of 9 evaluable diary sheets from 3 subjects (2, 3, and 4 per subject) in the primary efficacy study 96042A. There were a total of 293 subjects enrolled in that study. The ability of 3 women who kept their diary records to accurately record the information in the IVRS system is not sufficient to draw conclusions about the ability of the other 290 women to accurately record their symptoms in the IVRS system.

Based on the evidence in this submission, it is my opinion that the initial concerns about the accuracy of the data on frequency and severity of vasomotor symptoms in Study 96042A have not been adequately addressed.

Katherine B Meaker, M.S.  
Mathematical Statistician

Concur: Dr. Welch

cc:

Archival NDA 21-258

HFD-580

HFD-580/PPrice, DShames

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Mike Welch  
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Concur with review.

**Statistical Review and Evaluation**  
**Clinical Studies<sup>1</sup>**

Date: 6/15/01

NDA #: 21-258

Applicant: BERLEX Laboratories, Inc.

Name of Drug: Climarapro (estradiol/levonorgestrel transdermal delivery system)

Indication: treatment of vasomotor symptoms associated with menopause

Documents Reviewed: Vol. 1.1, 1.2, 1.69-1.81

Statistical Reviewer: Kate Meaker, M.S. (HFD-715)

Medical Input: Phill Price, M.D. (HFD-580)

Summary of Studies

This application requested consideration of three Climarapro patch strengths:

- E<sub>2</sub> 4.4 mg + LNG 1.39 mg (22 cm<sup>2</sup>)
- E<sub>2</sub> 4.4 mg + LNG 2.75 mg (22 cm<sup>2</sup>)
- E<sub>2</sub> 4.5 mg + LNG 3.75 mg (30 cm<sup>2</sup>)

The submission contained two primary clinical studies to assess safety and efficacy. One study (96042A) compared the two higher doses to placebo, while the other included all three doses with an active-comparator arm (see Table 1).

Study 96042A was a 12-week study designed to assess efficacy for the treatment of moderate-to-severe vasomotor symptoms (MSVS) in postmenopausal women. It was a multicenter, randomized, double-blind study which used a double-dummy approach to blind the two different patch sizes. The treatment patches were to be worn for 7 days and replaced once a week. Each week the women applied two patches, one 22 cm<sup>2</sup> and the other 30 cm<sup>2</sup>, one of which was a blinded placebo. The four efficacy measurements are the frequency and severity of vasomotor symptoms at week 4 and week 12 on treatment. This information was collected in daily diaries.

Study 96043A was a 1-year study primarily designed to assess endometrial protection. This was also a multicenter, randomized, double-blind study which used a double-dummy approach to blind the two different patch sizes. The treatment patches were to be worn for 7 days and replaced once a week. Each week the women applied two patches, one 22 cm<sup>2</sup> and the other 30 cm<sup>2</sup>, one of which was a blinded placebo. The primary efficacy variable was the incidence of endometrial hyperplasia at 1 year. The four MSVS efficacy

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<sup>1</sup> Keywords: Clinical studies; data auditing/data integrity

variables were measured (using daily diaries) as secondary variables in only a subset of the patients.

Table 1: Summary of Randomized, Controlled, Clinical Studies

Study Number (Dates Conducted)	# of Centers (Locations)	Treatment Arms (# Randomized)	Study Design	Duration of Treatment
96042A (6/98 – 10/99)	32 (all U.S.)	Total n=293 E <sub>2</sub> 4.4 mg + LNG 2.75 mg (22 cm <sup>2</sup> ) n=96 E <sub>2</sub> 4.5 mg + LNG 3.75 mg (30 cm <sup>2</sup> ) n=104 Placebo n=93	Multicenter, Randomized, Double-blind, Double-dummy, Placebo-controlled, Parallel group	Three 28-day cycles; 12 weeks total
96043A (6/98 – 3/00)	73 (all U.S.)	Total n=845 E <sub>2</sub> 4.4 mg + LNG 1.39 mg (22 cm <sup>2</sup> ) n=212 E <sub>2</sub> 4.4 mg + LNG 2.75 mg (22 cm <sup>2</sup> ) n=211 E <sub>2</sub> 4.5 mg + LNG 3.75 mg (30 cm <sup>2</sup> ) n=213 E <sub>2</sub> 4.4 mg + placebo (22 cm <sup>2</sup> ) n=204	Multicenter, Randomized, Double-blind, Double-dummy, Active-controlled, Parallel group	Thirteen 28-day cycles; 1 year total

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## STUDY #96042A

### Background

Study 96042A was a 12-week study designed to assess efficacy for the treatment of moderate-to-severe vasomotor symptoms (MSVS) in postmenopausal women. It included the two higher Climarapro doses (E<sub>2</sub> 4.4 mg + LNG 2.75 mg (22 cm<sup>2</sup>); E<sub>2</sub> 4.5 mg + LNG 3.75 mg (30 cm<sup>2</sup>)) and a placebo comparator arm. The intent was to compare each of the Climarapro dose groups to the placebo group to meet the DRUDP guidance criteria for the vasomotor symptoms indication.

This study was multicenter, randomized, and double-blind and used a double-dummy approach to blind the two different patch sizes. The treatment patches were to be worn for 7 days and replaced once a week. Each week the women applied two patches, one 22 cm<sup>2</sup> and the other 30 cm<sup>2</sup>, one of which was a blinded placebo. The subjects were postmenopausal women, 45 years or older, who had at least 7 MSVS per day or 60 per week during the screening period. The subjects were randomized to one of the 3 treatment groups using a 1:1:1 ratio. They received treatment for 12 weeks.

The four co-primary efficacy variables were the frequency and severity of vasomotor symptoms at week 4 and week 12 on treatment. This information was collected in daily diaries. Each of the 2 Climarapro doses would be compared to placebo on all 4 endpoints. The protocol planned for a Bonferroni adjustment for the two sets of comparisons.

The study was adequately planned, with the appropriate patient population, sample size, and statistical plan. However, the sponsor changed the data collection procedure regarding the daily diary information. The subjects were to record vasomotor symptoms (hot flushes or sweats) on a paper diary, then report them using a phone recording system (IVRS). During the study, the sponsor changed the directions given to the study sites, resulting in the clinic staff not retaining the paper diaries. The agency was not notified of the change until the Division of Scientific Investigations (DSI) audited the sites.

The DSI investigator and the Medical Officers consider the paper diaries to be the source documents for the efficacy data. The diaries were also the basis for meeting inclusion criteria for the frequency of MSVS during the screening period. There is no way to verify the eligibility or efficacy results. Therefore the DSI review recommended that study 96042A not be used to support approval.

### Conclusions - Study #96042A

The efficacy results from this study could not be verified in the DSI audit. The Medical Officers agree with the DSI recommendation that the data from this study cannot be used to assess efficacy. No statistical review is needed for this study.

## STUDY #96043A

### Background

Study 96043A was a 1-year study primarily designed to assess endometrial protection. It included all 3 dose levels of Climarapro, along with an estrogen-alone active-comparator arm. It was a multicenter, randomized, double-blind study which used a double-dummy approach to blind the two different patch sizes. The treatment patches were to be worn for 7 days and replaced once a week. Each week the women applied two patches, one 22 cm<sup>2</sup> and the other 30 cm<sup>2</sup>, one of which was a blinded placebo.

Subjects were postmenopausal women, ages 45 to 75 with an intact uterus. Women who had at least 15 vasomotor symptoms (of any severity) in a week during the screening period were enrolled in a symptoms substudy. The frequency of symptoms required for entry into this symptoms substudy was lower (less conservative) than what is required for study with vasomotor symptoms as the primary objective.

The primary efficacy variable was the incidence of endometrial hyperplasia at 1 year. For each treatment arm a 95% confidence interval (CI) was used to assess the efficacy. The DRUDP guidance requires that the upper bound of the CI exclude 4% for each dose level.

The four MSVS efficacy variables were measured (using daily diaries) as secondary variables in only a subset of the patients (n=126 total). The entry criterion for this substudy was a minimum of 15 hot flushes of any severity over 7 days. That is much lower than the entry criteria for a vasomotor symptoms study of a minimum of 60 moderate-to-severe hot flushes over 7 days. The patient population in the substudy would not adequately address efficacy for the vasomotor symptom indication. Also, as in study 96042, the paper diary forms were not retained at the clinics, so that data cannot be assessed.

A total of 845 patients were randomized to the four treatment groups. There was a fairly high dropout rate (47% overall) during the study, primarily due to adverse events (see Table 2). For the endometrial hyperplasia analysis, the applicant defined two types of withdrawals. A Type I withdrawal referred to a subject who withdrew prematurely and no post-baseline biopsy data was available, either because a biopsy wasn't done, or there was insufficient tissue to assess. A Type II withdrawal referred to a subject who withdrew prematurely and had a post-baseline biopsy which showed no evidence of endometrial hyperplasia.

Table 2: Subject Disposition: (Study #96043A)

	E <sub>2</sub> 4.4 mg + LNG 1.39 mg (22 cm <sup>2</sup> )	E <sub>2</sub> 4.4 mg + LNG 2.75 mg (22 cm <sup>2</sup> )	E <sub>2</sub> 4.5 mg + LNG 3.75 mg (30 cm <sup>2</sup> )	E <sub>2</sub> 4.4 mg + placebo (22 cm <sup>2</sup> )
Randomized	213 (100%)	212 (100%)	216 (100%)	204 (100%)
All Treated	212 (99%)	211 (99%)	213 (99%)	204 (100%)
Discontinued	99 (47%)	104 (49%)	100 (47%)	89 (44%)
Adverse Event	69 (33%)	66 (31%)	66 (31%)	55 (27%)
Other	30 (14%)	38 (18%)	34 (16%)	34 (17%)
Completed Treatment	113 (53%)	107 (50%)	113 (52%)	115 (56%)
Type I Withdrawals	63 (30%)	71 (33%)	67 (31%)	53 (26%)
Type II Withdrawals	45 (21%)	46 (22%)	44 (20%)	38 (19%)

Source: Vol. 1.74, Text Tables 7, 11, 18 and 19.

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### Endometrial Protection Analysis

The applicant calculated 95% 2-sided confidence intervals (CI) on the incidence rate of endometrial hyperplasia for each of the four treatment groups. The CI were calculated once using only Type I Withdrawals, and again using both Type I & II Withdrawals. These results are shown in Table 3. The applicant's analyses are appropriate, and I confirmed the applicant's results.

The results when the Type I Withdrawals are dropped are the main focus. For each of the Climarapro treatment groups the upper bound of the CI is less than 4%, which meets the DRUDP criteria for endometrial protection. The second analysis, dropping both the Type I & II Withdrawals is a more conservative approach, and still the results meet the criteria.

Table 3: Applicant's Results: (Study #96043A)

	E <sub>2</sub> 4.4 mg + LNG 1.39 mg (22 cm <sup>2</sup> )	E <sub>2</sub> 4.4 mg + LNG 2.75 mg (22 cm <sup>2</sup> )	E <sub>2</sub> 4.5 mg + LNG 3.75 mg (30 cm <sup>2</sup> )	E <sub>2</sub> 4.4 mg + placebo (22 cm <sup>2</sup> )
Intent-to-Treat	N=210	N=209	N=209	N=201
<b>Exclude Type I Withdrawals:</b>				
N	147	138	142	148
# Cases	0	0	0	19
Incidence Rate	0.0%	0.0%	0.0%	12.8%
95% CI	(0.0%, 2.5%)	(0.0%, 2.6%)	(0.0%, 2.6%)	(7.1%, 18.6%)
<b>Exclude Type I &amp; II Withdrawals:</b>				
N	102	92	98	110
# Cases	0	0	0	19
Incidence Rate	0.0%	0.0%	0.0%	17.3%
95% CI	(0.0%, 3.6%)	(0.0%, 3.9%)	(0.0%, 3.7%)	(9.8%, 24.8%)

Source: Vol. 1.74, Text Tables 18 & 19.

### Conclusions - Study #96043A

The results for the incidence of endometrial hyperplasia meet the criteria to support the endometrial protection issue for hormone replacement therapy. Specifically, the upper bound on the 95% confidence interval for each of the three Climarapro doses was less than 4%.

The vasomotor symptom data collected in a substudy of patients from 96043A could not be verified because the source documents had not been retained. Therefore those results were not reviewed here. This study cannot provide any support for the vasomotor symptom indication.

Summary

The primary efficacy endpoints for the vasomotor symptoms indication are the frequency and severity of moderate-to-severe vasomotor symptoms (MSVS) at week 4 and week 12 on treatment. In both studies submitted in this application, this information was recorded by the patients on paper daily diaries, then collected using a phone system. However, the clinic staffs at the sites did not retain the paper diaries. This was not specified in the protocols, and the agency was not notified. The DSI investigator was not able to audit the eligibility criteria or the efficacy results, and concluded that the diary data from both of these studies should not be used to support this indication.

There is insufficient evidence to support this application for the vasomotor symptom indication. A well-designed, placebo-controlled, 12-week vasomotor study is needed to assess the efficacy endpoints. The endometrial protection data from study 96043 is sufficient to meet the DRUDP guidance for that safety endpoint.

Katherine B Meaker, M.S.  
Mathematical Statistician

Concur: Dr. Nevius

Dr. Welch

cc:

Archival NDA 21-258

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HFD-580/PPrice, SAllen

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HFD-715/ENevius, MWelch, KMeaker, CAnello

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Concur with review.

NDA 21-258

Climarapro™ (estradiol transdermal system) estradiol/levonorgestrel 0.045/0.015, 0.045/0.030  
and 0.045/0.040 mg per day

Berlex laboratories, Inc.

**Statistics review(s) and memoranda regarding dissolution and/or stability**

The statistical review of drug stability is included in the Chemistry review dated May 7 2001

*Aiane Moore 6/11/01*