CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-375/S-016

MEDICAL REVIEW

Medical Officer's Summary of NDA Supplement 20-375

1. NDA 20-375-S016
M.O. Review #1

Submission Date: June 2, 2000
Review Completed: March 26, 2001

Drug: Estradiol Transdermal System

Generic name: 17-Beta Estradiol

Trade name: Climara®

Chemical name: Estradiol USP (estra-1,3,5, (10)-triene-3, 17B

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

Pharmacologic Category: Estrogen

Clinical Indication: Estrogen Replacement Therapy

Route of Administration and Dosages: All dosages are transdermal; Pending approval dosage is 0.025mg estradiol/day via 6.5cm^2 patch; previously approved dosages are 0.050mg estradiol/day via 12.5cm^2 patch, 0.75mg estradiol/day via 18.5cm^2 patch, and 0.1mg estradiol/day via 25.0 cm^2 patch.

NDA Drug Class: 3S

Related Drugs: Approved estradiol transdermal patches are Estraderm®, Climara®, Vivelle®, Menorest®, Alora® and Esclim®.

Summary/Issues:

This 38-volume submission from Berlex contains two well-designed studies, one placebo-controlled study and one comparative study to support Climara® (0.025mg/day) in the treatment of moderate-to-severe vasomotor symptoms. On December 22, 1994, the 0.05mg/day and 0.1mg/day estradiol dosages were approved for the treatment of moderate to severe vasomotor symptoms. On March 23, 1998 the 0.75mg/day estradiol dosage was approved for moderate-to-severe vasomotor symptoms. Subsequently, on March 5, 1999 (supplement S-011) was approved for the prevention of postmenopausal osteoporosis with the 0.025 mg/day estradiol dose of Climara®. Supplement 011 did not provide for a vasomotor indication, therefore, supplement 016 is submitted to support a vasomotor indication.

Related Review: See statistical review dated: 2/28/2001

2. Table of Contents: Page(s)

3. Material Reviewed: Volumes 1-38

4. Chemistry/Manufacturing Controls: See Chemist review

5. Pharmacology/Toxicology: See Pharmacologist review

6. Clinical Background:

Estradiol is largely responsible for the development and maintenance of the female reproductive system and of secondary sexual characteristics. During the reproductive years the main source of estrogens is the dominant follicle and the corpus luteum it forms after ovulation. The principle estrogen produced is estradiol. By direct action, estrogen causes growth and development of the vagina, uterus, and fallopian tubes. In concert with prolactin, progesterone and other hormones, estrogens stimulate growth and development of the breast through ductal growth, stromal development and accretion of fat. Estrogens contribute to the shaping of the skeleton, to the maintenance of tone and elasticity of urogenital structures, to changes in the epiphyses of the long bones that allow for the pubertal growth spurt and its termination, to the growth of axillary and pubic hair, and the pigmentation of the nipples and genitals.

Loss of ovarian estradiol secretion after menopause can result in inability of thermoregulation causing hot flushes, associated with sleep disturbances and excessive sweating, and urogenital atrophy, causing dyspareunia and urinary incontinence. Estradiol replacement therapy alleviates many of these symptoms of estradiol deficiency in the menopausal women.

Transdermal administration of estrogen produces therapeutic serum levels of estradiol with lower circulating levels of estrone and estrone conjugates and required smaller doses than does oral therapy. Because estradiol has a short half-life (1 hour), transdermal administration of estradiol allows a rapid decline in blood levels after systems are removed, e.g. in a cycling regimen.

6.1 Relevant human experience

Climara® was submitted for approval by 3M Pharmaceuticals and was approved on December 22, 1994 under NDA 20-375. All rights of NDA 20-375 were transferred to Berlex Laboratories on November 2, 1995. On March 23, 1998 Berlex received approval of supplement S-009 which provided for a 0.075mg/day dose in the treatment of moderate to severe vasomotor symptoms. On March 5, 1999 Berlex received approval of supplement S-011 which supported a new indication, the prevention of postmenopausal osteoporosis.

7. Description of Clinical Data Sources

The sponsor conducted two new clinical investigations to support the approval of this supplement under IND 40,928. 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 (0.025mg/day); 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 compared to oral conjugated estrogens.

8 **Clinical Studies**

8.1 Study 97074

8.1.1 Objective/rationale

The primary objective of this study was to determine the effectiveness of continuous administration of transdermal estradiol compared with transdermal placebo in decreasing the frequency and severity of hot flushes in postmenopausal women. The secondary objective was to evaluate the effectiveness of the treatment regimen in relieving urogenital symptoms.

8.1.2 Design

This was a multicenter, double-blind, randomized, parallel-group, placebo-controlled study of 200 postmenopausal women conducted at 18 centers in the US comparing a continuous regimen of transdermal estradiol to transdermal placebo.

8.1.3 Entrance Criteria

The goal was to enroll approximately 200 postmenopausal women in order to have 150 subjects, 75 in each group, to complete the double-blind treatment phase. Subjects were attended by the principal investigator or a designated physician throughout the study.

Inclusion Criteria

Women were permitted to enter the study if they met all of the following criteria:

- Age $\geq$ 45 years of age
- Amenorrhea for $\geq$ 12 months, or amenorrhea for < 12 months and longer than 6 months and serum FSH (follicle stimulating hormone) levels > 50 mIU/L and serum estradiol levels < 20 μg/mL, or surgical menopause (bilateral oophorectomy) subjects may enter the study 2 weeks after surgery;

- Seven or more moderate to severe hot flushes daily, or 60 or more flushes in 1 week during screening preceding study entry;
- In nonhysterectomized women, endometrial biopsy without evidence of endometrial hyperplasia or carcinoma. In amenorrheic women a valid negative biopsy done within 6 months prior to study was acceptable. In women with bleeding, the biopsy must have been done at screening. If a biopsy was inadequate, and in the absence of bleeding, a subject could be enrolled if transvaginal ultrasound showed the endometrium was < 5mm in thickness;
- Negative pregnancy test (if subject did not have oophorectomy/hysterectomy and had less than 1 year of amenorrhea); and
- Subjects had to have signed a consent agreement.

Exclusion Criteria:

Women who had any one of the following were excluded from the study:

- Hormone replacement therapy within 8 weeks prior to qualification for the study;
- Any disease or condition that compromised the function of the body systems and resulted in altered absorption, excessive accumulation, impaired metabolism, or altered excretion of the study drug;
- Known or suspected disease which might interfere with the conduct of the study or the interpretation of the results;
- Urinary tract infection;
- Abnormal baseline laboratory values that were considered clinically significant and which gave suspicion of a specific organ dysfunction;
- Myocardial infarction within the last 6 months prior to screening or coronary heart disease severe enough to have required treatment with antiarrhythmic or antianginal drugs;
- Congestive heart failure;
- Uncontrolled hypertension; sitting systolic blood pressure $\geq$ 160 mm Hg or diastolic blood pressure $\geq$ 95 mm Hg;
- History of stroke or transient ischemic attacks;
- Thrombophlebitis or thromboembolic disorders within the last 3 years that were unrelated to estrogen therapy, or a history of these condition at any time with previous estrogen therapy;
- Treatment with anticoagulants (heparin or warfarin);
- Insulin dependent diabetes mellitus;
- Increased frequency or severity of headaches including migraines during previous estrogen therapy;
- History of drug addiction or alcohol abuse (within the last 2 years);
- Current or significant past history of depression; and
- Received an investigational drug within the last 3 months prior to study entry.

Removal of subjects from treatment or assessment:

Subjects had the right to withdraw from the study at any time. If a subject withdrew before completing all evaluations, whenever possible, the reason for discontinuing was reported, and a complete examination, including physical examination and clinical tests, were performed at time of withdrawal. The principal investigator, on the appropriate page of the case report form, specified the circumstances of discontinuation. Subjects were to be withdrawn from the study for the following reasons:

- Occurrence for the first time of migraine headaches or more frequent occurrence of unusually severe headaches;
- Sudden perceptual disorders (e.g. disturbances of vision or hearing);

- First signs of thrombophlebitis or thromboembolic symptoms (e.g. unusual pain in or swelling of the legs, stabbing pains, pain when breathing, or coughing for no apparent reason);
- A feeling of pain and tightness of the chest;
- Pending operations (6 weeks beforehand);
- Immobilization (e.g. following accidents);
- Onset of jaundice;
- Onset of hepatitis;
- Itching of the whole body;
- Epileptic seizures;
- Significant (per the investigators discretion) rise in blood pressure; and
- Any condition described in the exclusion criteria.

Comment: Inclusion and exclusion are consistent with other estrogen replacement therapy protocols and are acceptable. Since this clinical trial began in January 1998, some of the entrance criteria are not as strict (e.g. bilateral oophorectomy after 2 weeks, and endometrial biopsy screening) as recommended in the Draft For Clinical Evaluation of Combination Estrogen and Estrogen/Progestin Drug Products For Hormone Replacement Therapy of Postmenopausal Women of November 1999. The reasons given for possible withdrawal of the subject from this study are appropriate since these reasons may predate the actual occurrence of an untoward event.

8.1.4 Study Procedures

During the screening period subjects were given a daily diary card to record weekly observations of urogenital symptoms and were 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.

Subjects who met the inclusion criteria and who experienced sufficient *moderate-to-severe* hot flushes (7/day or greater than or equal to 60 in 1 week) during any week of the run-in period were immediately eligible for the study. They were randomized to receive one or two-double-blind treatments for 3 cycles (12 weeks).

A complete medical, surgical, and gynecological history was obtained at baseline, which included a history of medication usage (including previous use of sex hormones). The start and stop dates of any medication use in the last 3 months were recorded. Other evaluations performed at baseline and at specified times during the study included evaluation of mammography, physical examination, vital signs, and laboratory test (hematology, chemistry, and lipid profile).

Eligible subjects who passed the screening assessment and who met all the inclusion and exclusion criteria were enrolled in the study. After completion of the screening evaluations, there were 3 office visits scheduled. If the final visit occurred prior to Visit 4, every attempt was made to complete the final visit evaluations specified for the final visit.

Trial medication for each medication consisted of one of the following transdermal systems, estradiol transdermal system (E_2 TDS) (6.5cm^2) delivering 0.025mg estradiol/day or a matching placebo (6.5cm^2). The subjects applied a patch once weekly to a clean dry location of the abdomen or buttock. At the end of 1 week, the patch was removed and a new patch was applied to a new site on the anterior trunk. Patches were applied on the same day of the week for the duration of the study. The time and date of application of each patch was recorded. One patch was worn for 7 days. The study drug

patches were supplied by the sponsor in foil pouches. All study patches were identical in appearance to maintain the double-blind nature of the study.

Patches were not to be removed except for scheduled weekly replacement. If a patch became dislodged between applications, it was to be reapplied. If a patch lifted from the skin, it was to be pressed back in place. If a patch fell off prematurely, a new patch was applied for the remainder of the week. The regular weekly cycle of patch replacement was then resumed. If another patch fell off during the same cycle, it was not replaced; a new patch was to be applied at the end of the week and the weekly cycle of patch wear resumed.

Subjects were instructed not to use a sauna, or steam bath or swim or bathe while wearing a patch during the study (showering was permitted). Use of a nonmedicated soap was permitted, however, subjects were instructed to keep the area as dry as possible, and not to expose the patches to sunlight.

Comment: Restrictions not to use a sauna, steam bath, swim or bathe are consistent with the previous use of Climara®. More recently approved patches have studied the use of a sauna, steam bath, swimming or bathing without restrictions. This sponsor's label should state the actual use of Climara® in their clinical trials.

8.1.5 Efficacy

Based on a standard deviation of 36 (sigma) for the baseline weekly hot flush rate in a similar population, it was determined that 75 completers pe treatment group were required to detect a between group difference at Cycle 3 of ½ sigma with a power = 86% at 2 tailed alpha = 0.05.

The following 2 sets of analyses were performed for the efficacy assessments: an intent-to-treat analysis and a valid subjects' analysis.

- Intent-to-treat analysis: All subjects randomized to study.
- Valid subject analysis: All subjects randomized to study who took no prohibited medications, had a 75% compliance or higher, and had not major violations of the inclusion/exclusion criteria.
- End point analysis: Data from a subject last value carried forward to the last scheduled visit.
- Completer analysis: Defined as a subject who completed the 3 cycle study period or who discontinued the study after at least 6 successfully completed weeks on study drug. This analysis was only done at the last scheduled visit.

For severity of symptoms Extended Cochran-Mantel-Haenszel (CMH) test was performed. For the remaining continuous variables ANOVA models assuming normality were analyzed. For categorical data Extended CMH tests were performed. Severity scores were tabulated as: none = 0, mild = 1, moderate = 2, and severe = 3.

Comment: The statistical plan is consistent with other ERT trials in that an ITT population and a valid subject group populations is identified and studied. However, significant portions of the sponsor's submitted data included substantial tabulations with mild vasomotor symptoms. This is not consistent with the Guidance For Clinical Evaluation of Combination Estrogen and

Estrogen/Progestin-Containing Drug Products Used For Hormone Replacement Therapy of Postmenopausal Women of 1995. It is clearly stated in that Guidance document that only moderate-to-severe VMS will be evaluated as the primary efficacy variable. Therefore, data to be reviewed will include only moderate-to-severe VMS. The valid subject analyses appears to be very similar to an "evaluable analyses." The valid analyses will be reviewed only in the context of supportive data for the ITT treatment population (or any major differences in study results). The "completer" analysis also appears quite lax in that completion of only 6/12 weeks allowed the sponsor to state that the subject was a "completer." This data will not be reviewed since this is not the usual definition of a "completer" subject.

8.1.6 Safety Considerations

Safety was assessed from the following parameters: AEs, vital signs, a physical examination including a pelvic examination and a Pap smear, and clinical laboratory tests. Endometrial biopsies were not performed during the study since in both protocols, 97074 and 97095 the dosages used were the lowest for the product and treatment was for three months.

8.1.4.1 Results

A total of 186 subjects were randomized at 18 study centers in the US. Of these 186 subjects, 92 subjects were allocated to receive active treatment with (E_2TDS) and 94 were allocated to receive placebo. A total of 164 subjects were "completers" defined as a subject who completed the 3 cycle study period or who discontinued the study after at least 6 successful completed weeks on study drug. Table 1 shows the disposition of subjects in this study:

Table 1
Subject Disposition by Treatment

			Completed		
Treatment group	**Screened (n)**	**Randomized (n)**	**Cycle 1 (n)**	**Cycle 2 (n)**	**Cycle 3 (n)**
E_2 TDS		92	89	86	79
Placebo Patch		94	83	76	73
Total	343	186	172	162	152

E_2-TDS – estradiol transdermal system

Of the 186 subjects who entered the study at baseline, 173 (89%) subjects were included in the sponsor's efficacy valid subject evaluation. To be included in this efficacy evaluation, subjects must have either had no major violation of the inclusion/exclusion criteria and a compliance of 75% or higher.

Comment: To be a "completer" a subject had to either completed 3 cycles of treatment, or had discontinued the study after at least 6 successfully completed weeks on study drug. As stated earlier this is unusual and will not be used in my efficacy evaluation.

Table 2 shows subject disposition by Treatment group and Valid Cycle:

Table 2

sponsor's table 6 Vol. 5

Treatment	Cycle 1 (n)	Cycle 2 (n)	Cycle 3 (n)
E_2 TDS	88	85	79
Placebo	82	75	72
Total	170	160	151

Ten (10) subjects were excluded from the study, 8 were in the placebo group and 2 were in the E_2 TDS group.

Table 3 shows the frequency of withdrawal by reason and treatment group:

Table 3

sponsor's table 8 Vol. 5

	E_2 TDS (N=92)	Placebo (N=94)	Total (N=186)
Reason	n (%)	n (%)	n (%)
Adverse event	0 (0.0)	2 (2.1)	2 (1.1)
Lack of efficacy	3 (3.3)	7 (7.5)	10 (5.4)
Protocol deviation	0 (0.0)	2 (2.1)	2 (1.1)
Withdrawal of consent	2 (2.2)	6 (6.4)	8 (4.3)
Other[a]	1 (1.1)	2 (2.1)	3 (1.6)
Total	6 (6.5)	19 (20.2)	25 (13.4)

[a] Other includes: Lost to Follow-up
N = total number of randomized subjects
n (%) = number (percent) of withdrawing subjects

Baseline demographics showed the majority of subjects were Caucasian with a mean overall age of 52 years. Approximately 155 (83%) were White, 23 (12%) were Black, 5 (3%) were Hispanic, and 2% were Other nationalities. The treatment groups were comparable with respect to weight and height. Systolic and diastolic blood pressure and heart rate were comparable. There were no significant differences in treatment groups with regard to estradiol and FSH levels.

Of the 186 subjects in both treatment groups, 130 (70%) had a hysterectomy and 72 (39%) had bilateral oophorectomy prior to entering the study. Fifty of 56 subjects with a uterus had an endometrial biopsy out of a total of 186 subjects. A negative endometrial biopsy was acceptable if it had been done 6 months prior to the screening period. Of the 50 biopsies, 36 (19%) had an inactive/atrophic endometrium, 7 (4%) had a proliferative endometrium, 6 (3%) had tissue insufficient for diagnosis, and 1 had a progestational secretory endometrium. Three subjects were noted to have benign endometrial polyps.

A total of 185 (99%) subjects had a mammogram at baseline. One hundred sixty-five (89%) subjects had a normal mammogram; 20 (11%) had an abnormal mammogram which was not clinically significant, and 1 (1%) subject (Subject 7407001) did not have a mammogram.

Concomitant medications were taken by 94 of 186 subjects (50.5%) at some time during the study. The most often reported concomitant medications were anti-inflammatory

agents, analgesics, antibiotics, antihistamines, and antitussives. No subject received any hormone replacement therapy or medications listed under the exclusion criteria.

Compliance was defined as wearing of the systems by the subject 75% of the time. Nine subjects were excluded due to less than 75% patch compliance and 1 subject was excluded due to not meeting the hot flush criteria.

Efficacy

The run-in period was up to 1 cycle or 4 weeks in duration. Hot flushes, frequency and severity of hot flushes, and urogenital symptoms were recorded. Subjects could qualify for the study by having the required number of hot flushes during any consecutive 7 days of the run-in period. There were individual subjects with minimum weekly and daily frequencies below the required number who were, nevertheless, eligible for the study.

Comment: It is clear at study start not all subjects had the minimum daily and number frequency of hot flushes, but the overall number (> 60/week) during that 4 week run-in period allowed the sponsor to enter these subjects. However, having the minimum number and frequency for any consecutive days in the run-in period allowed the sponsor to enroll these subjects.

The baseline mean weekly number of all hot flushes (mild, moderate, and severe) was 84.9 for the E_2 TDS group and 98.6 for the placebo group; the mean daily number of hot flushes was 12.1 for the E_2 TDS group and 14.1 for the placebo group. There were no statistically significant differences between the 2 treatment groups in either the mean weekly or mean daily number of hot flushes. Subjects also kept a diary on vaginal dryness, pain during intercourse, frequent urination, difficulty/pain during urination, involuntary urination and urination at night. There were no significant differences in secondary symptoms between the treatment groups.

Comment: Note the sponsor included mild hot flushes. The clinical indication is moderate-to-severe VMS. Note the weekly number of moderate to severe hot flushes at baseline is lower in the following Tables 4-6 than is shown in the above paragraph. This reviewer will focus only on moderate-to-severe symptoms in the ITT population since the primary indication is treatment of moderate-to-severe vasomotor symptoms.

Table 4 shows the Mean Number of Moderate-to-Severe Hot Flushes for Study 97074:

Mean Daily Number of Moderate-to-Severe Hot Flushes
Study 97074A by Treatment Week –ITT

Table 4

Modified from sponsor's Table 12 Vol. 38

Treatment Group	Statistics	Baseline @	Week 1	Week 2	Week 3	Week 4	Week 8	Week12	All Endpoint
E_2 TDS–	n	89	86	89	89	83	85	68	91
	Mean	10.15	7.36	5.37	4.14	3.70	2.40	2.27	2.54
	Median	8.88	6.93	5.00	3.33	2.67	1.50	1.82	1.83
	SD	4.29	4.16	3.78	3.61	3.85	2.68	2.50	2.81
	Minimum								
	Maximum								
	p-value[1]		<=0.001	<=0.001	<=0.001	<=0.001	<=0.001	<=0.001	<=0.001
Placebo	n	92	88	90	87	84	72	66	92
	Mean	11.25	8.49	7.14	6.31	6.20	5.68	5.51	5.70
	Median	9.43	7.17	6.43	6.00	5.54	5.52	5.76	5.57
	SD	7.90	5.82	4.96	4.39	4.13	4.26	4.85	4.92
	Minimum								
	Maximum								
	p-value[1]		<=0.001	<=0.001	<=0.001	<=0.001	<=0.001	<=0.001	<=0.001

[1] P-value for comparison of baseline within treatment group using the paired t- test.
@ Baseline value is the averaged daily moderate-to-severe hot flush frequency from run-in period.
n = number of subjects contributing to data

Note by week 3 there is a decrease in at least 2 moderate-to-severe hot flushes per day in the E_2 TDS group compared to the placebo group that continues and widens until treatment week 12. Mean and median values are consistent.

Comment: If one compares reviewer's Table 4 (sponsor's Table12) to sponsor's Table 15 (the following Table) which is the change from baseline in mean daily number of moderate-to-severe hot flushes, the values for n equals number of subjects contributing data, are slightly different for weeks 4, 8 and 12.

The sponsor constructed table15 that reports the change from baseline in the mean number of moderate-to-severe hot flushes:

Change from Baseline in Mean Daily Number of Moderate-to-Severe Hot Flushes—Study 97074A

Table 5

Modified from sponsor's Table 15 Vol. 38

Treatment Group	Statistics	Week 1	Week 2	Week 3	Week 4	Week 8	Week12	All Endpoint
E_2 TDS	N	85	87	87	82	84	68	89
	Mean	-2.78	-4.83	-6.02	-6.45	-7.69	-7.56	-7.66
	Median	-2.50	-4.04	-5.86	-6.42	-7.24	-7.07	-7.21
	SD	3.63	4.62	4.52	4.65	4.76	4.64	4.84
	Minimum							
	Maximum							
Placebo	N	87	89	86	83	71	65	91
	Mean	-2.70	-4.17	-5.15	-5.11	-5.98	-5.98	-5.56
	Median	-2.02	-3.33	-3.19	-4.10	-4.49	-4.42	-4.42
	SD	4.35	6.60	7.91	7.43	8.63	9.69	8.50
	Minimum							
	Maximum							
	p-value[1]	0.640	0.064	0.011	0.002	0.002	0.003	<=0.001

[1]Treatment effect p-value obtained from the following model based on ranks: Y=TMT INV, where y = outcome variable, TMT = treatment group, and INV = investigator
[2] n = number of subjects contributing to data

Note the change from baseline in the mean number of moderate-to-severe hot flushes is very similar to the mean number of moderate to severe hot flushes. A statistical trend begins at week 2 and by week 3 there is a statistically significance between treatment groups and this significance continues until week 12.

Comment: Tables 4 and 5 correlate well with other approved low dose transdermal products in relief of moderate-to-severe symptoms by the 4th treatment week and this effectiveness is continued through the remaining 8 weeks of treatment.

The second part of the primary efficacy variable is the mean daily severity of hot flushes. Previously approved products have shown a diminution of the severity of VMS as the treatment progresses through the treatment weeks:

Table 6 shows the Mean Daily Hot Flush Severity in Moderate-to-Severe Hot Flushes for Study 97074

Table 6

Modified from sponsor's Table 18 Vol. 38

Treatment Group	Statistics	Baseline @	Week 1	Week 2	Week 3	Week 4	Week 8	Week12	All Endpoint
E_2 TDS	n	89	86	89	89	83	85	68	91
	Mean	2.42	2.36	2.16	1.85	1.61	1.36	1.35	1.39
	Median	2.45	2.45	2.36	2.03	2.03	1.75	2.00	2.00
	SD	0.28	0.40	0.62	0.79	0.99	1.09	1.07	1.10
	Minimum								
	Maximum								
	p-value[1]		0.010	<=0.001	<=0.001	<=0.001	<=0.001	<=0.001	<=0.001
Placebo	N	92	88	90	87	84	72	66	92
	Mean	2.44	2.38	2.34	2.29	2.27	2.09	1.91	2.02
	Median	2.47	2.49	2.40	2.42	2.38	2.36	2.31	2.34
	SD	0.29	0.45	0.46	0.57	0.60	0.82	0.96	0.89
	Minimum								
	Maximum								
	p-value[1]		0.311	0.024	0.005	0.004	<0.001	<=0.001	<=0.001

[1] p-value for comparison of within treatment group using the paired t- test.
@ Baseline value is the averaged daily moderate to severe hot flush frequency from run-in period.

Comment: If one compares reviewer's Table 6 (sponsor's Table 18) to sponsor's Table 21 which is the change from baseline in mean daily number of moderate-to-severe hot flushes, the values for n equal number of subjects contributing data are slightly different for weeks 4, 8 and 12.

Severity of symptoms is also improved. As compared to the mean number and mean change of moderate-to-severe hot flushes, statistical significance is seen by the 2nd treatment week (compared to mean number of VMS) and continues throughout the remaining 10 weeks of treatment.

Comment: Review of Study 97074 shows that the mean number, change from baseline, and the severity of hot flushes are improved when compared to placebo. This diminution of hot flushes is seen by the 4th treatment week and continues through the remaining weeks of treatment.

The sponsor also conducted ITT analyses on multiple secondary efficacy variables such as vaginal dryness, pain during intercourse, frequency of urination, difficulty/pain during urination, involuntary urination and urination at night. None of the above secondary efficacy variables showed a statistically difference from placebo in the proportion of subjects improved by E_2 TDS except by treatment center interaction during various weeks or cycles of treatment.

Safety

AEs that occurred during the study were documented in the case report forms (CRF) regardless of attribution. A complete subject listing of AEs for all treatment groups is reported. Each AE is listed by the investigator's term and the equivalent Hoechst Adverse

Reaction Terminology System (HARTS) term. The listing also includes severity of the AE, relationship to the study drug, time of onset, duration of AE, action taken, and the outcome.

The following Table reports the number of Adverse Events by Body system:

Adverse Events: Incidence by Body System

Table 7

sponsor's Table 38 Vol.5

	Treatment Group	
	E_2 -TDS (N =92	Placebo (N = 94)
Body System	**Number (%) of Subjects**	
Overall	51 (55.4)	47 (50.0)
Body as A Whole	14 (15.2)	16 (17.0)
Skin	15 (16.3)	9 (9.6)
Respiratory	11 (12.0)	14 (14.9)
Urogenital	10 (10.9)	7 (7.4)
Nervous	5 (5.4)	10 (10.6)
Digestive	5 (5.4)	8 (8.5)
Cardiovascular	4 (4.3)	4 (4.3)
Special Senses	3 (3.3)	2 (2.1)
Metabolic and Nutritional	2 (2.2)	2 (2.1)
Hemic and Lymphatic	2 (2.2)	1 (1.1)
Musculoskeletal	1 (1.1)	3 (3.2)
Endocrine	1 (1.1)	0 (0.0)

Of the 186 subjects in the study, 98 subjects (52.7%) experienced 1 or more AE. AEs occurred most frequently in the "Body as a Whole" (16.1% of subjects), the respiratory system (13.4% of subjects), and the skin (including breast [12.9%]). Only two body systems had a slightly higher incidence of AEs, the skin (E_2 TDS 15 [16.3%] compared to 9 [9.6%]) placebo, and the nervous system (E_2 TDS 5 [5.4%] compared to 10 [10.6%] in the placebo group).

Table 8 shows the number of adverse events at >2% of subjects:

Table 8

sponsor's Table 39 Vol. 5

	Treatment Group		
	E_2 –TDS (N = 92	Placebo (n = 94)	Total (n = 186)
AE	Number of Subjects		
Overall	51 (55.4)	47 (50.0)	98 (52.7)
Upper respiratory infection	7 (7.6)	9 (9.6)	16 (8.6)
Application site reaction	5 (5.4)	5 (5.3)	10 (5.4)
Breast pain	6 (6.5)	0 (0.0)	6 (3.2)
Headache	3 (3.3)	3 (3.2)	6 (3.2)
Sinusitis	1 (1.1)	5 (5.3)	6 (3.2)
Infection	4 (4.3)	1 (1.1)	5 (2.7)
Rash	2 (2.2)	3 (3.2)	5 (2.7)
Diarrhea	2 (2.2)	2 (2.1)	4 (2.2)
Flu syndrome	1 (1.1)	3 (3.2)	4 (2.2)
Surgery	3 (3.3)	1 (1.1)	4 (2.2)

Note a very low incidence of AEs. This is consistent and expected of a low dose transdermal product such as E_2 TDS.

There were two serious AEs requiring hospitalization reported in this study. Subject 7411011 received E2 TDS and experienced an accidental tear of the right rotator cuff. She was compliant and remained in the study. Subject 7420007 received E_2 TDS and underwent dermatologic surgery. She had skin cancer removed from her nose. The subject was compliant and remained in the study. Neither of these SAEs was considered to be related to treatment drug.

One additional subject (subject #7418002) randomized to the placebo group, discontinued from the study on April 1, 1998. She reported that her primary physician had found an ovarian mass. This mass was later diagnosed as ovarian carcinoma, Stage 3. This AEs is not related to study drug.

Other serious AEs reported were 2 (2.2%) in the E_2 TDS group and 4 (4.3%) in the placebo group. In the E_2 TDS group one subject was reported to have an accidental injury and the other erythema nodosum. In the placebo group, subjects were noted to have abdominal pain, an abnormal laboratory test, a severe migraine, and diarrhea.

Of the 186 subjects evaluated in the study, a total of 2 (1.1%) subjects in the placebo discontinued because of an adverse event. These subjects discontinued due to moderate generalized edema and nausea.

Laboratory tests of hematology, serum chemistry, and urinalysis test were performed prior to trial treatment and at the end of the treatment period. There were no clinically significant changes in laboratory values reported. Vital signs, including blood pressure remained stable throughout the study.

8.1.6 Reviewer's Comments/Conclusion of study results

In this randomized, placebo-controlled study of twelve weeks duration, the 0.025mg/day E_2 TDS (Climara®) patch was statistically significantly better than placebo in the reduction of the frequency and severity of VMS. Efficacy was noted by the fourth week of treatment and was maintained throughout 12 weeks of treatment. Safety in this study is comparable to other low-dose estrogen transdermal patches. The usual AEs associated with ERT were seen at a lesser rate than would be seen at higher dosages. Application site reactions were reported in 10 (5.4%) of all subjects in this study.

8.2 Study 97095

8.2.1 Objective

The primary objective of this study was to determine the effectiveness of the continuous administration of transdermal estradiol to daily oral administration of conjugated equine estrogens 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.

8.2.2 Design

This was a twelve week, multicenter, double-blind, active-controlled, randomized-parallel group study comparing a continuous regimen of transdermal estradiol to daily oral dosing of Premarin®. The subjects were evaluated for up to three, 28-day cycles.

8.2.3 Source and number

The study was conducted at 19 centers in the US. All study centers were private practices or investigational institutions experienced in the conduct of clinical studies in female health care. At each center, the principal investigator was responsible for the study, and the study protocol was approved by the IRB. Monitoring of the study was carried out by Berlex Laboratories Inc. and

8.2.4 Entrance Criteria

Inclusion Criteria:

Inclusion criteria are identical to Study 97074

Exclusion Criteria:

Exclusion criteria are identical to Study 97074

8.2.5 Study Procedures

Study procedures are consistent with Study 97074 with the exception of the active control Premarin® 0.3mg/day, which is manufactured by Wyeth-Ayerst.

8.2.3.6 Efficacy Considerations

Based on a standard deviation of 36 (sigma) for the baseline weekly hot-flush rate in a similar population, it was determined that 75 completers per treatment were required to detect a between group difference at Cycle 3 of ½ sigma with power = 86% at 2-tailed

alpha = 0.05. Although this is a problem of equivalence, the sample size was calculated using the conventional approach of test of significance. The analysis will present confidence intervals only for the variables representing the mean weekly number of hot flushes for cycles 1, 2, and 3.

Statistical procedures are identical to study 97074 with an ITT population, a valid subject analysis, an end-point analysis and a completer analysis. As in study 97074, this review will focus *only* on the ITT treatment population with moderate-to-severe VMS at baseline.

To evaluate equivalence of the 2 active treatments, 95% confidence intervals for the treatment difference with respect to the change from baseline were computed for cycles 1, 2, and 3 using the Bootstrap method. This method is a non-parametric method intended to make corrections for bias and accelerations.

The 95% Boothstrap confidence intervals were computed for the treatment difference with respect to the change from baseline in mean weekly mild to severe hot flushes for cycles 1, 2, and 3. Note that the treatment difference was computed from a linear model with treatment and center as terms.

The primary efficacy variable was hot flushes and their severity. They were recorded using the IVRS throughout the study. The mean daily number and mean number of hot flushes were analyzed by cycle and overall. The mean daily maximum severity of hot flushes was analyzed by day and determined by averaging a subject's maximum daily rating across cycle weeks. Severity scores were: none = 0, mild = 1, moderate = 2, and severe = 3.

Comment:

Consultation with the statistical review team suggests that the sponsor's proposed comparisons for equivalence between the two products are invalid. The original protocol planned for within-group paired test for Week 4 and Week 12 to baseline. However, within-group comparisons are not appropriate to assess efficacy for this indication. Comparisons between the Climara arm and the CEE arm to show equivalence are not appropriate because *this study was not adequately designed to reach efficacy conclusions based on those comparisons.*

8.2.7 Safety Considerations

Safety was assessed from the following parameters: AEs, vital signs, physical examinations, including a pelvic examination and Pap smear, and clinical laboratory tests.

8.2.8 Results

A total of 193 subjects were randomized at 19 centers in the US. Of these 193 subjects, 95 subjects were allocated to receive active treatment with 17β-estradiol transdermal patches (E_2-TDS) and 98 were allocated to receive active oral conjugated equine estrogen (CEE) capsules. A total of 173 subjects were "completers" defined as subjects who completed the 3 cycle study period or who discontinued the study after at least 6 successful completed weeks on study drug. Table 9 shows the disposition of subjects in this study:

Table 9

Subject: Disposition by Treatment

			Completed		
Treatment group	Screened	Randomized	Cycle 1	Cycle 2	Cycle 3
E_2 TDS		95	90	83	79
CEE		98	91	86	81
Total	326	193	181	169	160

E_2-TDS – estradiol transdermal system
CEE- conjugated equine estrogen

The following table shows the subject disposition by Treatment Group and Cycle Valid Case

Table 10

sponsor's Table 6 Vol. 20

Treatment	Cycle 1	Cycle 2	Cycle 3
E_2 TDS	86	82	78
CEE	87	84	79
Total	173	166	157

Disposition table is based on the IVRS hot flush data.

Of the 193 subjects who entered the study at baseline, 179 (92.7%) were included in the valid case efficacy evaluation. To be included in the sponsor's efficacy evaluation, subjects must have had no major violations of the inclusion/exclusion criteria, and a compliance of 75% or higher.

Note of the 14 excluded cases by the sponsor, 8 were in the CEE group and 6 were in the E_2 TDS group. Of these 14 excluded cases, 13 out of 14 were related to the subjects being non-complaint with either use of the patch or the capsule. One subject (9505009) did not meet the hot flush criteria.

The following table shows the frequency of withdrawal by reason and by treatment group:

Table 11

End of Study Medication—Frequency of Discontinuation of Study Medication

sponsor's Table 8 Vol. 20

	E_2 TDS (N=95)	CEE (N=98)	Total (N=193)
Reason	n (%)	n (%)	n (%)
Adverse event	5 (5.3)	6 (6.1)	11 (5.7)
Lack of efficacy	2 (2.1)	1 (1.0)	3 (1.6)
Protocol deviation	2 (2.1)	2 (2.0)	4 (2.1)
Withdrawal of consent	3 (3.2)	1 (1.0)	4 (2.1)
Other[a]	4 (4.2)	5 (5.1)	9 (4.7)
Total	16 (16.8)	15 (15.3)	31 (16.1)

[a] Other includes: Lost to Follow=up, geographical relocation, non-compliant, unknown
N = total number of subjects
n (%) = number (percent) of subjects

Four (4) subjects (2 E_2 TDS and 2 CEE) withdrew from the study due to protocol violations. Three of the four protocol violators were non-compliant and the fourth subject in the CEE group completed the study 1 week early.

Baseline demographics showed the majority of subjects were Caucasian with a mean age of 52.0 years. Approximately 162 (84%) were White, 20 (10%) were Black, 9 (5%) were Hispanic, and 2 (1%) were other nationalities. The treatment group were comparable in all baseline characteristics (such as height, weight, blood pressure, heart rate, E_2 and FSH levels) except for age variable (p=0.0008), with the mean age of the E_2 TDS being 53.3 years and the CEE mean age being 50.8 years.

Comment: It is unclear if 2.5 years difference in moderate-to-severe VMS would make a difference in either frequency or severity of symptoms.

Of the 193 subjects in both treatment groups, 138 (72%) had a hysterectomy and 55 (28%) had not had a hysterectomy. One hundred twenty-one (121 [63%]) had not had an oophorectomy and 72 (37%) had a bilateral oophorectomy. Of the 55 subjects who had a uterus, 53 had an endometrial biopsy. A negative endometrial biopsy was acceptable if it had been done 6 months prior to the screening period. In women with bleeding, the biopsy was done at screening. Of the 53 biopsies, 42 (79.2%) had an inactive/atrophic endometrium, 5 (9.4%) had tissue insufficient for diagnosis, 5 (9.4%) had proliferative endometrium, and 1 (1.8%) had menstrual-type endometrium.

A total of 193 (100%) subjects had a mammogram at baseline. One hundred seventy-four (90%) had a normal mammogram; 19 (10%) of subjects had an abnormal mammogram which was not clinically significant.

Concomitant medication was taken by 76 of 193 subjects (39%) at some time during the study. The most often reported concomitant medications were anti-inflammatory agents, analgesics, antibiotics, antihistamines, and antitussives. No subject received any hormone replacement therapy or medications listed under the exclusion criteria.

Compliance was defined as wearing of the systems (or taking the capsule) by the subject 75% of the time. Thirteen subject were excluded due to less than 75% patch/or capsule compliance and 1 subject was excluded due to not meeting the hot flush criteria.

Efficacy

The run-in period was up to 1 cycle or 4 weeks in duration. Hot flushes, frequency and severity, and urogenital symptoms were recorded. Subjects could qualify for the study by having the required number of hot flushes during any consecutive 7 days of the run-in period. There were individual subjects with minimum weekly and daily frequencies below the required number who were, nevertheless, eligible for the study.

Comment: It is clear at study start not all subjects had the minimum daily and number frequency of hot flushes, but the overall number (> 60/week) during that 4 week run-in period allowed the sponsor to enter these subjects. However, having the minimum number and frequency for any consecutive days in the run-in period allowed the sponsor to enroll these subjects.

The baseline mean weekly number of hot flushes was 94.1 for the E_2 TDS group and 94.1 in the CEE group; the mean daily number of hot flushes was 13.4 for the E_2 TDS group and 13.4 for the CEE group. There were no statistically significant differences between the 2 treatment groups in either the mean weekly or mean daily number of hot flushes. Subjects also kept a diary on vaginal dryness, pain during intercourse, frequent

urination, difficulty/pain during urination, involuntary urination and urination at night. There were no significant differences between the treatment groups.

Comment: Note the sponsor included mild hot flushes. The clinical indication is moderate-to-severe VMS. My review will focus on moderate-to-severe symptoms in the ITT population since that is the intended indication. The statistician concluded that the protocol specified within-group comparisons are not appropriate to assess efficacy comparisons of Climara® and CEE. In addition the sponsor did not prospectively identify a clinically meaningful difference upon which to base equivalency claims.

Table 12 shows the mean number of moderate-to-severe hot flushes for study 97095:

Table 12

Mean Daily Number of Moderate-to-Severe Hot Flushes
Study 97095 by Treatment Week –ITT

Modified from sponsor's table 13, Vol. 38

Treatment Group	Statistics	Baseline @	Week 1	Week 2	Week 3	Week 4	Week 8	Week12	All Endpoint
E_2 TDS	n	95	90	91	89	88	83	75	94
	Mean	11.09	8.84	6.38	4.87	3.86	2.94	2.27	2.52
	Median	9.93	8.00	5.86	4.21	3.07	1.67	0.29	1.00
	SD	4.39	4.47	4.37	4.00	3.56	3.75	3.78	4.14
	Minimum								
	Maximum								
CEE	n	98	87	93	93	91	83	74	96
	Mean	10.99	9.08	6.61	5.17	4.07	2.18	1.83	2.94
	Median	9.09	7.29	4.86	3.43	2.43	1.17	0.34	0.93
	SD	6.78	7.35	8.44	8.09	6.14	2.72	2.61	7.95
	Minimum								
	Maximum								
	p-value[1]	0.859							

[1] p-value for Comparison of treatment groups at baseline using model Y=TMT INV, where Y= Outcome variable, TMT = Treatment group, and INV= Investigator.
@ Baseline value is the averaged daily moderate to severe hot flush frequency from run-in period.

Note by week 3 there has been a reduction of at least 2 hot flushes/per day and this trend of diminution of hot flushes continues to decrease throughout the remaining weeks of study.

Comment: This is consistent with other ERT products approved for the relief of VMS. This study supports study 97074 in that the decrease in the mean number of hot flushes are very similar.

The sponsor constructed the following table that shows the change from baseline in mean daily number of moderate-to-severe hot flushes:

Change from Baseline in Mean Daily Number of Moderate-to-Severe Hot Flushes –ITT—Study 97095
Table 13

Modified from sponsor's table 16

Treatment Group	Statistics	Week 1	Week 2	Week 3	Week 4	Week 8	Week12	All Endpoint
E_2 TDS	n	90	91	88	88	83	75	94
	Mean	-2.18	-4.72	-6.02	-7.07	-7.91	-8.29	8.29
	Median	-1.55	-4.40	-5.72	-7.21	-7.87	-8.09	-8.02
	SD	3.83	3.94	3.94	4.17	4.74	4.53	4.80
	Minimum							
	Maximum							
CE0E	n	87	93	93	91	83	74	96
	Mean	-1.92	-4.53	-5.88	-6.97	-8.14	-8.44	-8.10
	Median	-1.40	-3.82	-5.81	-6.64	-7.29	-7.80	-7.73
	SD	4.00	6.04	6.03	5.79	4.90	4.88	6.05
	Minimum							
	Maximum							

Note the similar change from mean baseline hot flushes. These decreased changes are present by week 4 and are maintained thorough weeks 8 and 12. Of primary importance is that similar change from mean baseline values support those seen in Study 97074.

The following table shows the Mean Daily Hot Flush Severity in Moderate-to-Severe

Hot Flushes—Study 97095—ITT

Table 14

Modified from sponsor's table 19

Treatment Group	Statistics	Baseline @	Week 1	Week 2	Week 3	Week 4	Week 8	Week12	All Endpoint
E_2 TDS	n	95	90	91	89	88	75	75	94
	Mean	2.43	2.41	2.18	1.97	1.75	1.42	1.11	1.25
	Median	2.45	2.50	2.35	2.13	2.03	1.86	0.57	1.61
	SD	0.26	0.34	0.62	0.80	0.91	1.06	1.11	1.12
CEE	n	98	87	93	93	91	83	74	96
	Mean	2.40	2.37	2.13	1.85	1.66	1.33	1.07	1.19
	Median	2.43	2.45	2.27	2.00	2.00	1.43	0.50	1.39
	SD	0.25	0.44	0.59	0.84	0.95	1.10	1.15	1.14
	p-value[1]	0.424							

[1] p-value for comparisons of E_2 TDS with CEE at baseline using model Y=TMT INV where Y = Outcome variable, TMT = treatment group, and INV = INVESTIGATOR

[@] Baseline value is the averaged daily moderate to severe hot flush frequency from run-in period.

As demonstrated with the mean number of hot flushes and the change from baseline of hot flushes, the mean severity data shows decreases similar to those found in Study 97074 and support that study.

As in study 97074 the sponsor conducted ITT analyses of multiple secondary efficacy variables such as vaginal dryness, pain during intercourse, frequency of urination, difficulty/pain during urination, involuntary urination, and urination at night. <u>There was no difference in the above secondary efficacy variables when E_2TDS was compared to conjugated equine estrogens.</u>

Safety

All adverse events that occurred during the study were documented in the CRF regardless of attribution. A complete listing of AEs for both treatment groups is reported. Each AE is listed by investigator's term and the equivalent of HARTS term. The listing also includes severity of the AE, relationship to the study drug, time of onset, duration of the AE, action taken, and the outcome.

Of the 193 subjects in the study, 109 subjects (56.5%) experienced 1 or more AE. AEs occurred most frequently in the "body as a whole" (17.6%) of subjects, the nervous system (16.1%) of subjects) and the skin (including breast [15.5% of subjects]).

The following table reports the number of adverse events by Body System:

Adverse Events: Incidence by Body System

Table 15

sponsor's Table 39

	Treatment Group	
	E_2 –TDS (N –95	CEE (N = 98)
Body System	**Number (%) of Subjects**	
Overall	58 (61.1)	51 (52.0)
Body as A Whole	19 (20.0)	15 (15.3)
Nervous System	13 (13.7)	18 (18.4)
Skin	13 (13.7)	17 (17.3)
Respiratory	12 (12.6)	7 (7.1)
Digestive	11 (11.6)	8 (8.2)
Urogenital	10 (10.5)	11 (11.2)
Musculoskeletal	4 (4.2)	5 (5.1)
Metabolic and Nutritional	4 (4.2)	6 (6.1)
Cardiovascular	2 (2.1)	1 (1.0)
Special Senses	1 (1.1)	3 (3.1)

Note the fairly equal distribution of AE attributed to both products with no obvious differences. Overall, as expected AEs related to the body system are low when compared to higher dosages of transdermal patches.

The following table reports most frequent adverse event which occurred at ≥ 2%:

Table 16

Adverse Events: Incidence of all Adverse Events ≥2%

sponsor's Table 40

	Treatment Group		
	E_2 –TDS (N = 95	CEE (N = 98)	Total (N = 193)
AE		Number (%) of Subjects	
Overall	58 (61.1)	51 (52.0)	109 (56.5)
Headache	5 (5.3)	8 (8.2)	13 (6.7)
Application site reaction	7 (7.4)	5 (5.1)	12 (6.2)
Upper respiratory infection	5 (5.3)	3 (3.1)	8 (4.1)
Breast pain	4 (4.2)	4 (4.1)	8 (4.1)
Insomnia	3 (3.2)	5 (5.1)	8 (4.1)
Back pain	3 (3.2)	3 (3.1)	6 (3.1)
Laboratory test abnormal	3 (3.2)	3 (3.1)	6 (3.1)
Dizziness	2 (2.1)	4 (4.1)	6 (3.1)
Peripheral edema	2 (2.1)	4 (4.1)	6 (3.1)
Flatulence	3 (3.2)	2 (2.0)	5 (2.6)
Sinusitis	3 (3.3)	1 (1.0)	4 (2.1)
Urinary tract infection	3 (3.2)	1 (1.0)	4 (2.1)
Nausea	2 (2.1)	2 (2.0)	4 (2.1)
Pain	1 (1.1)	3 (3.1)	4 (2.1)
Vaginal hemorrhage	1 (1.1)	3 (3.1)	4 (2.1)

Note the very low incidence of AEs. This is consistent and expected of a low dose transdermal product and the lowest approved dose of oral conjugated estrogens.

There were 3 serious AEs reported requiring hospitalization in this study. Subject 9501003 received CEE. She experienced severe constipation and was hospitalized. This was not considered to be drug related. Subject 9506004 received E_2 TDS and experienced severe leg cramps, dizziness, hypertension, chest pain, and was hospitalized. The patient's hypertension was considered possibly related to drug therapy. Subject 9519003 received CEE during the study. She experienced polymicrobial bacteremia and was hospitalized. The patient had a repair of an oral antral fistula and tooth extraction. The investigator did not consider this AE to be related to the study drug.

There were 13 other serious AEs reported, 7 (7.4%) in the E_2 TDS group and 6 (6.1%) in he CEE group. Of these serous AEs most were of a generalized nature and included back pain, headache, insomnia, colitis, constipation, and abnormal liver test, sinusitis, acne and taste perversion. One patient reported an application-site reaction in the E_2 TDS group.

Eleven (11) AEs were reported that lead to withdrawal from the study. There were 6 in the CEE group and 5 in the E_2TDS group. Only one of these AEs was definitely related to either drug; subject 9504001 experienced an application site reaction. There most frequently reported AEs leading to discontinuation was rash (2 subjects [1.0%]).

Clinical laboratory test of hematology, serum chemistry, and urinalysis test were performed prior to trial treatment and at the end of the treatment period. There were no clinically significant laboratory values reported. Small lipid changes were generally not

significant between treatment groups. Vital signs, including blood pressure, remained stable throughout the study.

8.2.9 Reviewer's comments/Conclusions of study results

In this randomized, double-blind, multi-center study of twelve weeks duration, the 0.025mg/per day Climara patch was compared to conjugated equine estrogens (0.3mg/day) for the ability to decrease the frequency and severity of hot flushes. Results in the ITT treatment population appear to show no statistically significant differences between treatment groups in the relief of hot flushes in either the mean number or the percent change from baseline for the two treatment groups. However, the protocol originally planned for within-group paired tests for Week 4 and Week 12 from baseline. In review of ERT products, within-group comparisons are not appropriate to assess efficacy for this indication. Comparisons between the E_2TDS arm and the CEE arm to show equivalence are not appropriate because this study was not adequately designed to reach efficacy conclusions based on those comparisons. Safety is comparable to other low dose estrogen products. AEs usually associated with ERT were seen at a lesser rate than would be seen at higher dosages. Application site reactions were reported in 12 (6.2%) of subjects in this study.

9 Overview of Efficacy

The sponsor submitted two studies, a randomized placebo controlled study (study 97074) and a comparative study (study 97095) comparing E_2 TDS 0.025mg/day against conjugated equine estrogens 0.03mg/day. Both studies were for 12-weeks duration. Three hundred seventy-nine subjects (379) were randomized with 187 receiving E_2 TDS, 98 receiving conjugated estrogens and 94 receiving placebo. Study results show E_2 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 E_2 TDS 0.025mg/day to have similar efficacy results when compared to conjugated equine estrogens at 0.3mg/day. Because of design deficiencies, this study can only be used to support study 97074.

10 Overview of Safety

The sponsor included 379 subjects in their summary of safety. Overall 109 (58.3%) of subjects in the E_2 TDS, 51 (52%) of subjects in the CEE group, and 47 (50%) of subjects in the placebo group reported an adverse event by body system. There were no deaths in this trial, including follow-up. Serious AEs requiring hospitalization involved 1 case of severe constipation, one case of an oral antral fistula and tooth extraction, and a case of hypertension with chest pain. Other serious AEs were non-specific except for 3 cases of skin reaction associated with E_2 TDS. In the 13 (3.4%) subjects who withdrew from the study because of an adverse reaction, 1 case of application site reaction was clearly related to E_2 TDS. Clinically significant changes in laboratory tests due to study drug administration did not occur with any degree of repetitiveness in either study to warrant concern. Vital signs, including blood pressure, remained stable throughout both studies.

11 Labeling Review

Labeling is reviewed from sponsor's submission of June 2, 2000. Major changes consistent with the Labeling Guidance for Noncontraceptive Estrogen Drug products of November 1999 have been made to the following sections: Box Warning, Pharmacokinetics (including a special populations section), drug interactions, and an adhesion section. Under the Clinical Studies section the following table (labeled Table 3), should be added with the following text:

Table 3

Treatment Group	Statistics	Week 4	Week 8	Week12
E_2 TDS	N	82	84	68
	Mean	-6.45	-7.69	-7.56
	SD	4.65	4.76	4.64
Placebo	N	83	71	65
	Mean	-5.11	-5.98	-5.98
	SD	7.43	8.63	9.69
	p-value	<0.002		<0.003

A second active control trial of 193 randomized subjects was supportive of the placebo control trial.

Extensive changes were also made to the Warnings section of the label.

Breast Cancer (1b) should now be added which states:

While some epidemiologic studies suggest a very modest increase in breast cancer risk for estrogen alone users versus non-users, other studies have not shown any increased risk. The addition of progestin to estrogen may increase the risk of breast cancer over that noted in non-hormone users more significantly (by about (24-40%), although this is based solely on epidemiologic studies, and definitive conclusions await prospective, controlled clinical trials.

#2 Under Thromboembolic disorders, two paragraphs should be inserted:

Venous thromboembolism. Several epidemiologic studies have found an increased risk of venous thromboembolism (VTE) in users of estrogen replacement therapy (ERT) who did not have predisposing conditions for VTE, such as past history of cardiovascular disease or a recent history of pregnancy, surgery, trauma, or serious illness. The increase risk was found only in current ERT users; it did not persist in former users. The risk appeared to be higher in the first year of use and decreased thereafter. The findings were similar for ERT alone or with added progestin and pertain to commonly used oral and transdermal doses, with a possible dose-dependent effect on risk. The studies found the VTE risk to be about one case per 10,000 women per year among women no using ERT and without predisposing conditions. The risk in current ERT users was increased to 2-3 cases per 10,000 women per year

Cerebrovascular disease. Embolic cerebrovascular events have been reported in women receiving postmenopausal estrogens.

Under the Adverse Reactions section older text relating to comparisons to other products should be deleted. The following text should be added:

> Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rtes observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Under Dosage and Administration section the following text should be revised:

> Under "Initiation of Therapy" the first sentence should be modified to "For the treatment of vasomotor symptoms, treatment should be initiated with the 6.5cm^2 (0.25mg/day) Climara ® system applied to the skin once weekly.

12 Conclusions

The sponsor has demonstrated with one adequate placebo controlled trial and one supportive comparative trial, the safety and effectiveness of E_2TDS (0.025mg/day) in reducing moderate to severe vasomotor symptoms associated with the menopause.

13 Recommendation

Approval of E_2 TDS (0.025mg/day) after acceptable labeling revisions (after concurrence from all disciplines once reviews are completed).

Phill H. Price, M.D.
March 26, 2001

This review is 25 pages with additional pages of clinical investigators.

Addendum to Primary Review, NDA 20-375 –S016

SAFETY UPDATE

On March 27, 2001 the sponsor Berlex Laboratories, submitted a letter stating that there was no new safety information learned about Climara® (0.025mg/day) that may reasonably affect the Contraindications, Warnings and Adverse Reactions sections in the labeling.

During the reporting period of June 2, 2000 to March 20, 2001 there was one spontaneous report from marketing experience in the US. That occurred in a female of unspecified age and race who was using Climara® 0.025 mg/day.

The subject discontinued use of Climara® due to cramping and was admitted to the hospital for an appendectomy for appendicitis. The physician reports no causal relationship between appendectomy and Climara®.

Phill H. Price, M.D.
March 28, 2001

/s/

Phill H. Price
4/2/01 02:26:15 PM
MEDICAL OFFICER

Shelley Slaughter
4/3/01 02:27:05 PM
MEDICAL OFFICER

Addendum to Primary Review, NDA 20-375 –S016

SAFETY UPDATE

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Phill H. Price, M.D.
March 28, 2001