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*APPLICATION NUMBER:*

**21-258**

**MEDICAL REVIEW(S)**

Medical Officer's Summary of NDA Supplement

NDA 20-258 N-000

Name of Drug: Climara Pro™ (estradiol/levonorgestrel transdermal system)

Sponsor: Berlex

Proposed Clinical Use: Treatment of Moderate to Severe Vasomotor Symptoms Associated with the Menopause

Dosage/Form/Route: 0.045 mg estradiol/0.015 mg levonorgestrel administered daily via a transdermal 22 cm<sup>2</sup> system in a continuous combined regimen. The transdermal system is intended to be applied once weekly for all four weeks of a 28-day cycle.

Date of Submission: September 19, 2003

Re: COMPLETE RESPONSE TO NON-APPROVAL LETTER

On September 19, 2003, the sponsor submitted a complete response to the October 8, 2002 non-approvable action letter. The following three items were included:

1. Copies of Facsimiles submitted to the Agency on August 4, 8 and 20, 2003 providing justification for the 0.015 mg levonorgestrel dose, justification for the 0.045 mg estradiol dose, and a statement to be contained in the label relative to the lowest effective dose. A timeline for a Phase IV vasomotor symptoms study was included in the August 20, 2003 fax.
2. Labeling, revised to include the post-WHI study information recommended by the Agency, as well as the lowest effective dose statement included in the August 4, 2003 fax. The labeling submitted includes only the 0.045 mg estradiol/0.015 mg levonorgestrel dosage strength. The Sponsor stated that they were seeking approval for only this lowest dosage strength, and that references to the two higher dosage strengths (0.045 mg estradiol/0.030 mg levonorgestrel and 0.045 mg estradiol/0.040 mg levonorgestrel) had been removed except in circumstances where reference to bioequivalence of the 0.045 mg estradiol/0.015 mg levonorgestrel dose to the 0.045 mg estradiol/0.030 mg levonorgestrel dose was necessary. In addition, Clinical Pharmacology information relating to levonorgestrel was added to labeling.
3. A brief safety update, presenting a summary of safety data from additional estradiol/levonorgestrel transdermal system studies which were conducted in the US and Europe in the period since submission of the original NDA on June 29, 2000.

Reference is made to a telephone conference between the Division Director and Berlex. During that telecon an agreement was reached between the Division and Berlex to reevaluate the IVR system in the review of this product. Refer to the "Division Director's Summary Review of NDA 21-258. Since the decision is to approve this product, from the medical officer's perspective, my present review will concentrate on this supplement which has been recorded as a complete response:

1. The dosage form to be marketed vs. the dosage form which was studied in the 12- week vasomotor symptom study (VMS), study 96042A.
2. Revised labeling submitted on September 19; this has been reviewed and modified.
3. The sponsor's safety update that reports all safety data received by the sponsor from January 2000 to July 2003.

### Dosage Forms

Reference is also made to my 3 previous reviews of Climara Pro™ dated June 26, 2001, February 2, 2002 and February 6, 2003. In the February 6, 2003 review, the safety and efficacy review of (estradiol 0.045mg and levonorgestrel 0.030mg) was finalized. This study (96042A) was a 12-week randomized placebo-controlled study that compared estradiol 0.045mg/levonorgestrel 0.030mg to placebo. In this study, the sponsor used the IVR system to document vasomotor symptoms (VMS) not the original source documentation that was a previous source of dispute between the Division and Berlex. The 0.045 estradiol and levonorgestrel 0.030mg was shown to be statistically significantly better than placebo at weeks 4 and 12 in the relief of moderate to severe VMS. However, the to-be-marketed product, Climara Pro™ (estradiol 0.045mg and levonorgestrel 0.015mg) was not studied in study 96042A. To demonstrate that the estradiol 0.045mg and levonorgestrel 0.015 is bioequivalent to the estradiol 0.045 and levonorgestrel 0.030 the sponsor conducted 2 bioequivalence studies. Refer to the Biopharmaceutics section in the approval document. The conclusion of Biopharmaceutical reviewer was that the two dosage strengths are bioequivalent with respect to estradiol.

### Product Labeling Review

Labeling modified in accordance with the Agency's 2003 draft labeling guidance entitled, "Labeling Guidance for Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy symptoms – Prescribing Information for Health Providers and Patient Labeling" was submitted on September 19, 2003. The labeling submitted includes only the 0.045 mg estradiol/0.015 mg levonorgestrel dosage strength.

Minor revisions were added to the **BOXED WARNING**, the **CLINICAL PHARMACOLOGY** section, and **Pharmaceutics** subsection. The sponsor updated Table 1: Summary of Mean Pharmacokinetic Parameters and incorporated information relating to levonorgestrel.

Significant revisions have been made to the proposed label. They include the **CLINICAL PHARMACOLOGY** section and **Clinical Studies** subsection. The sponsor revised Tables 2 and Table 3 under **Effects on vasomotor symptoms** and Figure 1 under **Effects on Uterine Bleeding or Spotting**.

In the **Indications** sections, the sponsor removed:

The \_\_\_\_\_ subsection has been deleted. In the Women's Health Initiative (WHI) Study, combination estrogen with progestin therapy

increased the level of high-density lipoprotein (HDL) and lowered the level of low-density lipoprotein (LDL), yet no beneficial effect on the development or progression of coronary artery disease was detected. — has been deleted.

As of November 21, 2003, the Division and Berlex are in concurrence with a final draft label.

### **Safety Update**

The sponsor has submitted a safety update form January 2000 to July 2003. These dates correspond to the cut-off date for inclusion of data into NDA21-258 and the finalization date of the study report of the latest completed study 96113 (report A10079).

This safety update describes only new data obtained during this interval. SAE narratives are included in the SAE section of the studies. One study (protocol #98189) was conducted in the US; the others were conducted in Europe. The studies are listed as follows:

- Study 98189 (report A01918) – 1 year extension of study 96043A on endometrial safety and bleeding patterns (report B529)
- Study 98073 (report B151) – bleeding pattern and metabolic parameters compared to Evorel conti®
- Study 303123 (report A10078) – 1 year extension of study 98073 on endometrial safety and bleeding pattern (report B151); and
- Study 96113 (report A10079) – prevention of osteoporosis over 2 years.

### **Study 98189**

Of primary importance to this review is the extension study (Protocol 98189) a 1-year extension study of study 96043A. This was a multicenter comparison of continuous transdermal estradiol/levonorgestrel combinations examining the effect on the endometrium and bleeding patterns in previously randomized postmenopausal women who had completed 13 cycles of estradiol/levonorgestrel hormone therapy.

Transdermal continuous combined estradiol/levonorgestrel treatment was continued in 172 subjects who successfully completed 13 cycles in the initial study 96043A. This study was extended to fulfill the European HRT Guidelines with regard to the number of biopsies required. The mean age of the subjects was between age 54 and 56. Three groups received patches containing either E<sub>2</sub> 4.4mg + LNG 1.39mg (60 subjects), E<sub>2</sub> 4.4mg + LNG 2.75mg (53 subjects) or E<sub>2</sub> 4.5mg + LNG 3.75mg (59 subjects) for 13 28-day cycles.

As reported in the primary US endometrial protection study, the most frequently reported AEs in all treatment groups were application site reactions, vaginal bleeding (vaginal bleeding is coded as vaginal hemorrhage in European study reports pertaining to this safety report) and upper respiratory tract infections. Application site reaction was experienced between 36.7% and 49.1% of subjects in the 3 treatment groups; vaginal bleeding was experienced by 22.6% and 32.2% of subjects in the 3 treatment groups. A total of 43 (25%) of 172 subjects experienced AEs of severe intensity during treatment.

There was 1 SAE in a subject on the E<sub>2</sub> 4.5mg + LNG 3.75mg. This subject (#51013) had an enlarging uterine fibroid. The subject underwent a TAH/BSO; pathological specimen revealed no evidence of hyperplasia or dysplasia.

No deaths were reported.

No subjects in any of the 3 E<sub>2</sub>/LNG groups had endometrial hyperplasia and/or cancer during the course of the initial and extension studies. The distribution of endometrial biopsy categories across groups was similar. Most patients had atrophic endometrium. Two patients had polyps. No cases of breast cancer were reported.

### **Studies 98073, 303123 and 96113**

The studies listed above will be reviewed in a combined manner rather than separately because these studies were conducted outside the US and most importantly, these studies enrolled patients who did not use Climara Pro (estradiol 4.4mg + LNG 1.39mg) but used instead the 2 higher dose formulations (estradiol 4.4mg + LNG 2.75mg and estradiol 4.5mg + LNG 3.75mg) for which approval is not being sought.

In reviewing these 3 studies AEs are consistent with those seen in the US clinical trials that is, application site reactions and vaginal hemorrhage are seen in a significant number of patients. However, in Protocol 98073 three cases of breast cancer were reported and one case of endometrial cancer where reported. The endometrial cancer case is important because this is the first case where hyperplasia or cancer was reported in any estradiol/levonorgestrel formulations. In essence, no prestudy endometrial biopsy was performed in a patient who had previously been on hormone therapy for 4 years. She took E<sub>2</sub> 4.5mg + LMG 3.75mg for 6 months but discontinued secondary to continued bleeding. This SAE is considered possibly related to study drug although a causal relationship is unlikely do to the induction time needed to develop endometrial cancer.

In Protocol 303123 the most frequent AEs were application site reactions, back pain, enlarged uterine fibroids, and arthralgia. There was one case of ovarian cancer diagnosed 9 months after beginning treatment. This is probably not related to hormone therapy. No cases of endometrial hyperplasia were reported and no deaths were reported.

In Protocol 96113 the most frequent AEs were application site reactions, vaginal hemorrhage, breast pain and respiratory tract infections. There was a total of 13 SAEs. Of this total 5 were reported in the placebo group with one case being reported as deep vein thrombosis. There were two cases of benign ovarian neoplasm.

There was one death in this study in the E<sub>2</sub> 4.4mg + LNG 2.75mg who died with an elevated blood alcohol level and methadone and diazepam in her blood stream. This case was presumed to be chronic alcoholism with a contribution of methadone drug abuse based on the medical-legal autopsy results. There appeared to be no known relationship to study drug and the final diagnosis suggest suicide.

In conclusion, no AEs or SAEs are reported in this Safety Update that is at an increased incidence or frequency than was reported in the US primary efficacy studies. There was one reported death. The cause of this death was presumed to be chronic alcoholism with a contribution of methadone. Application site reactions and vaginal hemorrhage were the most common reasons for discontinuation from these studies. Overall, the information in this Safety Update is consistent with the safety profile in the original NDA 21-258.

#### Conclusion

From this reviewer's viewpoint, this product remains non-approvable. Review of IVRS data from study 96042A appears to show that 0.045mgestradiol/0.030mg is statistically significantly better than placebo in the relief of moderate to severe vasomotor symptoms. Submitted worksheet data from the sponsor's did not verify the IVRS data from this study. Baseline data (placebo run-in period prior to 12 weeks of treatment are not verifiable because there is *no linkage* between worksheet data and data submitted in the IVRS. In the 3 worksheets submitted from study 96042A worksheet data was only verifiable for 1 placebo patient. Submitted statistical concordance data relating to VMS did not appear valid and was driven by this 1 placebo patient.

Submission of worksheet data from study 96043A to support VMS is not appropriate because this study enrolled a different patient population, data related to VMS collected was collected as a secondary endpoint, and the use of this data would only be considered exploratory since the study was not designed as a primary VMS study. Statistical concordance data is not appropriate because VMS were a small fraction of the overall total data.

#### Recommendation

This reviewer does not recommend approval of this product. The decision to approve this product rests with the Division Director.

Phill H. Price, M.D.  
November 21, 2003

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Phill H. Price  
11/21/03 11:45:27 AM  
MEDICAL OFFICER

## Division Director's Summary Review of NDA 21-258

### 1.0 BACKGROUND

In NDA 21-258, the sponsor sought approval for a combination estrogen/progestin patch. Two controlled clinical studies, 96042 and 96043, were submitted in support of this application. They were:

Study 96042, a multicenter, randomized, double-blind, placebo-controlled, parallel-group 3-armed study designed to evaluate two dose levels of E2/LNG for 3 continuous 28-day treatment cycles compared to placebo for the treatment of VMS associated with the menopause. The three arms were 45µgE2/40µg LNG, 45µg E2/30µg LNG and placebo.

Study 96043, a 1-year, multicenter, randomized, double-blind, parallel-group, 3-armed study in non-hysterectomized women that was designed to evaluate the safety and efficacy of the E2/LNG combination patch in the prevention of the development of endometrial hyperplasia.

### 2.0 REGULATORY HISTORY OF NDA 21-258

NDA 21-258 was submitted on June 29, 2000. The application was not approvable on June 27, 2001. Deficiencies included non-acceptance of study 96042 (VMS study) in support of safety and efficacy due to inability to verify study data because source documentation for the studies was not available.

The investigators gathered data for study 96042 by patient worksheets for the run-in and first cycle of the study (5 weeks) and Interactive Voice Recording system (IVRS) for the entire 12-week study. The IVRS was a touch-tone telephone system study subjects used to report their symptoms. The reviewers' were concerned that the study data could not be validated against the source data (worksheets) because they were unavailable at the primary investigator's sites (as per the inspection by the Division of Scientific Investigation (DSI)). Therefore, because the reviewers believed that there was no way to validate the link between the patient worksheets (considered source documents) and IVRS, Berlex was asked to perform a new study.

Rather than conduct a new VMS study, Berlex requested formal dispute resolution as to what constituted source documentation for data generated by study 96042. The sponsor maintained that the worksheets were not source documents but merely aids in the beginning of the study for the patients and not required for recording of data in the IVRS system.

The response to the appeal informed Berlex that according to the protocol for study 96042, the worksheets were the source documentation for the "run-in" phase and cycle 1 of the treatment phase. Berlex was offered three options to address the data validation

issue: 1) submit a new clinical study, 2) submit documentation that subjects were assessed before entering the study, on their ability to successfully use the IVRS to accurately report the frequency and severity of their vasomotor symptoms and that the IVRS could reliably capture the data, and 3) submit an analysis of data from any worksheets that could be located to show that data in the IVRS could be verified.

Berlex responded to options 2 and 3 above, on April 8, 2002. The medical officer found the response insufficient because 1) information submitted regarding the instruction given to subjects on how to access the IVRS and the subjects successful access of the IVRS to receive a PIN number did not demonstrate the subject's ability to successfully enter a complex set of data such as vasomotor symptoms which can occur frequently and at varying intensities several times a day and 2) the 10 worksheets from three subjects that were located were too few to adequately demonstrate a correlation between the worksheets and data entered into the IVRS. A not approvable letter was issued on October 8, 2002 that reiterated the lack of validation of data for study 96042 and again requested submission of another clinical study

After the October 8, 2002 not approvable action, Berlex again requested reconsideration of the IVRS as a validated instrument for capturing vasomotor symptom data for study 96042. As part of the response to this request, the medical officer completed review of the data supporting efficacy and safety of Climara Pro. The reviewer concluded that study data showed that 45µgE2/40µg LNG and 45µg E2/30µg LNG were statistically significantly better than placebo in the relief of moderate-to-severe vasomotor symptoms but that the lowest effective doses for both the E2 and LNG components had not been identified and that concerns regarding validation of the data against source documentation remained an issue. In addition, the reviewer also commented that the IVRS script of questions to elicit subject responses on study drug (patch) use and VMS symptoms had changed.

The Division and Office continued to communicate with Berlex regarding the issues identified by the medical officer by letter on February 19, 2003 and teleconference on February 26, 2003. Specifically, Berlex was notified of the following issues which required resolution:

1. Data integrity, worksheets versus IVRS
2. Lowest effective dose for E2 and LVG
3. Change of IVRS script
4. DMF review

### **3.0 REVIEW**

Berlex responded to the above issues in their March 18, 2003, submission to NDA 21-211. The following is a review and conclusions regarding each of these issues.

### 3.1 Data integrity, worksheets versus IVRS

With regard to trial 96042, a key issue was whether the worksheets represented source documents or not. I believe that review of the protocols and instructions to investigators for trial 96042 were unclear as to the primary purpose of worksheets. I believe that the conclusion (that the data was invalid because of lack of source documentation which would link the worksheet and IVRS information) by the reviewers of the original submission, which resulted in the June 27, 2002, not approvable, was appropriate.

The sponsor responded to the not approvable action (April 8<sup>th</sup>, 2002) by submitting information to support a linkage between the worksheet and IVRS data. They submitted 3 worksheets from study 96042 (study in question) and 10 or less from another study (96043). Although the sponsor concluded that there was 98% correlation between worksheet and IVRS data, I agree with the reviewers that the information was insufficient to support the sponsor's conclusions.

As part of the continuing evaluation of this issue, the Division requested information from the sponsor to explore whether data produced through study subject use of an IVRS to record VMS symptoms or symptoms of equivalent frequency and complexity, could independently provide substantial evidence to demonstrate data integrity for study 96042.

In response to this request, on March 18, 2003, the sponsor submitted information from trials 97074 and 97075, conducted in support of safety and efficacy for Climara (estradiol transdermal system), to demonstrate significant correlation between worksheet and IVRS data.

The Climara application, NDA 20-375, submitted by 3M Pharmaceuticals for Climara 50 µg/day and 100 µg/day estradiol transdermal systems was approved on December 22, 1994. The approved indications were:

1. Treatment of moderate to severe vasomotor symptoms associated with the menopause.
2. Treatment of vulvar and vaginal atrophy.
3. Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure.
4. Treatment of abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology and only when associated with a hypoplastic or atrophic endometrium. Indications 2, 3, and 4 were granted based on estrogen class labeling.

All rights to NDA 20-375 was transferred to Berlex Laboratories on November 2, 1995. Berlex received subsequent approvals for additional strengths and indications for Climara through the following supplements to NDA 20-375:

1. Supplement 009 for a 75 mcg/day dose for the treatment of moderate-to severe vasomotor symptoms (VMS)—approved march 23, 1998.

2. Supplement 011 for a 25 µg/day for the prevention of postmenopausal osteoporosis—approved March 5, 1999.
3. Supplement 016 for 25µg/day for treatment of VMS—approved April 5, 2001.

Data submitted in support of the original NDA and supplement 009 were reported by study subjects in the conventional way—using paper worksheets or diaries.

The sponsor conducted two new clinical investigations to support the approval of supplement 016. These studies are: A) study 97074, a multi-center, double-blind, placebo controlled, randomized study to determine efficacy in the relief of hot flushes in women receiving transdermal estradiol (25µg/day) or placebo patch.; B) study 97095 a multi-center, double-blind, active-controlled, randomized study to determine efficacy in the relief of hot flushes in women receiving transdermal estradiol (25µg/day) compared to oral Premarin 0.3mg/day.

Both studies were for 12-weeks duration. Three hundred seventy-nine subjects (379) were randomized with 187 receiving E2 TDS, 98 receiving conjugated estrogens and 94 receiving placebo. Study results show E2 TDS to be statistically significantly better than placebo in the relief of hot flushes by the fourth treatment week and this treatment effect was maintained for the remaining 8 weeks of treatment. Study 97095 showed E2 TDS 25µg/day to have similar efficacy results when compared to conjugated equine estrogens at 0.3mg/day. The regulatory conclusion, in March, 2001, was to approve NDA 20-375 S 016, (25mcg/day E2 TDS) for VMS based on the submitted data.

The primary medical officer stated in his review (03/26/01) that “In both trials submitted in the NDA 20-375/S016 during the screening period, subjects were given a daily worksheet card to record weekly observations of urogenital symptoms. The subjects were also instructed to use the Interactive Response System (IVRS) to record the daily number and severity of hot flushes during the screening period as well as the study treatment period.” In other words, the data recorded for these trials were from the IVRS. In an email response to inquiries by the DRUDP Division Director, Berlex confirmed (May 15, 2003) that “The NDA data from both studies (97074, 97095) was obtained via IVRS only, not from paper worksheets.”

A DSI audit of study data was conducted for the original NDA for Climara (NDA 20-375) which confirmed data integrity and served as part of the basis for approval of that application. Consistent with CDER policy, a DSI audit was not requested for supplement 016 as the risk-benefit considerations were comparable to the already approved use in treating VMS, and the data produced by the supporting studies were consistent with data previously submitted to the NDA and earlier efficacy supplements.

For each of the two Climara studies, Berlex located original worksheets and conducted an analysis to support that the IVRS produced data were comparable to the worksheet data and included the worksheets and analysis in the March 18, 2003 submission to the ClimaraPro NDA (21-211). The submission contained 84 separate “data fields” (three data fields per day to capture “mild”, “moderate”, and “severe” hot flushes on each of 28

days). For each worksheet located, data was cross-checked in comparison to the data recorded in IVRS for that particular day. The data was considered "verified" if there was an entry for the type of hot flush for a particular field in both the worksheet and IVRS. If the data was "verified" then a determination was made as to whether the data in the worksheet field "matched" the data in the IVRS field.

For study 97074, 10 study sites responded with worksheets from 47 subjects and a total of 134 worksheets. An analysis revealed 9,246 data fields of these 9,104 "matched" (data in the worksheet and IVRS were the same in each field) for a matching rate of 98.5%. In study, 97095 6 study sites found worksheets from a total of 31 subjects. There were 3,531 "verified fields" and 3,405 matched for a rate of 96.4%.

Descriptions of the IVRS used in supplement 016 for NDA 21-258 and the IVRS used in NDA 21-258 provided by Berlex, support that the systems were virtually identical in function and method of use. Consistency between data recorded in the IVRS for Climara, supplement 016 (NDA 20-375) and data submitted to the original Climara NDA (20-375) and supplement 009 (NDA 20-375) support that study subjects can successfully report their VMS symptoms using the IVRS. Thus, the similarity between the IVRS systems and the successful use of the IVRS to record VMS symptoms for Climara support acceptability of the VMS data recorded through the IVRS for ClimaraPro.

As further support for the validity of the data recorded by the IVRS used in NDA 21-258, the division asked DSI to inspect the IVRS utilized in Berlex Study 96042 which was maintained by \_\_\_\_\_ (The original DSI inspection did not examine the IVRS but only the worksheets which were considered the source documents).

The DSI inspector stated that "The investigation indicated that audit trails were maintained by having each diary entry date, time and user stamped. Original data was maintained and coded to indicate whether an edit or deletion of the date was made. Data entry was limited to the study subject through the use of a PIN number selected by the subject in conjunction with valid site identification, protocol identification, and user access number. Subjects could modify diary entries retrospectively up to three days later. Such revisions are user, date and time stamped."

The inspector concluded that "The computer system, as inspected and used in the collection of data for this protocol by your firm ( \_\_\_\_\_ ), adheres to the requirements of computer systems as outlined in 21 CFR Part 11."

Conclusion: The IVRS data from trial 96042 is valid and the study results support the claim that 45µgE2/40µg LNG and 45µg E2/30µg LNG are efficacious for the treatment of VMS associated with the menopause.

### 3.2 Lowest Effective Dose.

It has been the policy of DRUDP to encourage sponsors to determine, in their drug development programs, the lowest effective doses (LED) for both the estrogen and progestin components of post-menopausal symptom therapy. This policy was described in the 1995 Guidance for industry for clinical evaluation of estrogen and progestin containing products for these indications and reiterated in the January 2003 published draft guidance on this subject. This policy was adopted because of the probability that thromboembolic events and endometrial hyperplasia are dose-related to estrogen therapy and the possibility that other serious adverse events such as breast cancer and myocardial infarction may be dose-related. Although adding progestins to estrogens decreases the risk of endometrial hyperplasia in postmenopausal women, the addition of progestins to estrogen therapy may be also be associated with increases in the risk of serious adverse events, such as breast cancer, thromboembolic events, and myocardial infarction.

The publication of data beginning in July of 2002, from the Women's Health Initiative Trials (WHI) heightened concerns about the safety of the use of hormonal therapy in post-menopausal women. The combination therapy arm of the WHI study was stopped early because the risks exceeded the benefits.

At that time, the division had several estrogen/progestin products under review and others in development that had not demonstrated lowest effective dose for one or both components. In addition, there were marketed products that may have also failed to demonstrate lowest effective dose. The Division has safety concern regarding administering higher than necessary doses of estrogen or progestin for treatment of post menopausal symptoms.

After consultation with the senior management of CDER, the division decided to manage the risk of combination post menopausal hormone therapy by evaluating data from all marketed and developing products to determine the whether LED had been determined. If LED had not been determined then labeling that notifies both prescribers and users of this fact would be requested. This labeling could be eliminated if data are provided that demonstrate LED for the particular combination product.

In the case of 45µg E2/15µg<sup>1</sup> LNG dose of Climara Pro (the dose approved in NDA20-375), it is clear the LED of the E2 component is not included in this product as the 25 µg Climara dose has been determined to be effective and is approved. As mentioned above, Study 96043, which was designed to evaluate the safety and efficacy of the E2/LNG combination patch in the prevention of the development of endometrial hyperplasia demonstrated that the 45µgE2/40, 30 or 15µg LNG were all equally effective for endometrial protection. Therefore, the sponsor will be encouraged to provide data or perform studies that demonstrate the LED for both the E2 and LNG components of ClimaraPro.

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<sup>1</sup> 45µg E2/15µg LNG was found to be bioequivalent to 45µgE2/30µg LNG by the office of Clinical Pharmacology and Biopharmaceutics in terms of the E2 component. Since 40, 30, and 15µg of LNG were all found to be equally effective in protecting the endometrium, 15µg LNG was considered most appropriate for the progestin component for the marketed product.

Conclusion: Further study of LED for both the E2 and LNG components can be addressed in phase 4 (postmarketing). Wording that informs the prescribers and patients that the approved dose is not the LED should be inserted in labeling.

### 3.3 Change of IVRS script

In study 96042A, subjects were asked to provide information on paper worksheets for the initial part of the study and through the IVRS for the entire study relating to their use of the study drug (patches), adherence of the patches, their vasomotor symptoms, and urogenital symptoms. Information on patch use and adherence was used to assess subject compliance. The questions relating to patch use and adherence and one question on urinary symptoms were changed in January 1999. The changes relating to patch use and adherence clarified for the subject to differentiate whether a patch replacement was because of non-adherence or due to the pre-planned weekly replacement. The revision to the question on urinary symptoms clarified that the response was a weekly, rather than daily, accounting of symptoms (urogenital symptom questions were only asked once a week).

The paper worksheet that was used by subjects during the study run-in phase (up to 4 weeks) and cycle 1 (first 4 weeks after randomization) provided space to record the same daily vasomotor and weekly urogenital symptoms as the IVRS questions. The worksheet also included definitions for degrees of menstrual bleeding and hot flushes. The worksheet was not revised when the IVRS script was because the worksheet did not prompt subjects to respond to adherence-related questions.

Out of 293 subjects, after randomization, 110 heard only the original script questions when using the IVRS, 141 heard only the revised script questions, and 42 were participating in the study before and after the script change. Of the 42, 6 experienced less than 4 weeks (1 cycle) of IVRS use after randomization but before the script change.

#### Conclusions:

- Since there was no mismatch between information on the worksheet and the IVRS script questions before or after they were revised, it was not a potential source of confusion.
- The revisions to the IVRS script did not include changes to the VMS questions so there was no impact on these data.
- The revisions to the IVRS script addressed patch use and adherence to assess compliance. Compliance with the drug regimen was not identified as an issue that could affect approvability.
- Only 6 subjects experienced the script change within 4 weeks of starting patch use so even if the changes were confusing to them (i.e., they might not have had enough time to feel completely comfortable with study procedures), temporary problems with data entry into the IVRS for the revised questions would not affect study outcomes.

Therefore, this issue does not impact on data validity for trial 96042.

### 3.4 DMF

This issue is resolved, see CMC review.

### 3.5 Next steps

The sponsor was informed that the above 4 items had been resolved and informed that a complete response to the October 8, 2002, not approvable letter need only include revised product labeling. On September 22, 2003, Berlex submitted their complete response. See MO and team leader reviews of the product labeling.

## **4.0 REGULATORY ACTION**

An approval letter will be sent to BERLEX for NDA 21-258, for CLIMARPRO 45µg E2/15µg LNG dose for treatment of moderate to severe vasomotor symptoms associated with the menopause.

Daniel A. Shames MD  
Director,  
Division of Reproductive and Urologic Drug Products  
CDER/FDA  
11/17/03

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**Climara Pro™ Team Leader Secondary Review****NDA 21-258**

**Proposed Tradename:** Climara Pro™ (Estradiol and Levonorgestrel Matrix Transdermal System)

**Sponsor:** Berlex Laboratories, Inc.  
340 Changebridge Road  
P.O. Box 1000  
Montville, NJ 07045-1000

**Proposed Indication:** Treatment of moderate to severe vasomotor symptoms associated with the menopause.

**Proposed Claim:**

**Dosage/Form/Route:** 0.045 mg estradiol/0.015 mg levonorgestrel administered daily via a transdermal 22 cm<sup>2</sup> system in a continuous combined regimen. The transdermal system is intended to be applied once weekly for all four weeks of a 28-day cycle.

**Date of Class 1 Resubmission:** September 19, 2003  
**Addendum to Clinical NDA Review:** February 6, 2002  
**Original Clinical NDA Review:** June 26, 2001

**Date of Memorandum:** November 20, 2003

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**Background and Regulatory History**

NDA 21-258 was originally received on June 29, 2000 and filed on August 28, 2000 for the treatment of moderate to severe vasomotor symptoms (VMS) associated with the menopause. The results of two Phase III clinical trials were submitted for review. The primary objective of 12-weeks placebo-controlled Study 96042A was to determine the effectiveness of continuous combined administration of two dosage strengths of estradiol/levonorgestrel (0.045 mg estradiol/ 0.030 mg levonorgestrel and 0.045 mg estradiol/0.040 mg levonorgestrel) compared with placebo in decreasing the frequency and severity of vasomotor symptoms in postmenopausal women. The primary objective of 12-month Study 96043A was to evaluate the effectiveness of three dosage strengths of continuous combined estradiol/levonorgestrel (0.045 mg estradiol/0.015 mg levonorgestrel, 0.045 mg estradiol/0.030 mg levonorgestrel, and 0.045 mg estradiol/0.040 mg levonorgestrel) compared to continuous estradiol alone to protect the endometrium from estradiol-induced endometrial hyperplasia or cancer.

Three clinical sites were inspected by the Division of Scientific Investigations (DSI) during the original review cycle of NDA 21-258. Per the DSI report, protocol-specified worksheets (which DSI regarded as source documents) used for recording daily hot flush number and severity, vaginal bleeding or spotting or adverse events were unavailable for review for Study 96042A and Study 96043A. Data for Study 96042A was collected using paper worksheets during the two-week run-in phase and during the first 4 weeks of treatment. Thereafter, an Interactive Voice Response System (IVRS) was used. The DSI recommended

that the IVRS-alone data not be considered for the treatment of moderate to severe vasomotor symptoms associated with the menopause indication.

On June 27, 2001, the Sponsor received a non-approvable action letter from the Agency. The deficiencies were summarized as follows:

1. "Efficacy of the estradiol and levonorgestrel transdermal system for the proposed VMS was not demonstrated in Study 96042A or Study 96043A." "Source documentation for these studies could not be verified, thereby precluding acceptance of the data from these studies in support of approval for these indications."
2. "The DMF is not adequate to support the NDA."

To address the above deficiencies, the Agency recommended that:

1. An additional 12-week clinical trial with two dosage strengths of the estradiol/levonorgestrel transdermal system is conducted to support the proposed VMS. The Agency recommended that the study include the 0.045 mg estradiol/0.015 mg levonorgestrel dosage strength since Study 96043A showed that the 0.045 mg estradiol/0.015 mg levonorgestrel dosage strength appeared to be the lowest effective dosage strength of the combinations studied for reducing the incidence of estrogen alone-induced endometrial hyperplasia.
2. All deficiencies in DMF are corrected prior to approval of the application.

Following a request for a formal dispute resolution regarding the source documentation for data generated in Study 96042A and Study 96043A, three options were forwarded to the Sponsor on February 22, 2002 to address the data validation issue:

1. "Submit a new clinical study as requested in the June 27, 2001 letter."
2. "Submit information that demonstrates that prior to study initiation subjects were able to use the IVRS successfully to report the frequency and severity of their vasomotor symptoms and that the system accurately captured that data. Validation of the IVRS would include information showing that the system could record data accurately, maintain study blinding, and preclude errors in data creation, modification, maintenance, archiving, retrieval, or transmission. (Refer to the Guidance for Industry: Computerized Systems Used in Clinical Trials)."
3. "Conduct and submit an analysis showing that the data recorded on the available worksheets verified the data in the IVRS. The analysis should include the history behind the worksheets (e.g., what was done to locate them, verify their authenticity, maintain their control, etc.) and how the analysis was conducted."

A submission dated April 8, 2002 constituted a complete response to the June 27, 2001 non-approvable action letter. The Sponsor submitted 10 completed worksheets (9 evaluable) from 3 subjects participating in Study 96042A in support of validation of the IVRS for the VMS indication. The Agency considered the submitted information inadequate, and the Sponsor received a non-approvable action letter on October 8, 2002 from the Agency.

The deficiencies were summarized as follows:

1. "Insufficient information was submitted to demonstrate that prior to study initiation subjects were able to use the IVRS to accurately record the data specifically related to the frequency and severity of their vasomotor symptoms. You provided evidence that your investigational staff was trained to instruct subjects on the use of the IVRS. You also provided evidence to support that prior to study initiation, subjects were able to use the IVRS system to successfully create a personal identification number. However, this does not provide evidence that prior to starting the baseline recording period, subjects were able to accurately record and report vasomotor symptoms. Therefore, submitted evidence does not support the IVRS system as a validated tool for capturing data for moderate to severe vasomotor symptoms."

2. "The analyses of the available study worksheets (subject diaries) do not verify the data in the IVRS. The analyses from the Phase 3 clinical trial (Study 96042A) submitted to verify the IVRS data was based on only 9 worksheets from 3 subjects out of 293 subjects in the Intent-to-Treat population. No data was presented on protocol-specified worksheets for the baseline period. The only baseline data submitted comes from one subject who composed her own diary."
3. "The DMF is not adequate to support the NDA."

To address the above deficiencies, the Agency again recommended that:

1. "An additional 12-week clinical trial with two dosage strengths of the estradiol/levonorgestrel transdermal system is conducted to support treatment of moderate to severe vasomotor symptoms. The study should include the 0.045mg estradiol/0.015 mg levonorgestrel dosage strength because that dosage strength appears to be the lowest effective dose for reducing the incidence of endometrial hyperplasia."
2. "All deficiencies of the DMF are corrected prior to approval of this application."

Following the October 8, 2002 non-approvable action letter, at the request of the Agency, the primary medical officer reviewed the frequency and severity of hot flushes data that had been collected by IVRS and reported in Study 96042A. Based on data collected in the IVRS, the 0.045 mg estradiol/0.030 mg levonorgestrel and the 0.045 mg estradiol/0.040 mg levonorgestrel dosage strengths were both shown to be statistically different from placebo at weeks 4 and 12 for both the frequency and severity of hot flushes (p-values <0.001 for all co-primary endpoints). It was noted, however, that the 0.045mg estradiol/0.030 mg levonorgestrel dosage strength in Study 96042A may not be the lowest effective dosage strength for either the estrogen or the progestin. Please see the Addendum to Medical Officer's Original Review of NDA 21-258 dated February 6, 2002.

In a telephone conference with the Sponsor on September 8, 2003, the Division of Reproductive and Urologic Drug Products reached an agreement to reevaluate the data collected in the IVRS in Study 96042A for a treatment of moderate to severe vasomotor symptoms associated with the menopause indication. Please see the Division Director's Summary Review of NDA 21-258, dated November 20, 2003, for additional information.

On September 19, 2003, the Sponsor submitted a complete response to the October 8, 2002 non-approvable action letter. The following three items were included:

1. Copies of Facsimiles submitted to the Agency on August 4, 8 and 20, 2003 providing justification for the 0.015 mg levonorgestrel dose, justification for the 0.045 mg estradiol dose, and a statement to be contained in the label relative to the lowest effective dose. A timeline for a Phase IV vasomotor symptoms study was included in the August 20, 2003 fax.
2. Labeling, revised to include the post-WHI study information recommended by the Agency, as well as the lowest effective dose statement included in the August 4, 2003 fax. The labeling submitted includes only the 0.045 mg estradiol/0.015 mg levonorgestrel dosage strength. The Sponsor stated that they were seeking approval for only this lowest dosage strength, and that references to the two higher dosage strengths (0.045 mg estradiol/0.030 mg levonorgestrel and 0.045 mg estradiol/0.040 mg levonorgestrel) had been removed except in circumstances where reference to bioequivalence of the 0.045 mg estradiol/0.015 mg levonorgestrel dose to the 0.045 mg estradiol/0.030 mg levonorgestrel dose was necessary. In addition, Clinical Pharmacology information relating to levonorgestrel was added to labeling.
3. A brief safety update, presenting a summary of safety data from additional estradiol/levonorgestrel transdermal system studies which were conducted in Europe in the period since submission of the original NDA on June 29, 2000.

In an amendment to NDA 21-258 dated November 6, 2003, the Sponsor withdrew

the drug product labeling submitted on September 19, 2003.

from

In an amendment to NDA 21-258 dated November 19, 2003, the sponsor submitted the following Phase IV commitment:

“Berlex agrees to a commitment to design a Phase IV clinical study to find the lowest effective dose of Climara Pro. The timelines for the commitment are as follows:

- Protocol submission – within 6 months of receipt of the NDA approval letter
- Study start – within 6 months of the protocol agreement
- Final report – within 6 months of study completion.”

#### **Clinical Pharmacology, Clinical Studies**

Per the Sponsor, the lowest levonorgestrel dosage strength, 0.015 mg, utilized in the 12-month protection of the endometrium study (Study 96043A) was expected to show only marginal protection of the endometrium. The results of Study 96043A showed, however, that the lowest combination dosage strength, 0.045 mg estradiol/0.015 mg levonorgestrel, provided endometrial protection from estradiol-induced endometrial hyperplasia (0% hyperplasia rate with the upper bound of the one-sided 95% confidence interval of 2.48%). Please see the Medical Officer's Original Review of NDA 21-258, dated June 26, 2001, for a full description of Study 96043A.

The 0.045 mg estradiol/0.015 mg levonorgestrel dosage strength, the subject of this review, was not included in the 12-week primary safety and efficacy clinical trials for VMS relief (Study 96042A included two dosage strengths: 0.045 mg estradiol/0.030 mg levonorgestrel and 0.045 mg estradiol/0.040 mg levonorgestrel). To demonstrate that the 0.045 mg estradiol/0.015 mg levonorgestrel dosage strength is bioequivalent to the 0.045 mg estradiol/0.030 mg levonorgestrel dosage strength, the Sponsor conducted a multiple dose study of 4-weeks duration (Study 304180). Study 304180 final study report was submitted for review on January 12, 2001.

Per the Clinical Pharmacology and Biopharmaceutics Review, dated May 7, 2001, the 0.045 mg estradiol/0.015 mg levonorgestrel dosage strength is bioequivalent to the 0.045 mg estradiol/0.030 mg levonorgestrel dosage strength. The average pharmacokinetic metrics for estradiol and estrone serum concentrations for both doses were shown to be almost identical, demonstrating comparability between the two dosage strengths. In addition, similar declines in sex hormone binding globulin (SHBG) serum concentrations obtained at 4 weeks of treatment in Study 304180 were observed between the 0.045 mg estradiol/0.015 mg levonorgestrel dosage strength and the 0.045 mg estradiol/0.030 mg levonorgestrel dosage strength.

Following discussions with the Sponsor on January 17, 2002, the Agency reached a regulatory decision that the results of the multiple dose estradiol bioequivalence study between the transdermal system delivering 0.015 mg levonorgestrel per day and the transdermal system delivering 0.030 mg levonorgestrel per day was suitable to demonstrate efficacy of the 0.045 mg estradiol/0.015 mg levonorgestrel dosage strength for a VMS indication.

#### **Chemistry, Manufacturing and Controls**

Per the Chemistry, Manufacturing and Controls Review of NDA 21-258 dated November 19, 2003, all deficiencies in DMF have been satisfactorily corrected. Chemistry, Manufacturing and Controls recommends approval of NDA 21-258.

#### **Safety Update**

A safety update was submitted covering the period January 2000 (cut-off date for inclusion of data into NDA 21-258) to July 2003. A total of 4 completed studies are included in the safety update, one conducted in the US and three non-US studies. Only the US study (Study 98189) included Climara Pro™. The three non-US studies included higher dosage strengths of levonorgestrel (2.75 mg and 3.75 mg of levonorgestrel) or an active comparator (Evorel Conti®, 3.2 mg estradiol/ 11.2 mg norethindrone acetate).

In Study 98189 (a 12-month extension of Study 96043A), the most frequently reported adverse events were application site reactions (range of 36.7% and 49.1% of subjects) and vaginal bleeding (range of 22.6% and 32.2% of subjects). No deaths were reported in Study 98189.

The adverse events reported in the three non-US studies (Studies 98073, 303123 and 96113) are consistent with those reported in US Study 98189, application site reaction and vaginal bleeding. In Study 98073, three cases of breast cancer were reported. In addition, in this same study, one case of endometrial cancer was reported after 6 months of use of 4.5 mg estradiol/3.75 mg levonorgestrel. However, no pre-study endometrial biopsy was performed and the subject gave a history of 4 years of prior hormone therapy. The investigators considered this case possibly related to study drug. One death was reported in Study 96113. This case was recorded as suicide/drug abuse.

Overall, the information provided in this Safety Update is consistent with the safety profile in the original NDA 21-258. See the Medical Officer's Original Review of NDA 21-258, dated June 26, 2001, for more complete information.

#### **Product Name**

The tradename Climara Pro™ was found to be acceptable to the Office of Drug Safety, Division of Medication Errors and Technical Support. See consult signed November 14, 2003.

#### **Product Final Labeling**

Labeling modified in accordance with the Agency's 2003 draft labeling guidance entitled, "Labeling Guidance for Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy symptoms – Prescribing Information for Health Providers and Patient Labeling" was submitted on September 19, 2003. The labeling submitted includes only the 0.045 mg estradiol/0.015 mg levonorgestrel dosage strength.

Minor revisions have been added to the **BOXED WARNING**, and the **CLINICAL PHARMACOLOGY, Pharmaceutics** subsection to update Table 1: Summary of Mean Pharmacokinetic Parameters and to incorporate information related to the levonorgestrel.

Revisions have been made to the **CLINICAL PHARMACOLOGY, Clinical Studies** subsection to update Table 2 and Table 3 under *Effects on vasomotor symptoms* and Figure 1 under *Effects on Uterine Bleeding or Spotting*.

The subsection has been deleted. In the women's health Initiative (WHI) Study, combination estrogen with progestin therapy increased the level of high-density lipoprotein (HDL) and lowered the level of low-density lipoprotein (LDL), yet no beneficial effect on the development or progression of coronary artery disease was detected.

Per the Agency's 2003 draft labeling guidance for noncontraceptive estrogen drug products, the following sections have been revised accordingly: **INDICATIONS AND USAGE, CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS.**

The **DOSAGE AND ADMINISTRATION** section of labeling has been specifically revised to read, "One Climara Pro transdermal system is available for the treatment of moderate to severe vasomotor symptoms associated with the menopause. Climara Pro delivers 0.045 mg of estradiol per day and 0.015 mg levonorgestrel per day. The lowest effective estradiol/levonorgestrel dose for the treatment of moderate to severe vasomotor symptoms has not been determined. (See **BOXED WARNING** and **WARNINGS.**)"

The **PATIENT INFORMATION** insert has been modified in compliance with the plain language initiative, recommendations from the Division of Drug Marketing, Advertising and Communications

(DDMAC) and the Division of Medication Errors and Technical Support (DMETS), and the Agency's 2003 draft labeling guidance for noncontraceptive estrogen drug products.

**Recommendations on Approvability**

The data presented in NDA 21-258 provides evidence to support the safety and effectiveness of Climara Pro™ (0.045 mg estradiol/0.015 mg levonorgestrel) for the treatment of moderate to severe vasomotor symptoms associated with the menopause.

Theresa H. van der Vlugt, MD, M.P.H.  
Acting Medical Team Leader

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NDA 21-258

NDA 21-258

Name of Drug: ClimaraPro™ (estradiol/levonorgestrel transdermal system)

Sponsor: Berlex Laboratories Inc.

Proposed Clinical Use: Hormone replacement therapy

Route of Administration and Dosage: Transdermal/E<sub>2</sub> 4.4mg/LNG, 1.39mg, E<sub>2</sub> 4.4mg/2.75LNG and E<sub>2</sub> 4.5mg/LNG 3.75

Date of Correspondence: April 8, 2002

Material Reviewed: Complete Response to Non-Approval Action

NDA 21-258 (Climara Pro) was submitted on June 29, 2000 and a non-approval letter was sent to Berlex on June 27, 2001. On February 22, 2002, Dr. Florence Houn, Director of the Office of Drug Evaluation III, sent a letter to Berlex that offered 3 options that Berlex could pursue in order to obtain approval of NDA 20-258. These options are:

1. Submit a new clinical study as requested in the June 21, 2001, letter.
2. Submit information that demonstrates that prior to study initiation, subjects were able to use the IVRS successfully to report the frequency and severity of their vasomotor symptoms and that the system accurately captured the data. An example of demonstrating patient success with using the system could be a test procedure used to show that instructions for using the system were understood and that the subject entered data correctly. Validation of the IVRS would include information showing that the system could record data accurately, maintain study blinding, and preclude errors in data creation, modification, maintenance, archiving, retrieval, or transmission. (Refer to the Guidance for Industry: Computerized Systems Used in Clinical Trials).
3. Conduct and submit an analysis showing that the data recorded on the available worksheets verifies the data in the IVRS. The analysis should include the history behind the worksheets (e.g. what was done to locate them, verify their authenticity, maintain their control, etc.) and how the analysis was conducted.

The sponsor has chosen options 2 and 3 in their response letter.

Background:

Reference is made to the Executive Summary in my original review of NDA 21-258, dated June 19, 2001. The most pertinent portion of the Executive Summary is as follows:

**I Recommendation**

This reviewer recommends non-approval of Climarapro, henceforth referred to as E<sub>2</sub> 4.4 mg/LNG 1.39mg, E<sub>2</sub> 4.4mg/LNG 2.75mg, and 4.5mg/LNG 3.75mg, respectively. The Division of Scientific Investigations (DSI) could not validate the

source documentation from three inspected sites for the data submitted in this NDA for study 96042A. Study 96042A was a 3-month double-blind, randomized, placebo-controlled study to determine the efficacy of E<sub>2</sub> 4.4 /LNG 2.75mg and E<sub>2</sub> 4.5/LNG 3.75mg in the relief of hot flushes.

## **II Summary of Clinical Findings**

The sponsor has not demonstrated efficacy for ClimaraPro (estradiol and levonorgestrel transdermal patch) in clinical trials. In study 96042A, source documentation for this study could not be verified and DSI recommended that data in study 96042A not be used to support approval of this NDA.

In study 96043A, three dosages (4.4mg E<sub>2</sub>/LNG 1.39mg, 4.4mg E<sub>2</sub>/LNG 2.75mg, and 4.5 E<sub>2</sub>/LNG 3.75mg) of the estradiol/levonorgestrel transdermal patch produced a statistically significant reduction in the incidence of estrogen-induced hyperplasia when compared to daily 4.4mg estradiol alone. The reduction in estrogen-induced hyperplasia was at the p <0.001 significance level with the upper bound of the 95% confidence interval at < 4% for each treatment group.

### Overview of Clinical Program

Climara® is an approved estradiol patch since December 22, 1994. It is presently approved to treat 1) moderate-to-severe vasomotor symptoms associated with the menopause, 2) vulvar and vaginal atrophy, 3) osteoporosis, and 4) treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure. The dosage strengths of Climara are 0.025mg/day (6.5cm<sup>2</sup>), 0.050mg/day (12.5cm<sup>2</sup>), and 0.1 mg/day (25cm<sup>2</sup>). Climara is applied once weekly to an area of the abdomen or buttock.

With this NDA, the sponsor is seeking approval for a combination estrogen/progestin patch. The two controlled clinical studies, studies 96042A and 96043A, which were designed to evaluate the safety and efficacy of E<sub>2</sub>/LNG combination patch in the relief of postmenopausal vasomotor symptoms and urogenital symptoms in non-hysterectomized and hysterectomized women, were submitted for evaluation. Study 96042A was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate two dose levels of E<sub>2</sub>/LNG (E<sub>2</sub> 4.4mg/LNG 2.75mg and E<sub>2</sub> 4.5mg/LNG 3.75mg) for 3 continuous 28-day treatment cycles compared to placebo.

Study 96043A was a 1-year, multi-center, randomized, double-blind, parallel-group study in non-hysterectomized women that was designed to evaluate the safety and efficacy of the E<sub>2</sub>/LNG combination patch in the prevention of the development of endometrial hyperplasia.

### Efficacy

Overall, the efficacy of E<sub>2</sub>/LNG could not be determined in this study. According to the IND protocol, subjects were to be provided with worksheets (diaries) for the daily recording of hot flushes and the weekly recording of urogenital symptoms during the run-in (baseline period) and the post-randomization

treatment. During the run-in period, subjects were also instructed on the use of the Interactive Voice Response System (IVRS) to record the daily number and severity of hot flushes and the weekly presence and severity of urogenital symptoms. During the treatment period subjects were to enter hot flush frequency and severity on a daily basis and enter the presence and severity of urogenital symptoms weekly into the IVRS. According to the IND Protocol, all original (source) data was to be included with the corresponding case report form (CRF) for review by the Monitor from Berlex Laboratories and copies of all CRFs were to be provided to the Principle Investigator for retention as required by applicable government regulations. No study source documentation could be verified after the initial baseline period for vasomotor symptoms. Source documentation was obtained at baseline with the use of a written record that was given to the subject; however, it was not used in the remaining portion of this study. The sponsor did not, a priori, notify the Division of Reproductive and Urological Products (DRUDP) of any modification of their study protocol, nor did the sponsor file a protocol amendment to apprise DRUDP that only the IVRS would be used, excluding written documentation. When study data was inspected by DSI at three sites source documentation could not be identified. Therefore, DSI could not recommend the use of data at these three sites from this study for support of the vasomotor symptoms (VMS) indication in this study. This reviewer concurs with that recommendation since deletion of at least 36 subjects from these sites substantially weakens the sponsor's database.

#### Safety

This product is not considered to be unsafe. Significant adverse events were reported in study 96043A relating to vaginal hemorrhage, application site reactions, and breast pain. These adverse events would not have prevented approval of this product.

#### **Review:**

##### Berlex's response---Option #2 Safety Validation

Submit information that demonstrates that prior to study initiation, subjects were able to use the IVRS (IVR system) successfully to report the frequency and severity of their vasomotor symptoms and that the system accurately captured the data. An example of demonstrating patient success with using the system could be a test procedure used to show that instructions for using the system were understood and that the subject entered data correctly. Validation of the IVRS would include information showing that the system could record data accurately, maintain study blinding, and preclude errors in data creation, modification, maintenance, archiving, Retrieval, or transmission. (Refer to the Guidance for Industry: Computerized Systems Used in Clinical Trials).

Review of submitted data appears to show that the "IVR system used by Berlex has the attributes of a system that could be validated or is validatable." Sponsor's Exhibits 2 and 4 appears to show that the investigators and the medical monitor were trained on how to use the IVR system. Clinical sites received a copy of directions for use of the IVR system prior to study initiation and the medical monitor was required to confirm training on the

IVR system. The IVR system was internally validated in 1998 by — under contract with Berlex, but validation, using vasomotor symptomatology, was not done.

This reviewer has little doubt that the IVR system used by Berlex is a system capable of recording data that is attributable, original, accurate, contemporaneous and legible. The primary problem is this *validation of the IVR system was not done with vasomotor symptoms prior to initiation of this study*. Dr. Houn's letter to Berlex describing documentation of system validation specifically states that "prior to study initiation, subjects were able to use the IVR system successfully to report the frequency and severity of their VMS and that the system accurately captured the data." Nothing presented in the sponsor's response supports *prior VMS validation of the IVR system before initiation of this study*. Subjects did receive training, but training was done in the baseline period (run-in) using worksheets as the primary source document in the IND submission. The distinction that this was the baseline period must be made because subjects experience more vasomotor symptoms and these symptoms were transcribed onto a worksheet and the IVR system. When worksheets are eliminated, could subjects successfully record the total number of VMS symptoms per day and the severity of VMS symptoms that were mild, moderate, and severe without worksheets? What was (is) the correlation between the worksheets and the IVR system at the end of the baseline period? Are they the same? Without prior study correlation of entry data relating to VMS between worksheets and the IVR system, this reviewer is unable to substantiate data recorded on worksheets and imputed data into the IVR system that supports the accuracy of the IVR system.

#### Berlex response-- Option #3 Subject Training

Conduct and submit an analysis showing that the data recorded on the available worksheets verifies the data in the IVRS. The analysis should include the history behind the worksheets (e.g. what was done to locate them, verify their authenticity, maintain their control, etc.) and how the analysis was conducted.

Berlex states that after communication with FDA they attempted obtain worksheets from all 37 sites involved in study 96042A. Twenty sites responded and stated that they did not collect or have any worksheets in the site's files. Five sites did not randomize subjects, seven sites could not be reached, and three sites did not return numerous telephone calls. No worksheets were located.

Following receipt of the June 27, 2001, non-approval letter, Berlex made a second attempt to obtain worksheets. This second request went to the eleven sites that had the largest number of subjects. Sites were asked to review their files for worksheets for studies 94042A and 96043A. Sites were requested to attempt to contact randomized subjects to locate worksheets.

From the eleven sites contacted, there were 143 subjects in study 96042A. Sixty(60) subjects were reached by the study sites. Of the 60 contacted 56 said they recalled using worksheets; four did not. Worksheets from 3 subjects were located. Two (2) subjects had worksheets at home. The third subject was located in the files of an investigator (Dr — who was mistakenly not contacted during the initial contact.

The sponsor also obtained worksheets from study 96043A, 61 of the 179 subjects were reached. Of the 61 reaches, 39 stated they had used worksheets, 22 said they had not.

Four (4) subjects had worksheets at home. One (1) site ( — ) had worksheets in the file for 10 subjects, including for 1 subject with a non-completed and non-evaluable worksheet.

The sponsor states the worksheets are authentic. They were at all times either in the possession of the subject or the site.

Berlex conducted an analysis of the worksheets that were obtained and compared them with the results recorded in the IVR system. This analysis is shown in Exhibit 13. Three(3) subject worksheets will be reviewed in detail from study 96042A, only. This is the study of interest because it recorded vasomotor symptoms in detail.

For subject 06004 Berlex has submitted worksheets with subject number 06809. Data is not consistent as to the baseline period. Weeks 1 to 4 are recorded as 52, 44, 12, and 2 moderate-to-severe hot flushes, respectively. This compares to the computer readout of 52 moderate-to-severe hot flushes at week -1, and 36, 10, 0, and 0 at weeks 1 to 4 of treatment. The worksheets for weeks 5 through 12 record no moderate-to-severe VMS and are consistent with the computer readout for weeks 5 through 12.

For subject 18001 Berlex has submitted worksheets with subject number 18804. No baseline data points are shown on the worksheets. Weeks 1 to 4 recorded data that is not legible. Two moderate hot flushes are recorded for week 5: one moderate hot flush is recorded for week 6, and no moderate-to-severe hot flushes are recorded for weeks 7 through 12. The computer readout reports a baseline entry (week -1) of 121 moderate-to-severe hot flushes with a notation by the sponsor that the "numbers are correct subject seems confused as to cycles/day". This reviewer notes 117 moderate to severe hot flushes during this same period. At weeks 1- 4, 66, 49, 13, and 4 moderate-to-severe hot flushes are reported, respectively via computer readout. At week 5 2-moderate hot flushes are reported; at week 6, 1-hot flush is reported, and weeks 7-12 report no moderate-to-severe hot flushes. Of note, some mild hot flushes are recorded on the computer printout and are included into the subject data compilation of data points throughout the treatment cycles. Mild hot flushes should not have been recorded.

Subject 96042 (subject 28012) did not use the sponsor's worksheet but recorded 15 weeks of detailed treatment including the baseline period. This personal diary recorded the week date, patch site right or left, bleeding, mild hot flush, moderate hot flush, severe hot flush, urination at bedtime, remarks, and the time the subject called into the IVR system. Recorded values correspond exactly to the worksheet that the subject personally made up. Of interest, this subject was receiving placebo. The subject baseline symptoms were primarily moderate hot flushes with a baseline of 52 per week. This improved over 12 weeks to a mean of 32.75 moderate hot flushes per week. This is an improvement of -21.75 hot flushes over the 12-week treatment period with the subject symptoms remaining moderate over that 12- week period.

Comment: Approximately 9 worksheets were evaluable in 3 subjects by this reviewer. Of these 9 worksheets, 4 appear to correlate consistently to the IVR system. These 4 handwritten worksheets from one subject (not sponsor's worksheets) report data points that are precisely recorded. In the remaining 5 worksheets (comprised of 2 subjects), *no baseline data is present*. Evaluable data points corresponding to the IVR system is fairly consistent, but is confounded by an attempt to make week 1 of treatment the last week in the run-in (baseline (-1)) period. The sponsor recorded subject (06004) data week -1 of treatment as the last week of baseline evaluation when actually it was week 1 of treatment. This is *not* consistent with the usual review process. In addition, after weeks 1-4, no additional mild-moderate-severe hot flushes are recorded for weeks 5-12. One could argue that this subject is equivocal as to being eligible for entrance criteria in that the subject does not meet the usual entrance criteria of 56-60 moderate-to-severe hot flushes. Additionally, in this reviewer's experience, it is quite unusual to have no moderate-to-severe hot flushes after only 4 weeks of treatment.

Subject 18001 is even more problematical in that there is no baseline data recorded *and* week 1 of treatment is illegible. Cycle 2, week 5, day 5 records 2 moderate-to-severe hot flushes, and Cycle 2, week 6, 1 hot flush is recorded. Thereafter, no additional moderate- to-severe hot flushes are recorded. Again, with no baseline data and illegible 1-4 week data, it is difficult for this reviewer to state that the IVR system is recording precise data from the worksheets.

Subject 28002 appears to correspond to what the subject and the IVR system can do *if data is entered as it was designed*. However, recorded data is not on the sponsor's worksheet and no reason is given as to why this subject would not use the worksheet that was originally provided. Therefore, source data from subject 28002 can be questioned.

Under tab 13, Volume 2 the sponsor has attempted to correlate individual responses from all worksheets after receipt of the non approval letter. The office (ODE III) and the division (DRUDP) were originally told that approximately 100 subject worksheets would be evaluable. Submitted data reveals 3 subjects (9 worksheets) for study 96042 and 14 subjects (107 evaluable worksheets) for study 96043. The sponsor had previously been told that the study of interest is study 96042 since the indication for this product is the treatment of moderate-to-severe vasomotor symptoms. Therefore, only responses related to study 96042 are appropriate and the specific review *is limited* to moderate-to-severe vasomotor symptoms. Study 96042 was designed as a 14-week study, 2 placebo run-in (baseline weeks) and 12 weeks of treatment with ClimaraPro or placebo. The sponsor calculated data points and deviations for 9 evaluable worksheets in study 96042. The sponsor states that 714 data points were identified for hot flushes with 3 (.42%) being inconsistent. It appears that this is incorrect because data points for subject 06004 at week 1 are incorrectly listed as week -1 without any true baseline data. Without appropriate baseline data points at weeks -2 and -1, all subsequent data points are questionable. Subjects who did not understand how to use the IVR system correctly during baseline period, where symptoms are greatest, may have improved recording techniques over time with increasing accuracy which does not show in the baseline period of the study. Therefore, the sponsor's attempt to calculate a high concordance rate does not appear to be statistically valid (See statistical comments for more detail). Secondly, the

**sponsor's high concordance rate is being driven by subject 28002 and this subject did not have a valid worksheet.**

**In summary, review of Berlex's response does not allow this reviewer to recommend approval of this product based upon submitted evaluable worksheet data. The reasons are as follows:**

- 1. Pre-study validation of the sponsor's IVR system in relationship to VMS was not confirmed in the sponsor's submitted response.**
- 2. Only 9 worksheets from 3 subjects were evaluable from study 096042.**
- 3. No baseline data is contained in the worksheets except for 1 subject; this subject's data is not recorded on the sponsor's worksheet.**
- 4. Worksheet data suggest subject 96042 had 52 moderate to severe vasomotor symptoms, 2 moderate to severe symptoms at week 4 and no additional hot flushes after week 4; subject 18001 had no legible data for weeks 1-4, 2 hot flushes during week 5, and 1 during week 6, with no other hot flushes after that point. Reviewed VMS data in these two subjects suggest that symptoms were either very mild at baseline, or ClimaraPro™ is unique in relieving moderate-to-severe hot flushes. In my opinion, after review of VMS data from many clinical trials, complete relief of moderate-to-severe symptoms after only 4 weeks of treatment is an infrequent event. The third subject was in the placebo group and appeared to have a clinical course consistent with the usual placebo group whereby symptoms are improved by 40% to 50% but are not totally relieved in the clinical trial. This subject recorded data not on the sponsor's worksheet.**
- 5. Submitted statistical concordance data relating to hot flushes does not appear valid and is driven by 1 subject who did not use the sponsor's worksheet.**

Phill H. Price, M.D.  
HFD-580  
October 3, 2002

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/

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Phill H. Price  
10/7/02 05:22:59 PM  
MEDICAL OFFICER

Shelley Slaughter  
10/7/02 05:29:45 PM  
MEDICAL OFFICER

Daniel A. Shames  
10/7/02 05:43:03 PM  
MEDICAL OFFICER

## ClimaraPro™ Team Leader Review

**NDA:** 21-258

**Proposed Trade name:** ClimaraPro™ (Estradiol and Levonorgestrel Matrix Transdermal System)

**Proposed Claim:** /

**Proposed Indications:** 1. Treatment of moderate-to-severe vasomotor symptoms /

**Dosage/Form/Route:** 0.045 mg 17-beta estradiol/0.015 mg levonorgestrel or 0.045 mg 17-beta estradiol/0.030 mg levonorgestrel administered daily via a transdermal 22 cm<sup>2</sup> system or 0.045 mg 17-beta estradiol/0.040 mg levonorgestrel administered daily via a transdermal 30 cm<sup>2</sup> system in a continuous combined regimen. The transdermal system is intended to be applied once weekly for all four weeks of a 28-day cycle.

**Applicant:** Berlex Laboratories, Inc

**Date of Submission:** June 29, 2000

**Primary Clinical NDA Review Completed:** June 21, 2001

**Date of Memorandum:** June 22, 2001

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### Background and Regulatory History

IND 51,188 was opened with a Phase 1 pharmacokinetic study submission on July-24, 1996. Study 97067, a relative bioavailability study was submitted on October 10, 1997. FDA comments on this protocol included a recommendation to the Sponsor that tape not be used to assure adhesion of the transdermal systems unless the product labeling would include the use of tape. The Phase 3 protocols for the primary studies supporting this NDA (Protocol 96042A and Protocol 96043A) were submitted to IND 51,188 on May 5, 1998. A pre-NDA meeting between the Agency and Berlex was conducted on February 8, 2000. Decisions from that meeting included the following:

- Adhesion data should be included in the labeling and should be from the to-be-marketed product.

- The PK profiles after single and multiple dosing should be described in the NDA, as well as in the label.
- There could be interactions with estradiol and levonorgestrel and sex hormone binding globulin (SHBG). Interactions with estradiol and levonorgestrel will be included in the labeling.
- The clinical trials to study vasomotor symptoms utilized the E<sub>2</sub> 0.045 mg + LNG 0.030 mg/day and the E<sub>2</sub> 0.045 mg + LNG 0.040 mg/day dosage strengths. The profile for the three strengths may not be linear. In order to establish the efficacy for the lowest dose, a multiple dose proportionality study may be necessary. Bioequivalence calculations should be made at steady state considering interactions between estradiol, levonorgestrel and SHBG. A bioequivalence study comparing the estradiol from the lowest dose (E<sub>2</sub> 0.045 mg + LNG 0.015 mg/day) system should be conducted where this system is compared to the other systems in a cross-over design study using single treatment groups and multiple applications. This study should be a 3-4 week study.
- Since the adhesive was changed between Phase 1 and Phase 2, a separate wear study is being performed; if a different adhesive was used for the to-be-marketed product, a linking study can be incorporated.
- Adhesion and irritation studies should be included in the submission.
- Clinical data should support the efficacy and safety of each dose.
- The Sponsor should clarify whether vasomotor symptom (VMS) trials enrolled only women with moderate-to-severe vasomotor symptoms. The primary efficacy variables for the VMS indication should be the change from baseline in the number and severity of moderate-to-severe VMS at week 4, 8 and 12.

NDA 21-258 was received on June 29, 2000 and was filed on August 28, 2000.

### Chemistry/Manufacturing

The chemistry, manufacturing and control information for the drug substance, and the drug product was provided in the type II DMF. The review determined that DMF is not adequate to support NDA 21-258. The review of the labeling information submitted with the NDA noted the following CMC deficiencies:

1. The storage condition in the pouch and carton labels should be revised to "store at 25°C (excursion permitted 15-30°C)". The inactive component should include the polyethylene backing and the polyester release liner.
2. Please correct the error on the carton label to read as follows: "contains X mg estradiol, USP and X mg levonorgestrel, USP per transdermal system".
3. The standard storage statement in the **How Supplied** Section should be revised to: "Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F)".
4. Since the drug product when disposed would contain a large quantity of the residual drug, it may pose a hazard by accidental use. Please provide a disposal procedure for the transdermal system in the **How Supplied** section.

With respect to chemistry, manufacturing and controls, the NDA is not approvable until all of the deficiencies noted in the DMF — as well as in the NDA are satisfactorily addressed.

### Microbiology

The microbiology information for the drug substance, and the drug product was provided in the type II DMF — The review determined that DMF — is not adequate to support NDA 21-258.

With respect to microbiology, the NDA is not approvable until all of the deficiencies noted in DMF — are satisfactorily addressed.

### Product Name

The tradename ClimaraPro™ was found to be unacceptable to Office of Post-Marketing Drug Risk Assessment (see consult signed 11/22/00).

### Preclinical Pharmacology

The following comments were discussed in the Pharmacology review:

No new toxicology was done on estradiol or levonorgestrel and none is needed.

The initial developmental transdermal system using — (later changed to — to eliminate a potentially toxic compound)) was tested in a variety of in vitro and in vivo tests which included: 1) several dermal sensitization studies in guinea pigs 2) several primary irritation studies in rabbits 3) a 7 day cumulative primary skin irritation study in rabbits 4) cytotoxicity test using L-929 mouse fibroblasts. No unusual toxicity, sensitization or irritation was seen in any test.

The adhesive matrix of the to-be-marketed transdermal system ( — ) was evaluated in three studies, a local and systemic tolerance study in rats, a modified maximization test in guinea pigs and a local tolerance test in rabbits.

— is a polymer consisting of the — acrylate. The toxicology — is well documented in the literature and no new toxicology studies are needed.

No local or systemic intolerance of the placebo system containing — was seen in rats following topical application for 4 weeks.

The sensitization potential of the transdermal system was determined following topical application to guinea pigs in a modified maximization test. No contact sensitization was observed following application of either E<sub>2</sub>/LNG transdermal systems or placebo systems. Punctiform and striate reddening in the system areas seen at 26 hrs after challenge system removal were not present 50 hrs after removal and were attributed to mechanical manipulation during application of the systems.

The local tolerance of the transdermal system contain — was determined following a single 4 hour application to intact skin of male and female rabbits. One hour after system

removal, no clear signs of local intolerance were observed. There were no changes in body weights.

The sponsor states that the final formulation of \_\_\_\_\_ did not induce gene mutations in bacteria in the absence or presence of extrinsic metabolic activation at concentrations up to those at which precipitation occurred. However, those data were not submitted to the NDA.

ClimaraPro™ is approvable from the standpoint of Pharmacology.

### Clinical Pharmacology and Biopharmaceutics

The following was discussed in the review:

All formulations used in the primary clinical pharmacology, bioavailability and clinical efficacy studies had the same qualitative and quantitative composition and were manufactured at the same facility as the proposed to-be-marketed formulation.

Data from the 4 pharmacokinetic and bioavailability studies are presented. These data reveal that with a single dose, mean estradiol exposure appears to increase with the levonorgestrel exposure. Upon multiple dosing, the exposure to estradiol decreases over time with an accumulation ratio of approximately 0.7 after 4 weeks. This decrease in exposure may be due to enhanced elimination secondary to levonorgestrel. Nevertheless the average reported C<sub>min</sub> values at the end of 4 weeks of treatment are all approximately  $\geq 27.5$  pg/ml, which was felt to be sufficient to provide a pharmacologic effect. The reviewer noted that the reported C<sub>min</sub> values were not the true C<sub>min</sub> values in at least one of the multiple dose studies. Instead, it was noted that these values were the concentrations at the end of the 4<sup>th</sup> transdermal system wear period. In contrast the true C<sub>min</sub> values in a few cases occurred in the middle of the dosing interval. Consequently, the true average C<sub>min</sub> will be slightly lower, but the conclusions should be the same. A similar effect of levonorgestrel is also seen on estrone as is seen with estradiol, i.e. an inverse relationship between levonorgestrel dose and estrone exposure with single dosing and decreased exposure over time. The average C<sub>min</sub> after 4 weeks with the lowest levonorgestrel dose is almost double the concentration observed with the highest dose. However, once a single outlier (who may not have been postmenopausal) is removed from consideration, C<sub>mins</sub> are similar across doses. A single dose effect of levonorgestrel on estrone sulfate is seen which was similar to that seen with levonorgestrel on estradiol. There is not sufficient data to discern the effect of multiple dosing patterns on estrone sulfate. For single doses of levonorgestrel the AUCs of the 3 formulations are roughly in a ratio of 1:2:3 in the order of the intended deliveries. For the lowest strength of levonorgestrel the AUC is approximately the same as observed with 3 x 30  $\mu$ g of levonorgestrel tablets. The T<sub>max</sub> increases as the levonorgestrel dose decreases, consequently the C<sub>max</sub> ratio of the higher strengths relative to the lower strengths are quite high and the C<sub>ave</sub> and C<sub>min</sub> ratios are much lower. This is seen in the different degrees of fluctuation observed with the 3 formulations, (23.2 %, 39.4% and 53.0% from the lowest to highest strengths). Upon multiple dosing there is too much variability in levonorgestrel metrics to clearly discern any patterns. However, T<sub>max</sub> is at 2-3 days, and by inspection the increase in exposure appears to be less than dose proportional.

The lowest strength transdermal system was not studied in the efficacy trial. However, it was evaluated in the endometrial safety study. Upon multiple dosing at 4 weeks, the lowest strength transdermal system (E<sub>2</sub>.0.045 mg + LNG 0.015 mg/day) is bioequivalent to the middle strength

(E<sub>2</sub> 0.045 mg + LNG 0.030 mg/day), with the estradiol exposure of the lowest strength somewhat higher than the middle strength system. However, the active metabolite, estrone, is not bioequivalent; the estrone exposure of the lower dose is approximate double that with the middle dose. Nevertheless, since the estradiol and estrone exposures are higher and not lower they should provide the same or better control of symptoms. When the data from the outlier (who was probably not menopausal) is excluded, the average pharmacokinetics metrics for estradiol and estrone for the middle and lowest doses become almost identical, and it's apparent even without recalculation that estradiol bioequivalence would be met.

There is insufficient data to determine product performance over time. However, there is no indication from the review that there is a product performance problem over time. The nominal delivery rate for estradiol for ClimaraPro™ is based upon a comparison of AUCs with Climara® and Cerulla™ (per the Sponsor Cerulla™ is an approved product in Europe). The nominal transdermal delivery rates for levonorgestrel is based upon a comparison of AUCs with a 90 µg oral dose of levonorgestrel. Referencing the transdermal delivery rate (TDR) of ClimaraPro™ to the TDR of Climara® based on AUC mean ratios appears to be acceptable, provided the Sponsor can substantiate the equivalence of Cerulla™ to Climara®. The referencing of levonorgestrel delivery rate to the exposure of levonorgestrel after an oral dose is based upon several explicit and implicit assumptions: including systemic oral and transdermal bioavailabilities of 1.0, dose proportionality, and lack of drug interaction with estradiol. Since there are currently no transdermal levonorgestrel products, referencing a nominal TDR to systemic oral exposure appears acceptable.

The possibility of *in vitro* – *in vivo* correlation was not examined. Transdermal system handling, application and wear instructions were consistent across studies. Thirty three (33%) – 100% of subject experienced application site reactions in the two single dose PK studies and 18% - 50% of subjects experienced application site reactions in the multiple dose studies. The incidence was always lowest with the lowest strength and size system (0.045 mg 17-beta estradiol/0.015 mg levonorgestrel) and increased with dose or size. Two subjects in one of the single dose studies had severe and prolonged application site reactions.

In the 4 primary pharmacokinetic studies, 8%-17% of the transdermal systems demonstrated some lifting and 0.56% of transdermal systems were replaced. An open-label adhesion study was conducted in 104 healthy subjects age range 45-75. The study utilized a placebo for the 22 cm<sup>2</sup> system which was applied to the upper outer abdomen. Approximately 87% of the transdermal systems demonstrate no lift. Of the total number of transdermal systems applied, approximately 9% showed complete detachment.

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluations II find the NDA acceptable.

#### **Division of Scientific Investigations (DSI) Report**

Three clinical sites were inspected. The sites were Portland, Oregon with principle investigator Engrique deCastro, MD, Lyndhurst, Ohio with principle investigator Julian L Peskin, MD and Littleton, Colorado with principle investigator Susan Savage, MD. The DSI report states that the data submitted in support of the NDA by Drs. deCastro, Peskin and Savage had similar findings. The protocol-specified worksheets (which DSI regards as source documents) for Study 96042A were unavailable for review. Per the DSI investigator, the worksheets were intended to collect information regarding the frequency and severity of hot flushes (the primary efficacy endpoint)

and other symptoms and without these source documents, DSI is unable to verify these data. Therefore, DSI recommends that data (which was to be collected on those worksheets) from these sites for Study 96042A not be used in support of the NDA. Similarly, for Study 96043A, the protocol-specified worksheets for a sub-study of VMS were unavailable for review at all three sites. DSI also recommends that this data not be considered. The primary efficacy endpoint for Study 96043A, the incidence of endometrial hyperplasia, was verified by a comparison of original biopsy reports with the respective CRFs. Further the DSI report states that DSI is concerned that the lack of source records for hot flush data may extend to other clinical sites.

### Clinical

The Sponsor submitted two controlled clinical trials. Study 96042A was a randomized, double-blind, placebo-controlled, multicenter, 12 week study intended to support the safety and efficacy of ClimaraPro™ in the treatment of moderate-to-severe vasomotor symptoms in postmenopausal women with a uterus. Study 96043A was a randomized, double-blind, parallel group (with an estrogen only-arm), multicenter, 52 week study

#### Study 96042A

The primary objective of Study 96042 A was to determine the effectiveness of continuous administration of transdermal estradiol/levonorgestrel combinations compared with placebo in decreasing the frequency and severity of hot flushes in postmenopausal women. A secondary objective was to evaluate the effectiveness of the treatment regimen in relieving urogenital symptoms. According to the protocol, subjects were to be provided with worksheets (diaries) for the daily recording of hot flushes and the weekly recording of urogenital symptoms during the run-in (baseline) period and the post-randomization treatment period. During the run-in period, subjects were also instructed on the use of the Interactive Voice Response System (IVRS) to record the daily number and severity of hot flushes and the weekly presence and severity of urogenital symptoms. During the treatment period, subjects were to enter hot flush frequency and severity on a daily basis and enter the presence and severity of urogenital symptoms weekly into the IVRS. According to the Protocol for Study 96042, all original (source) data was to be included with the corresponding case report form (CRF) for review by the monitor from Berlex Laboratories and copies of all CRFs were to be provided to the principal investigator for retention as required by applicable government regulations. Original source data should have included the subject-completed worksheets as well as the entries into the IVRS. Neither the original study protocol nor any subsequent protocol amendments delineated that the subject worksheets would not be considered original source data. According to the DSI report, no protocol-specified subject worksheets were provided to the investigator upon request. DSI has recommended that the data from the three inspected clinical sites for Study 96042A not be considered to support approval of NDA 21-258. Further the DSI report expresses concern that the lack of source records may extend to other clinical sites. Following the DSI recommendation to exclude data from the 3 investigated sites as well as the expression of concern regarding the likelihood that the source data from other clinical sites may not be available (and thus not verifiable), the primary clinical and statistical reviewer have decided not to review the data from Study 96042A provided by the Sponsor to support the indication of treatment of moderate-to-severe vasomotor symptoms

I concur in the decision not to review the data.

## Protocol 96043A

Study 96043A was a randomized, double-blind, parallel group (with an estrogen only-arm), multicenter, 52 week study. The primary objective of this study was to evaluate the efficacy of 13, 28-day cycles of continuous estradiol/levonorgestrel combinations compared to continuous estradiol by analysis of protection against hyperplasia in postmenopausal women. The analysis of bleeding patterns and the effect on frequency and severity of hot flushes and the relief of urogenital symptoms for the continuous estradiol/levonorgestrel combinations vs. continuous estradiol were to be compared as secondary objectives. The study was conducted at 73 centers in the U.S. Enrollment criteria were consistent with those specified for an endometrial protection study in the 1995 Guidance For Clinical Evaluation of Combination Estrogen/Progestin-Containing Drug Products Used For Hormone Replacement Therapy of Postmenopausal Women (HRT Guidance). However, subjects were not required in the study to meet the HRT Guidance document-specified criteria for hot flush frequency and severity of 7-8 per day or 60 moderate-to-severe hot flushes per week required for a VMS study. All subjects were given a worksheet to record vasomotor and urogenital symptoms and bleeding at baseline and throughout the study. Women with symptoms also were asked to record the symptoms using IVRS. Women who had  $\geq 15$  hot flushes during a 2-week run-in period were enrolled in a symptom sub-study. All subjects received a complete history, general and gynecology exam (including Pap smear) at screening. Mammography and endometrial biopsies were also performed at screening. Subjects were then randomized to 1 of 4 treatment groups. Pap smear, mammography (if one year had elapsed) and endometrial biopsy were performed at the end of study visit or at early termination. All treatment systems were applied to the abdomen avoiding the waistline. Two systems were applied simultaneously, 1 containing active drug and the other containing placebo. Systems were designed to deliver drug continuously over 7 days and were worn continuously over that 7 days and changed weekly. Systems were not to be removed except for the scheduled weekly replacement. If a system became dislodged between applications, subjects were instructed to attempt to reapply the system. If a system partially lifted from the skin it was pressed back into place. If it failed to remain adhered or became completely detached, a replacement system (system A or B) was applied. If a second system became dislodged during the same cycle, it was not replaced, a new system was applied at the end of the week and weekly cycle of system wear was resumed.

Eight hundred forty five (845) subjects were randomized to the following treatment groups:

- E<sub>2</sub> 0.045 mg/day + placebo – 204 subjects
- E<sub>2</sub> 0.045 mg + LNG 0.015 mg/day – 213 subjects
- E<sub>2</sub> 0.045 mg + LNG 0.030 mg/day – 212 subjects
- E<sub>2</sub> 0.045 mg + LNG 0.040 mg/day – 216 subjects

Of the 845 subjects randomized, a total of 5 subjects never used the study drug. A total of 448 subjects completed cycle 13 of the study. Three hundred ninety two (392) subjects of the 845 subjects randomized (46%) prematurely terminated the study. Two hundred fifty six (256) subjects (30.5% of those randomized) withdrew because of an adverse event, 17 subjects (2.0% of those randomized) were withdrawn because of protocol deviations and 15 subjects (1.8% of those randomized) withdrew because of lack of efficacy. The discontinuation rates were similar across all treatment arms with the lowest discontinuation rate of 43.6% occurring in the E<sub>2</sub> 0.045 mg/day + placebo arm and the highest rate of 49.3% occurring in the E<sub>2</sub> 0.045 mg + LNG 0.030 mg/day arm.

One of the sites-D (Site 34) was discontinued during the course of the study because of violations of Good Clinical Practice (GCP). Data from this site (from 8 subjects) was excluded

from the Sponsor's ITT efficacy analysis and this was acceptable. The data from three other subjects were also excluded from the efficacy analysis. Two of these subjects had neither baseline nor post-baseline endometrial biopsies (subject 04013 in the E<sub>2</sub> 0.045 mg/day group and subject 45004 in the E<sub>2</sub> 0.045 mg + LNG 0.040 mg/day group). One subject, 38029, in the E<sub>2</sub> 0.045 mg + LNG 0.040 mg/day group had endometrial hyperplasia on the baseline biopsy (and should have been excluded before randomization). Because of the high numbers of subjects who either withdrew without a post-baseline endometrial biopsy, had insufficient tissue on post-baseline biopsy or who withdrew with adequate tissue and no evidence of hyperplasia, the Sponsor performed analyses utilizing two different definitions of subjects who withdrew. Definition 1 included those subjects who withdrew from the study without a post-baseline endometrial biopsy or who had insufficient tissue on the biopsy attempt. Definition 2 included those subjects who withdrew from the study early, had an adequate endometrial biopsy and no evidence of hyperplasia. The Sponsor performed an analysis of the data that excluded definition 1 patients only and a separate analysis that excluded subjects who were included in both definition 1 and definition 2 categories. Only the former analysis (which excluded patients falling under the first definition) will be discussed, as this analysis is more consistent with an analysis of all evaluable subjects. This is the analysis usually done for the consideration of hyperplasia rates in other HRT trials submitted to the Division. The results of this analysis is presented in Table 1 (modified from the primary reviewer's Table 4).

Table 1. Endometrial Hyperplasia Rates

Treatment group	Endometrial Hyperplasia Rates		
	n <sup>b</sup>	%	Upper bound of 95% CI <sup>c</sup>
E <sub>2</sub> 0.045 mg/day + placebo N <sup>a</sup> = 148	19	12.8	18.57%
E <sub>2</sub> 0.045 mg + LNG 0.015 mg/day N <sup>a</sup> = 147	0	0	2.48%
E <sub>2</sub> 0.045 mg + LNG 0.030 mg/day N <sup>a</sup> = 138	0	0	2.64%
E <sub>2</sub> 0.045 mg + LNG 0.040 mg/day N <sup>a</sup> = 142	0	0	2.56%

<sup>a</sup>N = evaluable subjects

<sup>b</sup>n = number of subjects with endometrial hyperplasia

<sup>c</sup>CI = Upper 95% confidence limit for a single proportion. For the E<sub>2</sub> 0.045 mg/day group, a normal approximation was used, for the combination groups the exact method was used.

Of the 19 subjects in the E<sub>2</sub> 0.045 mg/day + placebo group noted to have endometrial hyperplasia, 17 of these were noted to be simple hyperplasias and 2 were noted to be atypical hyperplasias. No subject in any of the E<sub>2</sub>/LNG groups developed endometrial hyperplasia during the course of the study. The upper bound on the 95% confidence interval for the risk of hyperplasia in each of the E<sub>2</sub>/LNG groups was less than 4%.

The bleeding and spotting profiles were not good for the combination E<sub>2</sub>/LNG groups. Bleeding and spotting was analyzed at cycles 1, 3, 6, 9, 11, and 13. At all time points evaluated, no bleeding was noted in 69% of subjects in the E<sub>2</sub> 0.045 mg/day + placebo group. Forty six percent

(46.4%) of the E<sub>2</sub> 0.045 mg + LNG 0.015 mg/day group, 55.5% of the E<sub>2</sub> 0.045 mg + LNG 0.030 mg/day group and 53.6 % of the E<sub>2</sub> 0.045 mg + LNG 0.040 mg/day group noted no bleeding at all time points evaluated. At cycle 13, the cumulative amenorrhea rates were 75.6% in the E<sub>2</sub> 0.045 mg/day + placebo group, 41.2% in the E<sub>2</sub> 0.045 mg + LNG 0.015 mg/day group, 49.0% in the E<sub>2</sub> 0.045 mg + LNG 0.030 mg/day group, and 53.1% in the E<sub>2</sub> 0.045 mg + LNG 0.040 mg/day group.

The Sponsor analyzed a subgroup for treatment of vasomotor symptoms. The DSI recommendations, discussed earlier for Study 96042A (regarding exclusion of VMS data from the clinical sites inspected as well as calling into question these data from other clinical sites), were also applicable to the sub-study data in 96043A. Even if these DSI recommendations had not been made, patients for this sub-study analysis did not meet the HRT Guidance document enrollment criteria for frequency and severity of vasomotor symptoms and would not have been reviewed.

There were two deaths in this study. Subject 19003 in the E<sub>2</sub> 0.045 mg + LNG 0.030 mg/day group died secondary to cardiac arrest and subject 62013 in the E<sub>2</sub> 0.045 mg + LNG 0.040 mg/day group died due to metastatic lung cancer with brain metastasis. The Sponsor assessed these deaths as unrelated to study drug treatment. The clinical reviewers agree that the death due to metastatic lung cancer is most likely unrelated to any study drug use. The death due to cardiac arrest occurred in a smoker with a medical history of hypercholesterolemia. However, it can not be ruled out that study drug use (subject had 351 days of study drug treatment) may have had some causality in this event.

The Sponsor's Table 57 represents that 163 subjects (19.4% of the 840 subjects who took study drug) reported severe adverse events during the 52 weeks of the study. An adverse event was classified as severe if the subject was unable to perform her usual activities. The reviewer believes that given this definition these events are better classified as serious adverse events rather than severe adverse events. Application site reactions were seen in 5.7% of subjects. Vaginal hemorrhage (a broad term covering any vaginal bleeding) occurred in 2.3% of subjects, while breast pain, back pain and flu syndrome all occurred in about 1% of subjects. Breast pain appeared to be dose related while vaginal hemorrhage did not appear to follow a dose response.

Two hundred fifty six subjects (30.5% of the 840 subjects who took study medications) withdrew from the study because of adverse events. The most frequent adverse event that led to study withdrawal was vaginal hemorrhage which occurred in 39.8% (n = 102) of those subjects who withdrew. The rate of vaginal hemorrhage was 8.8% of subjects in the E<sub>2</sub> 0.045 mg/day + placebo group, 12.3% of subjects in the E<sub>2</sub> 0.045 mg + LNG 0.015 mg/day, 12.3% of subjects in the E<sub>2</sub> 0.045 mg + LNG 0.030 mg/day, and 15.0% of subjects in the E<sub>2</sub> 0.045 mg + LNG 0.040 mg/day group. The second most frequently reported adverse event that led to study withdrawal was application site reaction. The rate of application site reaction was 8.8% of subjects in the E<sub>2</sub> 0.045 mg/day + placebo group, 10.8% of subjects in the E<sub>2</sub> 0.045 mg + LNG 0.015 mg/day, 8.5% of subjects in the E<sub>2</sub> 0.045 mg + LNG 0.030 mg/day, and 5.6 % of subjects in the E<sub>2</sub> 0.045 mg + LNG 0.040 mg/day group). Breast pain occurred in 5.8% of those subjects withdrawing. The E<sub>2</sub> 0.045 mg/day + placebo group had no cases of breast pain, while the rates of breast pain in the E<sub>2</sub> 0.045 mg + LNG 0.015 mg/day, E<sub>2</sub> 0.045 mg + LNG 0.030 mg/day and the E<sub>2</sub> 0.045 mg + LNG 0.040 mg/day groups were 2.4%, 1.4% and 3.3% of subjects, respectively.

Mean HDL cholesterol rose slightly over 13 cycles in the E<sub>2</sub> 0.045 mg/day + placebo group, but mean HDL dropped in a dose dependent-manner for the E<sub>2</sub>/LNG groups.

### Discussion and Conclusions

The primary clinical study, 96042A, submitted to support treatment of vasomotor symptoms was not reviewed because the source documentation could not be verified. I agree with the primary clinical reviewer that the NDA can not be approved for the treatment of vasomotor symptoms

is supported by the data from study 96043A. If the Sponsor seeks to submit a new study(s) for the VMS a study(s) for osteoporosis and the data from such a study(s) is found to establish efficacy, then the results from Study 96043A could be used

The DMF supporting the CMC and Microbiology sections of the NDA was found to be deficient. The deficiencies in the DMF must be satisfactorily addressed before approval could be given to this drug product.

Shelley R. Slaughter, MD, Ph.D.  
Reproductive Medical Team Leader

cc: Division File NDAs 21-258

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/s/

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## EXECUTIVE SUMMARY

### I Recommendation

This reviewer recommends non-approval of Climarapro, henceforth referred to as E<sub>2</sub> 4.4 mg/LNG 1.39mg, E<sub>2</sub> 4.4mg/LNG 2.75mg, and 4.5mg/LNG 3.75mg, respectively. The Division of Scientific Investigations (DSI) could not validate the source documentation from three inspected sites for the data submitted in this NDA for study 96042A. Study 96042A was a 3-month double-blind, randomized, placebo-controlled study to determine the efficacy of E<sub>2</sub> 4.4/LNG 2.75mg and E<sub>2</sub> 4.5/LNG 3.75mg in the relief of hot flushes.

### II Summary of Clinical Findings

The sponsor has not demonstrated efficacy for ClimaraPro (estradiol and levonorgestrel transdermal patch) in clinical trials. In study 96042A, source documentation for this study could not be verified and DSI recommended that data in study 96042A not be used to support approval of this NDA.

In study 96043A, three dosages (4.4mg E<sub>2</sub>/LNG 1.39mg, 4.4mg E<sub>2</sub>/LNG 2.75mg, and 4.5 E<sub>2</sub>/LNG 3.75mg) of the estradiol/levonorgestrel transdermal patch produced a statistically significant reduction in the incidence of estrogen-induced hyperplasia when compared to daily 4.4mg estradiol alone. The reduction in estrogen-induced hyperplasia was at the p < 0.001 significance level with the upper bound of the 95% confidence interval at < 4% for each treatment group.

#### Overview of Clinical Program

Climara® is an approved estradiol patch since December 22, 1994. It is presently approved to treat 1) moderate-to-severe vasomotor symptoms associated with the menopause, 2) vulvar and vaginal atrophy, 3) osteoporosis, and 4) treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure. The dosage strengths of Climara are 0.025mg/day (6.5cm<sup>2</sup>), 0.050mg/day (12.5cm<sup>2</sup>), and 0.1 mg/day (25cm<sup>2</sup>). Climara is applied once weekly to an area of the abdomen or buttock.

With this NDA, the sponsor is seeking approval for a combination estrogen/progestin patch. The two controlled clinical studies, studies 96042A and 96043A, which were designed to evaluate the safety and efficacy of E<sub>2</sub>/LNG combination patch in the relief of postmenopausal vasomotor symptoms and urogenital symptoms in non-hysterectomized and hysterectomized women, were submitted for evaluation. Study 96042A was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate two dose levels of E<sub>2</sub>/LNG (E<sub>2</sub> 4.4mg/LNG 2.75mg and E<sub>2</sub> 4.5mg/LNG 3.75mg) for 3 continuous 28-day treatment cycles compared to placebo.

Study 96043A was a 1-year, multicenter, randomized, double-blind, parallel-group study in non-hysterectomized women that was designed to evaluate the safety and efficacy of the E<sub>2</sub>/LNG combination patch in the prevention of the development of endometrial hyperplasia.

#### Efficacy

Overall, the efficacy of E<sub>2</sub>/LNG could not be determined in this study. According to the IND protocol, subjects were to be provided with worksheets (diaries) for the daily recording of hot flushes and the weekly recording of urogenital symptoms during the run-in (baseline period) and the post-randomization treatment. During the run-in period, subjects were also instructed on the use of the Interactive Voice Response System (IVRS) to record the daily number and severity of hot flushes and the weekly presence

and severity of urogenital symptoms. During the treatment period subjects were to enter hot flush frequency and severity on a daily basis and enter the presence and severity of urogenital symptoms weekly into the IVRS. According to the IND Protocol, all original (source) data was to be included with the corresponding case report form (CRF) for review by the Monitor from Berlex Laboratories and copies of all CRFs were to be provided to the Principle Investigator for retention as required by applicable government regulations. No study source documentation could be verified after the initial baseline period for vasomotor symptoms. Source documentation was obtained at baseline with the use of a written record that was given to the subject; however, it was not used in the remaining portion of this study. The sponsor did not, a priori, notify the Division of Reproductive and Urological Products (DRUDP) of any modification of their study protocol, nor did the sponsor file a protocol amendment to apprise DRUDP that only the IVRS would be used, excluding written documentation. When study data was inspected by DSI at three sites source documentation could not be identified. Therefore, DSI could not recommend the use of data at these three sites from this study for support of the vasomotor symptoms (VMS) indication in this study. This reviewer concurs with that recommendation since deletion of at least 36 subjects from these sites substantially weakens the data base.

### Safety

This product is not considered to be unsafe. Significant adverse events were reported in study 96043A relating to vaginal hemorrhage, application site reactions, and breast pain. These adverse events would not have prevented approval of this product.

### Dosing

Of the three combination dosages studied it appears that the E<sub>2</sub> 4.4mg/LNG 1.39mg appears to be the lowest effective dose in reducing the amount of estrogen-induced hyperplasia.

### Special Populations

No special populations were studied.

## Clinical Review

### **I Introduction and Background**

Drug: Estradiol and Levonorgestrel transdermal system

Generic name: 17-beta estradiol and levonorgestrel, USP

Proposed Trade name: ClimaraPro

Chemical name: Estradiol USP (estra-1, 3,5, (10)-triene-3, 17β  
18,19-Dinorpregn-4-en-20-yn-3-one, 13-ethyl-17hydroxyl-, (17α)-

Sponsor: Berlex Laboratories, Inc.  
340 Changebridge Road  
P.O. Box 1000  
Montville, NJ 07045-1000  
(973) 276-2000

Pharmacologic Category: Estrogen/Progestin

Proposed Clinical Indication: 1) Treatment of moderate-to-severe vasomotor symptoms associated with the menopause

Dosages and Route of Administration: 22cm<sup>2</sup> 0.045mg/day estradiol combined with either 0.015 or 0.030 mg/day levonorgestrel; or 30 cm<sup>2</sup> 0.045mg/day estradiol combined with 0.040mg/day levonorgestrel for continuous wear

NDA Drug Class: 3S

Related Drugs: Approved transdermal patch for HRT is Combipatch™

Related Submission: IND 51,188

- II Chemistry, Animal Pharmacology and Toxicology, Microbiology: See Pharmacologist review
- III Human Pharmacokinetics and Pharmacodynamics: See Biopharmaceutics review
- IV Study 96043A

#### Objective

The primary objective of this study was to evaluate the efficacy of 13 28-day cycles of continuous E<sub>2</sub>/LNG combinations compared to continuous E<sub>2</sub> by analysis of protection of the uterus against hyperplasia in postmenopausal women. Secondary objectives included; the evaluation of the effect of E<sub>2</sub>/LNG compared to continuous E<sub>2</sub> on endometrial morphology and bleeding patterns; comparisons of E<sub>2</sub>/LNG to continuous E<sub>2</sub> on the well-being of postmenopausal women as assessed by the Women's Health Questionnaire (WHQ) and the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36); and evaluation of the effect of three 28-day cycles of continuous E<sub>2</sub>/LNG combination compared to continuous E<sub>2</sub> on the frequency and severity of hot flushes and it's effect on the relief of urogenital symptoms.

#### Design

This was a 52-week, multicenter, double-blind, randomized, parallel-group study of E<sub>2</sub> compared with 3 continuous combinations of E<sub>2</sub>/LNG. The subjects were evaluated for 13 28-day cycles.

#### Source and number

This study was conducted at 73 centers in the US. All study centers were private practices or investigational institutions experienced in the conduct of clinical studies involving female health care. At each center, the principal investigator was responsible for the study, and the study protocol was approved by the IRB.

### Entrance Criteria

Women who satisfied the following criteria were included into the study:

1. Age  $\geq 45$  and  $\leq 75$  years;
2. Intact uterus and diagnostically valid negative endometrial biopsy, or if inadequate tissue endometrial thickness  $< 5\text{mm}$  on transvaginal ultrasound (TVS);
3. Amenorrhea for  $\geq 12$  months, or if amenorrhea was  $< 12$  month duration, but  $\geq 6$  months, serum estradiol levels should have been  $< 20$  pg/mL and serum follicle stimulating hormone (FSH) level  $> 40\text{mIU/mL}$ ;
4. Negative pregnancy test, if appropriate (within one year of amenorrhea; and
5. Signed informed consent.

### Exclusion Criteria

A women was considered ineligible for the study if any of the following conditions were identified:

1. Baseline endometrial biopsy containing endometrial polyp (alone) or simple hyperplasia or worse;
2. Abnormal Pap smear suggestive of low-grade squamous intraepithelial lesion (LGSIL) or worse. Enrollment of subjects with atypical squamous cells of undetermined significance (ASCUS) interpretation must have been discussed with the sponsor;
3. Baseline ultrasound with abnormality that would preclude estrogen therapy;
4. Myocardial infarction within the last six months prior to Visit one or heart disease severe enough to require treatment with antiarrhythmic or antianginal drugs;
5. Idiopathic thrombophlebitis or thromboembolic disorders within the last three years that were unrelated to estrogen therapy or a history of these conditions at any time with previous estrogen therapy;
6. History of stroke or transient ischemic attacks;
7. Fasting baseline cholesterol  $\geq 300$  mg/dL, triglycerides  $\geq 300$  mg/dL, or glucose  $\geq 140$  mg/dL;
8. Hypertension; sitting systolic blood pressure (BP)  $\geq 160\text{mmHg}$  or sitting diastolic BP  $\geq 95\text{mmHg}$  at rest;
9. Congestive heart failure;
10. Known or suspected malignant or premalignant disease, including malignant melanoma (excluding other successfully treated skin cancers) or a history of these conditions;

11. History of sex steroid-dependent malignancy;
12. Abnormal clinically significant finding during gynecological examination which may in the opinion of the investigator worsen under hormone treatment;
13. Insulin-dependent diabetes mellitus;
14. Uncontrolled thyroid disorders;
15. Current or past history of clinically significant depression;
16. History of alcohol or drug abuse within the last two years;
17. Treatment with anticoagulants (heparin or warfarin);
18. Hormone therapy (oral, transdermal, intrauterine, or intravaginal administration) within eight weeks prior to start of study; intramuscular administration within six months prior to start of study; estrogen implants (still implanted or removed with less than eight weeks prior to start of study);
19. Participation in another clinical trial within one month or receipt of an investigational drug within the last three months prior to study entry;
20. Any disease or condition that compromises the function of the body systems and could result in altered absorption; excessive accumulation, impaired metabolism, or altered excretion of the study medication;
21. Severe systemic disease which might interfere with the conduct of the study or the interpretation of the results;
22. Current significant liver dysfunction or disease;
23. Abnormal baseline laboratory values that were considered clinically significant ;
24. Urinary tract infection; and
25. Increased frequency or severity of headaches including migraines during previous estrogen therapy.

**Comment: Inclusion and Exclusion appear consistent with other clinical trials for ERT and HRT except for #24 under exclusion criteria. Chronic renal disease would appear to be a more appropriate exclusion criterion.**

A subject had the right to withdraw from the study at any time, however, she was informed that it was extremely important that the reason for discontinuing be reported and that a complete final examination, including physical examination and clinical tests be performed at that time. In addition, in all subjects who withdrew, investigators were instructed to attempt to evaluate the endometrium by an endometrial biopsy. A transvaginal ultrasonography was performed if the tissue sample was insufficient. The principal investigator, on the appropriate CRF page, specified the circumstances of discontinuation.

Subjects were withdrawn from the study for any of the following reasons:

1. Development of endometrial polyp alone or simple hyperplasia or worse;
2. Occurrence for the first time of migrainous headaches or more frequent occurrence of unusually severe headaches;
3. Sudden perceptual disorders (e.g. Disturbances of vision or hearing);
4. First signs of thrombophlebitis or thromboembolic symptoms (e.g. Unusual pain in or swelling of the legs, stabbing pains on breathing, or coughing for no apparent reason);
5. A feeling of pain and tightness in the chest;
6. Pending operations (six weeks beforehand)
7. Prolonged immobilization (e.g. following accidents);
8. Development of LGSIL or worse by cervical cytology, colposcopy, and histology;
9. Onset of jaundice;
10. Onset of hepatitis;
11. Itching over the whole body;
12. Significant (per investigator's discretion) rise in blood pressure;
13. Development of other conditions described as exclusion criteria; and
14. Investigator reserved the right to discontinue women who were non-compliant.

## **V Study Procedures**

Potentially eligible subjects entered a screening period to assess tolerance of the transdermal system and the severity of menopausal symptoms related to estrogen deprivation. The study included subjects with or without vasomotor symptoms. Potential subjects who had vasomotor symptoms were to complete a screening assessment of the severity of these symptoms. All subjects who had not previously worn a transdermal estradiol delivery system were given a placebo patch and instructed to apply the patch for one week to a site on the abdomen. Subjects who had skin irritation greater than Grade 2 at the patch application site were not enrolled in the study. A complete medical, surgical, gynecological, and concomitant medication history was obtained at screening and a physical examination was performed. Vital signs, endometrial biopsy evaluation, pregnancy test (if applicable), mammography, and laboratory profile were obtained.

Postmenopausal women, with and without menopausal symptoms, who satisfied the inclusion/exclusion criteria, qualified for this study. Each subject was assigned to one of four treatment groups (three regimens of continuous E<sub>2</sub>/LNG and one regimen of continuous E<sub>2</sub>). Visit one constituted the initial screening visit. All subjects were given a worksheet to record their symptoms and bleeding patterns throughout the study. At visit two (which was performed within four weeks of Visit one) the investigator determined the

subject's eligibility for study participation. Women who qualified but did not have symptoms were randomized at visit 2. Women who qualified and had symptoms between Visits one and two were asked to record the frequency and severity (mild, moderate, severe) hot flushes by Interactive Voice Response System (IVRS) for the next two weeks. Upon return at Visit 2A, all women were randomized and, if a woman had  $\geq 15$  hot flushes during any consecutive seven days of a two-week run-in period, she was enrolled in a symptoms substudy. Subsequently, after a visit at one month, clinic visits were scheduled at 2, 3, and 4-cycle intervals for a total of thirteen, 28-day cycles.

If the final visit occurred prior to Visit 7 (end of cycle 13 or Final visit), every attempt was made to complete the final visit evaluations specified for Visit 7. This included a physical examination, vital signs and weight, pap smear, a mammography if  $> 1$  year, endometrial biopsy, transvaginal ultrasound (if endometrial biopsy contained tissue insufficient for diagnosis), and hematologic and blood chemistries including serum lipids, and a urinalysis.

Subjects were randomized to one of four active study drug treatment groups. Treatment was administered via a transdermal delivery system (patch). Active study drug was provided at a dosage of either E<sub>2</sub> 4.4mg, E<sub>2</sub> 4.4mg/ LNG 1.39mg, E<sub>2</sub> 4.4mg/LNG 2.75 mg, or E<sub>2</sub> 4.5mg/LNG 3.75mg. The sizes of the patches were 22cm<sup>2</sup> for patches containing E<sub>2</sub> 4.4mg and 30 cm<sup>2</sup> for patches containing E<sub>2</sub> 4.5mg. All patches were applied to the abdomen avoiding the waistline since tight clothing could dislodge the patch. Two patches were applied simultaneously, one containing active drug and one containing placebo.

Women were instructed not to use a sauna or steam bath while wearing the patches during the study. Use of non-medicated soap was permitted; however, subjects were instructed to keep the area as dry as possible, and not expose the patches to light. Patches were designed to deliver drug continuously over seven days.

Patches were worn continuously and changed weekly. At the end of each week two new patches were applied to different sites on the abdomen. Patches were not removed except for weekly scheduled replacement. If a patch became dislodged between applications, an attempt was made to reapply it. If a patch partially lifted from the skin, it was pressed back into place. If it failed to remain affixed or became completely detached, a replacement patch was applied.

Each cycle pack contained one additional Patch A and one additional Patch B that could be applied for the remainder of the week in case either of these patches fell off prematurely. The regular cycle of patch replacement was then resumed. If a second patch fell off during the same cycle, it was not replaced; new patches were applied at the end of the week and the weekly cycle of patch wear resumed.

### **Efficacy Considerations**

In order to compare treatments with 2-sided hypothesis testing and further estimate the dose response by calculating one-sided confidence intervals within each treatment group, two complementary sample size calculations were provided; the larger estimate was chosen.

Per the sponsor, the number of subjects per treatment group should be large enough for a power comparison of the treatments, and should also be large enough with respect to the precision of the confidence intervals.

#### Comparison of treatments:

Determination of a statistically adequate sample size is based on the incidence of hyperplasia in the endometrium. The incidence of hyperplasia (first surrogate marker for endometrial carcinoma) in subjects treated with E<sub>2</sub> alone is estimated to be 20% at 6 months and 21% at 12 months (Woodruff et al AJOG, 170:1213-23, 1994 and PEPI trial: JAMA 275:275:370-5, 1996); in subjects treated with an E<sub>2</sub>LNG combination the estimate of endometrial hyperplasia is 1% at 1 year. When the level of significance (with Bonferroni correction for 3 comparisons of opposed to unopposed estrogen) is present at 0.0167 (two-tailed) a sample of 120 subjects per group detects this treatment difference with a power of 99%.

#### Estimate of dose response relationship:

If neither hyperplasia nor cancer were observed in any group, the upper limit of within-group 95% confidence intervals should be no greater than 2%. This means that 150 subjects should be in each treatment group. Because a discontinuation rate of 25% is presupposed, 200 subjects per group were enrolled.

Based on the above sample size calculations, 800 subjects were to be enrolled in order for 600 subjects to complete 13 cycles (150 subjects per treatment group). An approximate 25% discontinuation rate was presupposed.

#### Subgroup analyses

Reduction from baseline in number and severity of hot flushes was analyzed for the subgroup of subjects who indicated during screening that they experienced symptoms. These subjects qualified, by demonstrating via daily IVRS records, that they had  $\geq 15$  hot flushes during any consecutive 7 days of a 2 week run-in period. This run-in period served as the subject's baseline. Qualifying subjects were then asked to record the number and severity of daily hot flushes for 12 treatment weeks.

#### Statistical Procedures

The assessment of efficacy was based on two study populations, the intent-to-treat (ITT) and the valid-case population. The primary analysis is based on the ITT for all women randomized. A subject was included in the valid-case population if she had 75% or greater compliance and no protocol deviations that might affect the primary target variable or any secondary target variable.

**Comment: The statistical plan for this study appears appropriate and in retrospect calculating a larger sample size was very important in validating the use of confidence intervals to reach a conclusion.**

#### Safety considerations

Safety was assessed based on the ITT population. The following parameters were assessed: AEs, vital signs, physical examinations, including Pap smear, endometrial biopsy, and clinical labor tests.

## Results

A total of 1511 subjects were screened in 76 study centers in the US. Of these 1511 subjects, 845 at 73 study centers were randomized to treatment. Two hundred-four (204) subjects were randomized to receive E<sub>2</sub> 4.4mg alone, 213 were randomized to receive the combination of E<sub>2</sub> 4.4mg/LNG 1.39mg, 212 were randomized to receive the combination of E<sub>2</sub> 4.4mg/LNG 2.75mg, and 216 were randomized to receive the combination of E<sub>2</sub> 4.5mg/LNG 3.75mg. Of the 845 subjects randomized, a total of 5 subjects never used the study drug: 1 subject (Subject 68004) in the E<sub>2</sub> 4.4mg/LNG 1.39mg treatment group, 1 subject (65006) in the E<sub>2</sub> 4.4mg/LNG 2.75mg treatment group, and 3 subjects (Subjects 08025, 28013, and 28018) randomized to the E<sub>2</sub> 4.5mg/LNG 3.75mg treatment group.

A total of 467 subjects reached Cycle 13 of the study: 118 in the E<sub>2</sub> 4.4mg group, 116 subjects in the E<sub>2</sub> 4.4mg/LNG 1.39 group, 115 subjects in the E<sub>2</sub> 4.4 mg/LNG 2.75mg group, and 118 in the E<sub>2</sub> 4.5mg/LNG 3.75mg group.

The following table shows subject disposition by treatment group:

Table 1

Sponsor table 7 Vol.36

Category	Treatment Group				Total
	E <sub>2</sub> 4.4mg	E <sub>2</sub> 4.4mg/LNG 1.39mg	E <sub>2</sub> 4.4mg/LNG 2.75mg	E <sub>2</sub> /4.5mg/LNG 3.75mg	
Subjects Screened	NA	NA	NA	NA	1511
Subjects Randomized	204	213	212	216	845
Visits Completed					
Baseline (0-14 days)	204	212	211	213	840
Cycle 1 (15-42 days)	201	209	211	211	832
Cycle 3 (43-140 days)	193	196	199	193	780
Cycle 7 (141-238 days)	168	151	153	147	619
Cycle 10 (239- 322 days)	136	128	125	128	517
Cycle 13 (> 323 days)	118	116	115	118	467

NA = Not applicable

Note at Cycles 7 and 10 a greater number of subjects are still receiving treatment drug in the E<sub>2</sub> 4.4 mg group. This was later confirmed by the sponsor who presented Figure 7 (not reproduced) which displayed Kaplan-Meier curves estimates of study continuation probability by treatment group. The Kaplan-Meier plots revealed that subjects in the E<sub>2</sub>/LNG treatments groups withdrew earlier compared to the E<sub>2</sub> group. The curves for the various E<sub>2</sub> LNG groups were similar.

The sponsor also presented a table 9 (Vol. 36) which reported the number of subjects who would have been excluded if a Valid Case Analyses were to be used by this reviewer. In all, 195 subjects would have been excluded if a Valid Case Analyses were to be used with the largest majority 170 for "Other" protocol violations and 144 relating to treatment schedule violations (Note subjects could have had more than 1 reason for exclusion).

There were three hundred ninety-two (392, 46.7%) of the 840 subjects who withdrew from the study and prematurely discontinued study medication. Among these subjects, 256/840 (30.5%) withdrew due to adverse events, 17/840 (2.0%) withdrew due to protocol deviations, and 15/840 (1.8%) withdrew due to lack of efficacy. There were two deaths during the study: one in the E<sub>2</sub> 4.5mg/LNG treatment group and one in the 4.4mg/LNG 2.75mg group. The following table gives a breakdown of the frequency of withdrawals by reason and treatment group:

Table 2

## Frequency of Withdrawal by Reason of Treatment Group

Sponsor Table 11, Vol. 36

Reason for Withdrawal	Treatment Group				Total N = 840 n (%)
	E <sub>2</sub> 4.4mg N=204 n (%)	E <sub>2</sub> 4.4mg/LNG 1.39mg N = 212 N (%)	E <sub>2</sub> 4.4mg/LNG 2.75mg N = 211 n (%)	E <sub>2</sub> /4.5mg/LNG 3.75mg N = 213 n (%)	
Adverse Event	55 (27.0)	69 (32.5%)	66 (31.3%)	66 (31.0%)	256 (30.5%)
Lack of Efficacy	13 (6.4%)	0 (0.0%)	1 (0.5%)	1 (0.5)	15 (1.8%)
Protocol Deviation	5 (2.5%)	4 (1.9%)	4 (1.9%)	4 (1.9%)	17 (2.0%)
Withdrawal of Consent	9 (4.4%)	12 (5.7%)	10 (4.7%)	8 (3.8%)	39 (4.6%)
Other <sup>a</sup>	7 (3.4%)	14 (6.6%)	22 (10.4%)	20 (9.4%)	63 (7.5%)
Death	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.5%)	2 (0.2%)
<b>Overall<sup>b</sup></b>	<b>89 (43.6%)</b>	<b>99 (46.7%)</b>	<b>104 (49.3%)</b>	<b>100 (46.9%)</b>	<b>392 (46.7%)</b>

N = Total number of subjects per treatment group

n = number of subjects withdrawn within a treatment group

<sup>a</sup> "Other" includes lost to follow-up

<sup>b</sup> A subject withdrawn for more than 1 reason was counted once when determining the overall number of withdrawals.

Note a difference in subjects at Visit 7 or Cycle 13 in Table 1. Four hundred sixty-seven (467) subjects were reported to have completed Cycle 13. However, of these 467 subjects, 19 prematurely discontinued study medication after completing Cycle 13,

therefore, the corrected subjects who were still on medication at the end of cycle 13 number is 448 subjects (467-19).

The following table gives an overview of all subject populations in this study. It should be noted that subjects in the efficacy valid case population will not be reviewed and subjects in the symptom substudy will be commented upon but will not be formally reviewed.

Table 3

Sponsor's table 12, Vol. 34

Subject Population	Treatment Group				Total
	E <sub>2</sub> 4.4mg	E <sub>2</sub> 4.4mg/LNG 1.39mg	E <sub>2</sub> 4.4mg/LNG 2.75mg	E <sub>2</sub> 4.5mg/LNG 3.75mg	
All Subjects	204	212	211	213	840
Efficacy ITT	202	210	209	211	832
Efficacy Valid Case	158	165	168	159	650
Symptoms Substudy	34	27	34	31	126
Safety ITT	204	212	211	213	840

During the study it was necessary to close a site (Site 34, Investigator Dorfner [8 subjects]) because of a number of deviations, including violations of Good Clinical Practices (GCPs). Dr. Dorfner's site was excluded from the pooled centers for the ITT population used for efficacy analysis but was included in the pooled centers for the demographic and safety analyses, in which the ITT population was used following the same pooling of centers criteria.

At one site, a subject in the E<sub>2</sub> 4.4mg group (Subject 43003) was inadvertently administered study medication for another subject (Subject 43008) in the E<sub>2</sub> 4.5mg/LNG 3.73mg group. Subject 43003 began taking study drug on October 13, 1998. The inadvertent dispensing of the incorrect drug occurred on May 24, 1999; the subject used four patches of incorrect drug prior to discontinuing the study on June 29, 1999.

Baseline demographic characteristics showed the majority of subjects were Caucasian 90.7% (762/840), African American 4.4% (37/840), Hispanic 3.45% (29/840), Asian <1% (8/840), and 4 "Other" < 1%. The age ranged was 44 to 76 years of age, with a mean age of 55.8 years. Four subjects did not meet the age inclusion criterion but were given exemptions and included in the study: two subjects in the E<sub>2</sub> 4.4mg group (44 and 76 years old), one subject in the E<sub>2</sub> 4.4mg/LNG 2.75mg group (44 year old), and one subject in the E<sub>2</sub> 4.5mg/LNG 3.75mg group (44 years old). Treatment groups were comparable with respect to weight, height, systolic and diastolic blood pressure, heart rate, smoking history, and the number of cigarettes per day. Estradiol, FSH and TSH levels were also comparable between treatment groups.

Estradiol was measured in 132 subjects and ranged from 1.4 pg/mL to 67.9 pg/mL. Eight (8) subjects had estradiol levels  $\geq$  20 pg/mL at baseline. Two additional subjects were amenorrheic less than 12 months and did not meet the estradiol level criterion; the protocol deviations were noted. The other six subjects were amenorrheic greater than 12 months and the assessment of E<sub>2</sub> was not required.

FSH was measured in 155 subjects and ranged from 24 to 163 mIU/mL. Eight (8) subjects had FSH levels of  $\leq 40$  mIU/mL at baseline. One subject was amenorrheic less than 12 months and did not meet the FSH inclusion criterion; a protocol deviation was noted. The other 7 subjects were amenorrheic greater than 12 months and assessment of FSH was not required.

Baseline gynecological history showed of 293 subjects, 64.8% (190/293) had not had bilateral oophorectomy while 34.8% (102/293) had bilateral oophorectomy. However, percentages are slightly reversed in regard to hysterectomy. Fifty-eight point seven percent (58.7%), [172/293] had a hysterectomy while 41.3% (121/293) did not have a hysterectomy.

The treatment groups were comparable with respect to the number of subjects who had endometrial biopsies. Of the 832 subjects who had biopsies, 614 (73.8%) subjects had a diagnosis of atrophic endometrium and 94 (11.3%) subjects had endometrial tissue that was insufficient for diagnosis. Subjects who had endometrial tissue that was insufficient for diagnosis were enrolled if a transvaginal ultrasound (TVS) showed an endometrial thickness of  $<5$ mm. Additionally, it was noted that 43 (5.2%) of subjects had proliferative endometrium, with equal distribution between treatment groups; two subjects had secretory endometrium and five had menstrual-type endometrium. One subject in the E<sub>2</sub> 4.5mg/LNG 3.75mg group was noted to have simple hyperplasia.

Eight subjects did not have a biopsy done at baseline: one in the 4.4mg E<sub>2</sub> group (patient refusal), one in the E<sub>2</sub> 4.4mg/LNG 1.39 group (previous biopsy  $< 6$  months in another study), three in the E<sub>2</sub> 4.4mg/LNG 2.75mg group (two subjects with prior biopsy and one subject with cervical stenosis), and three in the E<sub>2</sub> 4.5/LNG 3.75mg group (2 subjects with a prior biopsy and one subject with cervical stenosis).

Baseline mammography was required of all subjects. Summary data reported 91.5% (268/293) of all mammograms to be read as normal. In the placebo group 5.4% (88/93) were reported to have an abnormal mammogram, in the E<sub>2</sub> 4.4mg/LNG 2.75mg 3.1% (3/96) were reported to have an abnormal mammogram, and in the E<sub>2</sub> 4.5mg/LNG 3.75mg group 18.3% (17/104) subjects were reported to have an abnormal mammogram at baseline.

Medication history and concomitant medications were recorded. Seven hundred ninety-nine (799, 95.1%) subjects took one or more concomitant medications during the study. All medications taken by the subject during the course of the study were recorded on the concomitant medication record.

Subjects were required to return the unused study medication and empty pouches at each subsequent clinic visit. Drug compliance was assessed using the IVRS and drug inventory records. Women who were not compliant with the protocol could be excluded from the study at the discretion of the investigator.

The primary efficacy variable was the incidence of endometrial hyperplasia. Two subjects (subjects 04013 and 45004) were without any biopsy (either baseline or post-baseline) at any time during the study. Subject 38029 had a diagnosis of simple hyperplasia at baseline and was excluded from the efficacy analyses. Subject 04013 was in the E<sub>2</sub> 4.4mg group and subjects 45004 and 38029 were in the E<sub>2</sub> 4.5mg/LNG 3.75mg group.

**Comment: All three subjects represent screening failures and were appropriately not included into the efficacy evaluation.**

The sponsor used several different approaches to analyze endometrial hyperplasia because of the relatively high proportion of subjects who withdrew without a post-baseline biopsy (because they withdrew early) or with an insufficient biopsy. In addition there were subjects who withdrew with an adequate post-baseline biopsy but had no evidence of endometrial hyperplasia.

Two types of withdrawal were defined: Type I withdrawal and Type II withdrawal. A subject was defined as a Type I withdrawal if a subject prematurely withdrew from the study *without* a post-baseline biopsy done at the time of withdrawal or the sample was insufficient if a biopsy was attempted. A subject was defined as a Type II withdrawal if a subject prematurely withdrew *with* a post-baseline biopsy done at the time of withdrawal and if the biopsy showed no evidence of endometrial hyperplasia.

**Comment: This reviewer prefers Type I since this group had no post-baseline biopsy and is more consistent with the categorization of exclusions seen in other Phase 3 clinical trials that assess endometrial protection. In Type II the number is smaller but less patients are accounted for because a post-baseline biopsy was obtained and no hyperplasia was present. Both methods will be presented for comparison, but this reviewer's emphasis will be on Type I.**

The following table shows the proportion of subjects with an adequate biopsy showing endometrial hyperplasia and/or cancer at any time during the study, Type I withdrawals were excluded:

Table 4

Proportion of Subjects with Adequate Biopsy Showing Endometrial Hyperplasia and/or Cancer at Any Time During the Study—Type I Withdrawals Were Excluded  
Intent-To-Treat

Sponsor's Table 18 Vol.36

Statistics	Treatment Group				Overall p-value <sup>b</sup>
	E <sub>2</sub> 4.4mg (N=201) <sup>a</sup>	E <sub>2</sub> 4.4mg/LNG 1.39mg (N=210)	E <sub>2</sub> 4.4mg/LNG 2.75mg (N=209)	E <sub>2</sub> 4.5mg/LNG 3.75mg (N=209) <sup>a</sup>	
n <sup>c</sup>	148	147	138	142	<0.001*
No (%)	129 (87.2%)	147 (100.0%)	138 (100.0%)	142 (100.0%)	
Yes (%)	19 (12.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Lower <sup>d</sup>	7.11%	0.00%	0.00%	0.00%	
Upper <sup>d</sup>	18.57%	2.48%	2.64%	2.56%	
p-Value		<0.001 [*]	<0.001 [*]	<0.001 [*]	

N = number of Intent-to treat subjects within treatment group

<sup>a</sup> Subject 04013 and subjects 45004 and 38029 were excluded from the primary efficacy analysis.

<sup>b</sup> Overall effect p-value was obtained from the Fisher's Exact test. \* p <0.05

<sup>c</sup> n = (number of ITT subjects in the primary efficacy analysis) – (number of Type I withdrawals).

<sup>d</sup> Lower and Upper refer to the 95% lower and upper confidence limits for a single proportion. For the E<sub>2</sub> 4.4mg group, a normal approximation method was used, for the combination groups the exact method was used.

<sup>e</sup> p-values are for comparisons of each opposed dose against unopposed dose using the Fisher's Exact test. p-values were adjusted by the method of Bonferroni: [\*] p < 0.0167.

The following table presents the proportion of subjects with endometrial hyperplasia and/or cancer at any time during the study:

Table 5

Proportion of Subjects with Endometrial Hyperplasia and/or Cancer at  
Any Time During the Study—Both Type I and Type II Withdrawal  
Were Excluded—Intent to Treat

Sponsor's Table 19 Vol.36

Statistics	Treatment Group				Overall p-value <sup>b</sup>
	E <sub>2</sub> 4.4mg (N=201) <sup>a</sup>	E <sub>2</sub> 4.4mg/LNG 1.39mg (N=210)	E <sub>2</sub> 4.4mg/LNG 2.75mg (N=209)	E <sub>2</sub> /4.5mg/LNG 3.75mg (N=209) <sup>a</sup>	
N <sup>c</sup>	110	102	92	98	<0.001*
No (%)	91 (82.7%)	102 (100.0%)	92 (100.0%)	98 (100.0%)	
Yes (%)	19 (17.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Lower <sup>d</sup>	9.75%	0.00%	0.00%	0.00%	
Upper <sup>d</sup>	24.79%	3.55%	3.93%	3.69%	
p-Value		<0.001 [*]	< 0.001 [*]	<0.001 [*]	

N = number of intent-to-treat subjects within treatment group

<sup>a</sup> Subject 04013 and subjects 45004 and 38029 were excluded from the primary efficacy analysis.

<sup>b</sup> Overall effect p-value was obtained from the Fisher's Exact test. \* p < 0.05

<sup>c</sup> n = (number of ITT subjects in the primary efficacy analysis) – (number of Type I withdrawals).

<sup>d</sup> Lower and Upper refer to the 95% lower and upper confidence limits for a single proportion. For the E<sub>2</sub> 4.4mg group, a normal approximation method was used, for the combination groups the exact method was used.

<sup>e</sup> p-values are for comparisons of each opposed dose against unopposed dose using the Fisher's Exact test.

p-value were adjusted by the method of Bonferroni: [\*]  $p < 0.0167$ .

**Comment:** In comparing the previous two tables it is clear that Table 4 reflects data most consistent with an ITT treatment population (or an evaluable population in this trial). This table reflects data at any time during the study. Note that the upper bound of the 95% confidence interval is <3% with this analysis. Table 5 is the more conservative approach because only biopsy data is reviewed; the upper bound of the 95% confidence interval did not exceed <4%.

The sponsor also conducted a life table-like analysis to adjust for withdrawals. The following Table 6 represents a life table-like analysis. Of the 19 subjects in the E<sub>2</sub> 4.4mg treatment group with a diagnosis of endometrial hyperplasia, three subjects had a diagnosis of endometrial hyperplasia within 6 months of treatment and 16 subjects were diagnosed with endometrial hyperplasia after six months of treatment.

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## Endometrial Biopsy Results at Any Time During the Treatment Period by Treatment

Table 6

Intent to Treat

Sponsor's table 26, Vol. 36

	E <sub>2</sub> 4.4mg	E <sub>2</sub> 4.4mg LNG 1.39mg	E <sub>2</sub> 4.4mg LNG 2.75	E <sub>2</sub> 4.5mg LNG 3.75mg	Total
Total Number of Subjects	202	210	209	211	832
Biopsy					
Yes	163	156	150	150	619
Not Done/Unknown	39	54	59	61	213
Biopsy result					
Tissue Insufficient for Diagnosis	15 (9.2%)	9 (5.8%)	12 (8.0%)	8 (5.3%)	44 (7.1%)
Benign Surface and Glandular Lining	3 (1.8%)	3 (1.9%)	0 (0.0%)	1 (0.7%)	7 (1.1%)
Atrophic Endometrium	62 (38%)	76 (48.7%)	87 (58%)	91 (60.7%)	316 (51.1%)
Proliferative Endometrium	55 (33.7%)	35 (22.4%)	29 (19.3%)	29 (19.3%)	148 (23.9%)
Progestational Secretory Endometrium	0 (0.0)	2 (1.3%)	8 (5.3%)	8 (5.3%)	18 (2.9%)
Menstrual Type Endometrium	9 (5.5%)	30 (19.2%)	14 (9.3%)	13 (8.7%)	66 (10.7%)
Simple Hyperplasia	17 (10.4%)	0 (0%)	0 (0%)	0 (0.0)	17 (2.7%)
Complex Hyperplasia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Atypical Hyperplasia	2 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.3%)
Cancer	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Polyps					
Yes	3	1	4	4	12
No	160	155	146	146	607

**Comment:** Note the high number of biopsies which were either not done or are unknown. In this study 25.6% of subjects have no data relating to an end of treatment biopsy. Although this figure is high, it is not unusual and has been reported in other HRT clinical trials. Historically, subjects who leave a study for whatever reason, do not want an exit biopsy because the biopsy is uncomfortable. In reviewing the sponsor's attempt at constructing a life-table analysis, the biopsy results that are presented are consistent with a combination product. Note atrophic endometrium biopsy material shows a dose response in that the higher the dose of progestin, the greater the atrophic endometrium. There is similar effect upon proliferative endometrium, as the progestin is increased there is less proliferative endometrium.

The sponsor reported data on the proportion of subjects who had bleeding by treatment cycles 1, 3, 6, 9, 11, and 13. All subjects had been required to have amenorrhea for at least 6 months prior to study entry. At all endpoints, no bleeding was noted in 138 (69%) of subjects in the E<sub>2</sub> 4.4mg treatment group, and in 97 (46.4%), 116 (55.5%) and 113 (53.6%) of the E<sub>2</sub> 4.4mg/LNG 1.39mg, E<sub>2</sub> 4.4mg/LNG 2.75 mg, and E<sub>2</sub> 4.5mg/LNG 3.75mg, groups, respectively. At all endpoints there was a statistically significant difference found between the E<sub>2</sub> 4.4mg group and each of the E<sub>2</sub>/LNG treatment groups.

The number of bleeding days was also studied for treatment cycles 1, 3, 6, 9, 11, and 13. At all endpoints, the mean number of bleeding day was statistically significantly greater in the E<sub>2</sub> LNG<sub>1</sub> treatment groups compared to the E<sub>2</sub> 4.4mg group. Subject mean bleeding days were reported as 2.73, 3.56, 2.97, and 3.58 days of bleeding in the E<sub>2</sub> 4.4mg group, and in E<sub>2</sub> 4.4mg/LNG 1.39, E<sub>2</sub> 4.4/LNG 2.75mg, and E<sub>2</sub> 4.5mg/LNG 3.75mg groups, respectively.

The number of spotting days was also studied at treatment cycles 1, 3, 6, 9, 11, and 13. At endpoints through cycle 6, the E<sub>2</sub> 4.4mg group has statistically significant less spotting than the E<sub>2</sub>/LNG groups. In cycles 7 through 13 not all-pairwise comparisons were significant, but the trend was less bleeding in the E<sub>2</sub> 4.4mg group.

**Comment:** The number of amenorrhea cycles reported in this trial is disappointing. It is surprising that the E<sub>2</sub> 4.4mg group would show better cycle control than the combination products. The combination products were originally theorized to produce an inactive endometrium after the first 3-6 months while providing endometrial protection. This has been shown in other ERT products. It is evident that a substantial number of subjects are either bleeding, spotting or both throughout this trial and that cycle control was not achieved.

As one of the main secondary efficacy variables, the sponsor analyzed a subgroup of 126 subjects who indicated during screening that they experienced vasomotor symptoms. These subjects then qualified for substudy analyzes by demonstrating via daily IVRS records that they had  $\geq 15$  hot flushes (mild, moderate, and severe) during any consecutive 7 days of a 2-week run-in period. Of the 126 subjects who qualified for the symptom substudy, 4 subjects did not have baseline weekly hot flush results.

Results within each of the treatment groups show that the mean number of hot flushes was statistically significant lower from the respective baseline mean weekly number of hot flushes at each cycle, at all endpoints and at the completers endpoint.

**Comment:** This substudy was designed as supportive to the data in study 96042A. DSI recommended exclusion of subgroup data from 3 study sites therefore, data was not reviewed. However, even if this recommendation had not been made, under the 1995 Guidance For Clinical Evaluation of Estrogen and Estrogen/Progestin Containing Drug Products Used For Hormone Replacement

**Therapy in Postmenopausal Women (and the proposed revisions to this Guidance) this substudy would not qualify as supportive because the study does not contain the prerequisite number of moderate- to-severe VMS, that is, a minimum of 7-8 moderate-to-severe hot flushes per day or 50 to 60 per week. Therefore, this study was not reviewed.**

The sponsor reported data on a subset of subjects (n =26-34) with stress incontinence, nocturia, vaginal dryness and dyspareunia through cycles 1, 2, 3, 6, and cycle 13. The treatment groups were comparable at all timepoints. No consistent statistical trends were reported in any of the treatment groups.

The SF-36 questionnaire was given to most subjects in this study at baseline, and at cycles 3, 7, and 13 or the final visit. The change from baseline in standardized physical functioning and mental health scores for each treatment group showed that some statistically significant difference from baseline were present, but this was not consistent overall.

The WHQ was assessed at baseline and at cycles 3, 7, and 13 or the final visit. All treatment groups showed statistically significant improvement from baseline scores of vasomotor symptoms, sleep problems, or the total score at all timepoints (Note there was no placebo group in this trial, therefore, comparison outcome data is between treatment groups and will not support a labeling claim).

The sponsor reported data on 183 subjects who had baseline and end of study data of the effect of estrogen on the vaginal mucosa (maturation index [MI]). The MI was reported on 90 subjects in the placebo group, on 93 subjects in the E<sub>2</sub> 4.4mg/LNG 2.75mg group, and in 100 of the E<sub>2</sub> 4.5mg/LNG 3.75mg group. More than half of the subjects in the estrogen/progestin groups had a MI that was read as indeterminate epithelial or unsatisfactory/not available.

**Comment: No clear pattern was shown toward a mature vaginal epithelium and this data does not support a vulvar vagina atrophy claim.**

#### Safety

All AEs that occurred during the study were documented in the Case Report Forms (CRF). AEs were listed by the Investigator's term and by Hoechst Adverse Report Terminology System (HARTS) term, Version 2.3, as well as body system. Information about the intensity, severity, duration, action taken, and relationship to study drug was provided.

One or more AEs occurred in 753 subjects: 180 (88.2%) of the 204 subjects in the E<sub>2</sub> 4.4 mg group, 192 (90.6%) of the 212 subjects in the E<sub>2</sub> 4.4,g/LNG 1.39 mg group, 191 (90.5%) of the 211 subjects in the E<sub>2</sub> 4.4mg/LNG 2.75 group and 190 (89.2%) of 213 subjects in the E<sub>2</sub> 4.5mg/LNG 3.75 group. Of subjects who received the E<sub>2</sub> 4.4mg, the three most frequent AEs were application site reactions, vaginal hemorrhage, and upper respiratory tract infection. Of subjects who received the E<sub>2</sub> /LNG treatment groups the three most frequent AEs were application site reaction, vaginal hemorrhage, and breast pain.

The following table reports the incidence of treatment related adverse events by dictionary term and body system:

Table 7  
Incidence of Treatment-Related Adverse Events By Dictionary Term and Body System  
Reported by >2% of Subjects in any Treatment Group

Sponsors table 58 Vol.36

Body System/Adverse Event	E <sub>2</sub> 4.4mg (N=204)  n (%)	E <sub>2</sub> 4.4mg/LNG 1.39mg (N=212)  n (%)	E <sub>2</sub> 4.4mg/LNG 2.75mg (N=211)  n (%)	E <sub>2</sub> /4.5mg/LNG 3.75mg (N=213)  n (%)	Total (N = 840)  n (%)
Overall	136 (66.7%)	159 (75.0%)	157 (74.4%)	151 (70.9%)	603 (71.8%)
Body as a Whole					
Abdominal Pain	5 (2.45)	8 (3.8%)	13 (6.2%)	8 (3.8%)	34 (4.0%)
Asthenia	1 (0.5%)	6 (2.8%)	4 (1.9%)	2 (0.9%)	13 (1.5%)
Pelvic Pain	4 (2.0%)	3 (1.3%)	1 (0.5%)	1 (0.5%)	9 (1.1%)
Cardiovascular					
Hypertension	6 (2.9%)	3 (1.4%)	1 (0.5%)	2 (0.9%)	12 (1.4%)
Digestive					
Flatulence	10 (4.9%)	8 (3.8%)	9 (4.3%)	9 (4.2%)	36 (4.3%)
Metabolic and Nutrition					
Edema	3 (1.5%)	3 (1.4%)	8 (3.8%)	5 (2.3%)	19 (2.3%)
Weight Gain	8 (3.9%)	5 (2.4%)	10 (4.7%)	4 (1.9%)	27 (3.2%)
Nervous system					
Depression	4 (2.0%)	8 (3.8%)	1 (0.5%)	5 (2.3%)	19 (2.3%)
Emotional Lability	5 (2.5%)	5 (2.4%)	10 (4.7%)	2 (0.9%)	22 (2.6%)
Headache	5 (2.5%)	6 (2.8%)	8 (3.8%)	8 (3.8%)	27 (3.2%)
Skin					
Application Site Reaction	68 (33.3%)	83 (39.2%)	92 (43.6%)	65 (30.5%)	308 (36.7%)
Breast Enlargement	2 (1.0%)	1 (0.5%)	2 (0.9%)	7 (3.3%)	12 (1.4%)
Breast Neoplasm	5 (2.5%)	3 (1.4%)	0 (0.0%)	5 (2.3%)	13 (1.5%)
Breast Pain	20 (9.8%)	38 (17.9%)	33 (15.6%)	48 (22.5%)	139 (16.5%)
Urogenital					
Endometrial Disorder	16 (7.8%)	1 (0.5%)	2 (0.9%)	5 (2.3%)	24 (2.9%)
Endometrial Neoplasm	5 (2.5%)	2 (0.9%)	2 (0.9%)	4 (1.9%)	13 (1.5%)
Menstrual Disorder	4 (2.0%)	3 (1.4%)	5 (2.4%)	7 (3.3%)	19 (2.3%)
Urinary Tract Disorder	4 (2.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	5 (0.5%)
Vaginal hemorrhage	43 (21.1%)	77 (36.3%)	62 (29.4%)	79 (37.1%)	261 (31.1%)
Vaginitis	4 (2.0%)	3 (1.4%)	5 (2.4%)	6 (2.8%)	18 (2.1%)

N = total number of subjects in a treatment group

n = number of subjects within a treatment group who had a treatment-related adverse event.

<sup>a</sup> This table contains adverse events considered to be possibly, probably, or definitely related to study drug.

The following table is modified from the sponsor's Table 57, Volume 36 that reports the incidence of severe adverse events by body system. It should be noted that an AE was classified as severe by the Investigator if the subject was unable to perform her usual activities. Severe AEs were reported by 163 (19.4%) of 840 subjects. Because most percentages and number of subjects are <1% only N (number) greater than 5 will be presented by body system (except for endometrial disorder).

Table 8

Modified Incidence of Severe Adverse Events  
(Dictionary Term) by Body System

Sponsor's modified table 57

Body System/Adverse Event	E <sub>2</sub> 4.4mg (N=204)  n (%)	E <sub>2</sub> 4.4mg/LNG 1.39mg (N=212)  n (%)	E <sub>2</sub> 4.4mg/LNG 2.75mg (N=211)  n (%)	E <sub>2</sub> /4.5mg/LNG 3.75mg (N=213)  n (%)	Total (N=840)  n (%)
Overall	46 (22.5%)	34 (16.0%)	44 (20.9%)	39 (18.3%)	163 (19.4%)
Body as a Whole					
Abdominal Pain	1 (0.5%)	1 (0.5)	4 (1.9%)	0 (0.0%)	6 (0.7%)
Back Pain	0 (0.0%)	3 (1.4%)	2 (0.9%)	3 (1.4%)	8 (1.0%)
Flu Syndrome	5 (2.5%)	0 (0.0%)	3 (1.4%)	0 (0.0%)	8 (1.0%)
Pain	2 (1.0%)	0 (0.0%)	1 (0.5%)	2 (0.9%)	5 (0.6%)
Musculoskeletal					
Bone Fracture	2 (1.0%)	0 (0.0%)	3 (1.4%)	1 (0.5%)	6 (0.7%)
Respiratory System					
Sinusitis	1 (0.5%)	0 (0.0%)	0 (0.0%)	3 (1.4%)	4 (0.5%)
Upper Respiratory Infection	3 (1.5%)	0 (0.0%)	1 (0.5%)	2 (0.9%)	6 (0.7%)
Skin					
Application Site Reaction	11 (5.4%)	12 (5.7%)	17 (8.1%)	8 (3.8%)	48 (5.7%)
Breast Pain	1 (0.5%)	2 (0.9%)	0 (0.0%)	6 (2.8%)	9 (1.1%)
Urogenital					
Endometrial Disorder	2 (1.0%)	1 (0.5%)	0 (0.0)	0 (0.0%)	3 (0.4%)
Vaginal Hemorrhage	7 (3.4%)	4 (1.9%)	5 (2.4%)	3 (1.4%)	19 (2.3%)

N = total number of subjects in a treatment group

n = number of subjects within a treatment group who had a severe adverse event

A subject may have more than 1 severe adverse event.

**Comment: The sponsor's table 57 list severe adverse events. Given the definition (as listed above), I believe that these adverse events are more appropriately designated as serious. Note the high number of serious AEs associated with application site reactions 48 (5.7%) and the 19 subjects with vaginal hemorrhage. (Vaginal hemorrhage is a very broad term that includes all types of bleeding including, but not limited to, continuous bleeding, excessive bleeding and**

abnormal uterine bleeding.) There were no reported cases of blood transfusion and there does not appear to be a dose response associated with vaginal hemorrhage. As in other HRT studies, the higher the dosage in the combination of E/P, the greater the percentage of subjects with breast pain.

Ten subjects were excluded from the AE summary tables because their AE occurred > 30 days after stopping the medication. These include a case of uterine cancer (leiomyosarcoma) in a subject # 51011 (E<sub>2</sub> 4.4mg group) who stopped treatment on May 7, 1999 and had the above diagnosis on ———. Leiomyosarcoma is not an estrogen dependent tumor and this reviewer would not associate this tumor with the treatment regimen. In addition, two subjects continued to show skin reactions 2-4 months after stopping treatment in the E<sub>2</sub> 4.4mg group; and two subjects, one in the E<sub>2</sub> 4.4mg/LNG 2.75 and 1 in the E<sub>2</sub> 4.5/LNG 3.75 group had abnormal Pap smears. Again, abnormal Pap smears are not associated with estrogen treatment.

There was one other serious adverse event that occurred that has not been previously mentioned. Subject 11008 in the E<sub>2</sub> 4.4mg/LNG 2.75 had a diagnosis of ductal carcinoma of the breast at Cycle 7 which was possibly related to study drug.

Two deaths occurred during the conduct of this study. Subject 19003 in the E<sub>2</sub> 4.4mg/LNG 2.75 mg group died secondary to a cardiac arrest. This subject had a medical history of hypercholesterolemia and long term tobacco use. This subject took study drug for 351 days and died suddenly at home. Although the investigator assessed the cardiac arrest as unlikely related to the study drug, this death is questionable as to causality to this reviewer and an estrogen/progestin etiology is not ruled out. Subject 62013 in the E<sub>2</sub> 4.5mg/LNG 3.75mg group, took study drug for 7-8 months. This subject had a history of tobacco use for 40 years, as well as hypertension and hypercholesterolemia. She died at home due to metastatic small cell undifferentiated lung cancer with brain metastasis. The etiology of this death is probably not related to study drug, but rather to her long tobacco use.

In sponsor's table 61 (9 pages in length) adverse event that caused withdrawal from the study are reported. This table will be summarized due to its length. Two hundred fifty-six (256, 30.5%) of subjects who participated in this study discontinued due to an AE. The numbers who discontinued due to AEs were 54 (26.5%) in the E<sub>2</sub> 4.4mg group, 69 (32.5%) in the E<sub>2</sub> 4.4mg/LNG 1.39mg group, 66 (31.3%) in the E<sub>2</sub> 4.4mg/LNG 2.75mg group, and 67 (31.5%) in the E<sub>2</sub> 4.5mg/LNG mg group. One additional subject was withdrawn (subject 30012 in the E<sub>2</sub> 4.4mg group) due an AE of application site reaction which occurred more than 30 days after stopping treatment.

The most frequently reported AE that caused subjects to withdraw from the study was vaginal hemorrhage. Vaginal hemorrhage occurred in 102 of the 256 subjects who withdrew: 18 (8.8%) of subjects in the E<sub>2</sub> 4.4mg group, 26 (12.3%) of subjects in the E<sub>2</sub> 4.4 mg/LNG 1.39mg group, 26 (12.3%) of subjects in the E<sub>2</sub> 4.4mg/LNG 2.75mg group, and 32 (15.0%) of subjects in the E<sub>2</sub> 4.5mg/LNG 3.75mg group. One additional subject (Subject 58005 in the E<sub>2</sub> 4.4mg group) was withdrawn due to vaginal hemorrhage associated with an endometrial polyp.

The second most frequent AE that caused subjects to withdraw from the study was application site reaction. Application site reaction was experienced by 71 of the 256 subjects who withdrew: 18 (8.8%) subjects in the E<sub>2</sub> 4.4mg group, 23 (10.8%) in the E<sub>2</sub> 4.4mg/LNG 1.39mg group, 18 (8.5%) subjects in the E<sub>2</sub> 4.4mg/LNG 2.75mg group, and 12 (5.6%) subjects in the E<sub>2</sub> 4.4mg/LNG 3.75mg group.

The third most frequent AE that caused subjects to withdraw from the study was breast pain. Breast pain was experienced by 15 of the 256 subjects who withdrew: 0 (0.0%) in the E<sub>2</sub> 4.4mg group, 5 (2.4%) subjects in the E<sub>2</sub> 4.4mg/LNG 1.39mg group, 3 (1.4%) subjects in the 4.4mg/LNG 2.75mg group, and 7 (3.3%) subjects in the E<sub>2</sub> 4.5mg/LNG 3.75mg group.

Clinical laboratory test of hematology, serum chemistry, and urinalysis test were performed prior to trial treatment, at cycle 7 (week 28), and at the end of the study (Cycle 13). Two subjects (subjects 50009 and 45010) withdrew from the study because of elevated liver function tests (LFTs). Hyperlipidemia was observed in some subjects but this was not attributed to study drug except for one subject (subject 18001) in the E<sub>2</sub> 4.4mg group.

Lipid parameters were also evaluated prior to trial treatment, at Cycle 7 and at the end of Cycle 13. Total cholesterol, triglycerides, HDL, LDL, HDL/LDL ratio, and total cholesterol/HDL ratios were calculated. Some statistical changes were observed in various parameters, but they were not consistent. Importantly, mean HDL cholesterol rose slightly over 13 cycles in the E<sub>2</sub> 4.4mg group but mean HDL dropped in a dose response manner in the E<sub>2</sub> 4.4 or 4.5 LNG groups. Total cholesterol was stable in the E<sub>2</sub> 4.4mg group, but was noted to decline in all E<sub>2</sub> LNG groups over the first six months, and then stabilized at that level over the next six months. These changes were greater during the first six months of treatment and appeared to level out during the next six months. Overall, no statistically significant changes were found that would allow any claims to the estrogen class label.

#### Reviewer's comments/conclusion of study results

In this randomized, double-blind, estrogen-only controlled study, three doses of E<sub>2</sub>LNG were compared to an estrogen-only arm in a continuous wear regimen. The primary efficacy parameter was the incidence of endometrial hyperplasia in the ITT population at the end of 13-28 day cycles. The estrogen-only group at any time had an unadjusted hyperplasia rate of 12.8% (19 cases) and an adjusted rate (Adjusting for Type I and Type II withdrawals) of 17.3% (19 cases). The upper bound of the 95% confidence interval for the unadjusted or adjusted hyperplasia rate did not exceed 4%. While the p-value is highly significant and the confidence interval supports the p-value, it must be noted that 254 (30.64%) of subjects could not be included in the ITT population because of dropout at any one time. Subjects who prematurely withdrew and had an exit biopsy percentage of 48.49% (402/829). With the above in mind the sponsor constructed a life-table analysis which estimated the probability of endometrial hyperplasia after one year of treatment. Adjusting for withdrawal, the incidence of endometrial hyperplasia at the end of 1 year was 17.0% in the E<sub>2</sub> 4.4mg treatment group.

Application site reactions, vaginal hemorrhage, and breast pain were the most common AEs reported. Vaginal hemorrhage and breast pain was more common in the E<sub>2</sub>/LNG groups than the estrogen-only group. Approximately 48 (5.7%) of subjects had serious application site reactions in this study and another 19 (2.3%) had vaginal hemorrhage. Of the 256 subjects who withdrew, application site reactions occurred in 71/256 (27.73%) of subjects. Vaginal hemorrhage occurred on 102/256 (39.84%) subjects who withdrew. This clearly implies that a significant number of subjects were bleeding throughout this study and that the bleeding did not improve over time. Amenorrhea was reported in 69% of the E<sub>2</sub> 4.4mg treatment group, and was reported in 46.4%, 55.5%, and 53.6% of the E<sub>2</sub> 4.4mg/LNG 1.39mg, 4.4mg/LNG 2.75mg, and 4.5mg/LNG 3.75mg groups, respectively. Cumulative amenorrhea was reported in 75.6% of the E<sub>2</sub> 4.4mg treatment group, and was reported in 41.2%, 49.0%, and 53.1% of the E<sub>2</sub> 4.4mg/LNG 1.39mg, 4.4mg/LNG 2.75mg, and 4.5mg/LNG 3.75mg groups, respectively. Lipid parameters showed a beneficial decrease in LDL cholesterol, but also a decrease in HDL cholesterol, which is a

concern. Overall, bleeding and application site reactions may be a significant compliance issue with use of these patches.

## VI Integrated Review of Efficacy—Comparative results between studies

One primary study (96042A) of efficacy could not be reviewed due to a lack of source documentation. A second study (96043A) showed a statistically significant reduction in the amount of estrogen-induced hyperplasia when compared to an estrogen-only arm.

The sponsor conducted two-randomized, double-blind studies, one comparing the safety and efficacy of ClimaraPro (estradiol and levonorgestrel transdermal system) to placebo (Study 96042A) and one comparing the hyperplasia rate of ClimaraPro to that of an estrogen-only group (Study 96043A). In study 96042A two doses of E<sub>2</sub>LNG (E<sub>2</sub> 4.4mg/LNG 2.75mg and E<sub>2</sub> 4.5mg/LNG 3.75mg) were compared to placebo for a 12-week treatment period. Study source documentation for vasomotor symptoms could not be documented after the initial baseline period. Source documentation was obtained at baseline with the use of a written record that had been given to the subject; however, it was not used in the remaining portion of the study. A priori, the sponsor did not notify DRUDP of any modification of their study protocol, nor did the sponsor file a protocol amendment to apprise DRUDP that a telephone-only system would be used which excluded written documentation. Therefore, since source documentation could not be verified, DSI could not recommend use of non-verifiable data source. This reviewer concurs with that decision.

Study 96043A was a randomized, double-blind, estrogen-only controlled, 13 cycle (52 week) study in four parallel treatment groups. Eight hundred forty-five (845) subjects were randomized into this study. Two hundred fifty four (254) or 30.64% of subjects could not be included into the ITT population because of withdrawal from the study at any one time. Overall, in the E<sub>2</sub> 4.4mg treatment group, 19 cases (or 17.3%) of endometrial hyperplasia were reported compared to no (0%) cases in the estrogen plus progestin groups. For the E<sub>2</sub> 4.4mg/LNG 1.39mg, the E<sub>2</sub> 4.4mg/LNG 2.75, and the E<sub>2</sub> 4.5mg/LNG 3.75mg treatment groups the p-value was <0.001 for each treatment group when compared to the estrogen-only arm and the upper bound of the 95% confidence interval was 2.48%, 2.64%, and 2.56%, respectively. This is well within the 4% upper bound of the 95% confidence interval established by DRUDP in support of p-values for each treatment group. Therefore, the E<sub>2</sub>LNG groups are effective in reducing the risk of developing endometrial hyperplasia when compared to estrogen alone.

## VII Integrated Review of Safety

Significant adverse effects were reported in the number of subjects with vaginal hemorrhage, application site reactions, and breast pain. These three AEs were also significant reasons for withdrawal from this study. Significant vaginal hemorrhage and application site reactions are significant impediments to the continued use of this product.

A total of 840 subjects were randomized in the ITT population in study 96043A. Adverse events were reported by the Hoechst Adverse Report Terminology System (HARTS System). Overall, 603 (71.8%) of subjects reported an adverse event. Adverse events were reported by 136 (66.7%), 159 (75%), 157 (74.4%) and 151 (70.9%) of subjects in the E<sub>2</sub> 4.4mg, E<sub>2</sub> 4.4mg/LNG 1.39mg, E<sub>2</sub> 4.4mg/LNG 2.75mg, and the E<sub>2</sub> 4.4mg/LNG 3.75mg groups, respectively.

### Deaths

Two deaths occurred during the study. Subject 199003, in the E<sub>2</sub> 4.4mg/LNG 2.75mg group died of a cardiac arrest and Subject 62013 in the E<sub>2</sub> 4.5mg/LNG 3.75mg group,

died due to lung cancer with metastasis to the brain. Subject 199003 was assessed by the investigator as being unrelated to study drug. However, the possibility of an estrogen/progestin effect was never ruled out. Subject 62013 had a 40-year history of tobacco use and her death appears to be attributable primarily to tobacco use.

#### Significant/Potential Significant Events

Two hundred fifty-six (256, 30.5%) subjects who participated in this study discontinued due to an AE. The number of subjects who discontinued due to AEs was 54 (26.5%) in the E<sub>2</sub> 4.4mg group, 69 (32.5%) in the E<sub>2</sub> 4.4/LNG 1.39mg group, 66 (31.3%) in the E<sub>2</sub> 4.4mg/LNG 2.75mg group, and 67 (31.5%) in the E<sub>2</sub> 4.5mg/LNG 3.75mg group.

The most frequent reported AE that caused subjects to withdraw from the study was vaginal bleeding. Vaginal bleeding was experienced by 102/256 subjects who withdrew: 18 (8.8%) subjects in the E<sub>2</sub> 4.4mg group, 26 (12.3%) subjects in the E<sub>2</sub> 4.4mg/LNG 1.39mg group, 26 (12.3%) subjects in the E<sub>2</sub> 4.4mg/LNG 2.75mg group, and 32 (15.5%) subjects in the E<sub>2</sub> 4.5mg/LNG 3.75mg group. One additional subject (E<sub>2</sub> 4.4mg group) withdrew due to vaginal hemorrhage but this was listed under endometrial polyp. The second most frequent AE that caused subjects to withdraw from the study was application site reaction. Application site reactions were experienced by 71 of the 256 subjects who withdrew: 18 (8.8%) subjects in the E<sub>2</sub> 4.4mg group, 23 (10.8%) subjects in the E<sub>2</sub> 4.4mg/LNG 1.39mg group, 18 (8.5%) subjects in the E<sub>2</sub> 4.4mg/LNG 2.75mg group, and 12 (5.65) subjects in the E<sub>2</sub> 4.5mg/LNG 3.75mg group. The third most frequent AE that caused subjects to withdraw from the study was breast pain. Breast pain was experienced by 15 of the 256 subjects who withdrew: none (0%) subjects in the E<sub>2</sub> 4.4mg group, 5 (2.4%) subjects in the E<sub>2</sub> 4.4mg/LNG 1.39mg group, 3 (1.4%) in the E<sub>2</sub> 4.4mg/LNG 2.75mg group, and 7 (3.3%) subjects in the E<sub>2</sub> 4.5mg/LNG 3.75mg group.

Eight (8) cases of endometrial polyps developed during the study which were evenly distributed among treatment groups; there was one reported case of ovarian carcinoma and one case of transient ischemic attack in the E<sub>2</sub> 4.4mg group; two cases of elevated enzymes were reported, one in the E<sub>2</sub> 4.4mg/LNG 1.39mg group and one in the E<sub>2</sub> 4.4mg/LNG 2.75mg group; one case of a large pelvic uterine fibroid was reported in the E<sub>2</sub> 4.5mg/LNG 3.75mg group; and one case of angina pectoris was reported in the E<sub>2</sub> 4.4mg/LNG 2.75mg group.

Systemic adverse events occurred in 603 (71.8%) of subjects. Of this total 308 (36.7%) of subjects reported application sites reactions, 261 (31.1%) reported vaginal hemorrhage, and 139 (16.5%) reported breast pain. Other AEs reported at greater than 2% include abdominal pain, flatulence, weight gain, edema, depression, emotional lability, menstrual disorder, and headache. The sponsor did not report the incidence of patch adherence or the number of patches that "fell off" during this trial. Overall, it can be stated that the incidence of serious adverse reactions is significant and that application site reactions, vaginal bleeding and breast pain will be a significant hurdle for this product to overcome in the general population.

#### SAFETY UPDATE

The sponsor submitted a Safety Update dated May 9, 2001. Information in this safety update pertains primarily to ongoing studies numbered protocols 98189 and 96041 and sporadic data obtained in European data studies. This update contains no new SAEs in protocols 96042A and 96043A that are the subject of this NDA. In study 98189, with a reporting period of June 29, 2001 to May 3, 2001, 5 SAEs were reported. These SAEs are one case of increased hypertrophy of the uterus (probable), and one case each of sleep apnea, acute bronchitis, exacerbation of chronic obstructive pulmonary disease (COPD) and right knee surgery. The latter 4 cases are not associated with the treatment. In

protocol 96041, with a reporting period of June 29, 2000 to May 3, 2001 one case of breast carcinoma was reported (possible) and one case of a fracture of the lateral malleolus and one right hip fracture (not related).

In addition, in protocol 98189, a 9% rate of application site reactions and a 10% rate of upper respiratory tract infections was reported.

In ongoing studies in the EU for the indications of osteoporosis and endometrial safety discontinuations are reported as between 38% and 40%. Causes for discontinuations were not reported.

No deaths were reported.

In summary, no additional or worrisome data was reported in this safety update. However, the vaginal hemorrhage, application site reactions, and breast pain remain a significant concern with this product.

#### **Labeling review**

The proposed label will not be reviewed since it is recommended that this product not be approved.

### **VIII Use in Special Populations**

The sponsor conducted no special studies in the treatment population other than those usually associated with postmenopausal women. In addition, as in most studies for ERT/HRT, the primary treatment group was Caucasian women in a percentage of approximately 80-90%. This mirrors other studies and is not a concern.

No data was obtained in a Pediatric population, and this drug treatment would be contraindicated in a pediatric population.

### **IX Conclusions**

This product is non-approval. The sponsor has not demonstrated the efficacy for ClimaraPro (estradiol and levonorgestrel transdermal patch). In study 96042A source documentation of this study could not be verified and DSI recommended data in Study 96042A should not be used.

In study 96043A three dosages (4.4mg E<sub>2</sub>/LNG 1.39mg, 4.4mg E<sub>2</sub>/LNG 2.75mg, and 4.5 E<sub>2</sub>/LNG 3.75mg) of the estradiol/levonorgestrel transdermal patch produced a statistically significant reduction in the incidence of estrogen-induced hyperplasia when compared to daily 4.4mg estradiol alone. The reduction in estrogen induced hyperplasia was at p < 0.001 significance level with the upper bound of the 95% confidence interval at < 4% for each treatment group.

Significant adverse events reported are application site reactions (36.5%), vaginal hemorrhage (31.1%) and breast pain (16.5%). All three of these adverse events were significant reasons for subjects withdrawing from this clinical trial.

**Recommendation**

The sponsor should conduct a 12-week study with at least two dosages of the estradiol/levonorgestrel patch. This study should include the 4.4mg E<sub>2</sub>/LNG 1.39 dose since that dose appears to be the lowest effective dose for reducing the incidence of endometrial hyperplasia.

Phill H. Price, M.D.  
July 21, 2001

X **Appendix:** See list of investigators for both studies

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