CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020994, 020375/S011

MEDICAL REVIEW(S)

Medical Officer's Review of NDA 20994

1 General Information

1.1 NDA 20994

1.2 Applicant: Berlex Labs Inc.
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This NDA review has been discussed with other **FDA reviewers**:
Z. Jonathon Ma, PhD
Todd Sahlroot, PhD
(Statistics Reviewers)
Ron Kavanagh, PhD
(Biopharm. Reviewer)
Amit Mitra, PhD
(Chemistry Reviewer)

Randy Hedin, RPh (CSO)

1.3 Submission/review dates

1.3.1	Date of Submission:	5/1/98
1.3.2	CDER stamp date:	5/5/98 (HFD580); 5/13/98 (HFD510)
1.3.3	Date submission received by reviewer:	5/29/98
1.3.4	Date review begun:	5/29/98
1.3.5	Date review completed:	2/22/99

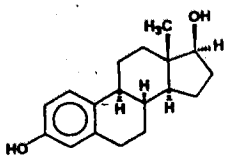
1.4 Drug Identification

1.4.1 Generic name: estradiol transdermal system 0.025, 0.05, 0.075, 0.1 mg

1.4.2 Proposed trade name: Climara

1.4.3 Chemical name: Estra-1,3,5(10)-triene-3,17β-diol

1.4.4 Chemical structure:



1.4.5 Molecular formula: $C_{18}H_{24}O_2$

1.4.6 Molecular weight: 272.37

1.5 Pharmacologic Category: Estrogen

1.6 Dosage form: Patches containing 4 dosages of estradiol:

Patch size (cm^2)	**Estradiol Contents** (mg)	**Estradiol Delivery** (mg/day)
6.5	2.04	0.025
12.5	3.9	0.05
*(15	4.68	approx. 0.06)
*18.75	5.85	0.075
25.0	7.8	0.1

*Note : It was not clear for which patch size the sponsor was requesting approval: the clinical trial protocol in the NDA described a 15 cm^2 patch containing 4.68 mg estradiol in its studies, but the labeling information lists a 18.75 cm^2 patch containing 5.85 mg. A clarification from the sponsor was requested: the sponsor wishes to market the 18.75 cm^2 patch.

1.7 Route of Administration: transdermal

1.8 Proposed Indication and Usage : Prevention of Postmenopausal Osteoporosis

1.9 Proposed Dosage and Administration: Transdermal System, applied weekly, to deliver 0.025, 0.05, 0.075, or 0.1 mg of estradiol per 24 hour period

1.10 Related Drugs: Estraderm transdermal system, conjugated (oral) estrogens

1.11 Material Reviewed:
1.11.1 NDA volumes reviewed: Volumes 1, 5-19,51-54 of NDA 20994, dated 5/5/98; Electronic file from Berlex

1.12 Regulatory Background
IND (10/27/92, submitted)
NDA20,375 (7/15/93 9/29/93 resubmitted; 12/22/94 - Climara 0.05, 0.075, 0.1 mg patches approved for vasomotor symptomatology; 11/2/95 ownership transferred to Berlex)
Meeting with DMEDP, FDA 11/8/93

Regulatory Recommendation:

Approval, pending
1) adequate final sponsor responses to FDA questions;
2) final Division of Scientific Investigation Report;
3) change in labeling, as requested by FDA.

Abbreviations are defined in the text and also below:
AE=adverse events; A-P=anteroposterior; BMD=bone mineral density; DEXA=x-ray absorptiometry for assessment of bone mineral density; LOCF=last observation carried forward or endpoint, referring to statistical analysis; NDA=New Drug Application; RCT=randomized clinical trial

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Summary

NDA 20994 (Climara, Berlex) has been submitted as a Type 6 NDA for approval of four doses of Climara estradiol transdermal systems for the prevention of postmenopausal osteoporosis. The 0.05, 0.075, and 0.1 mg patches have been previously approved (12/22/94) for the treatment of vasomotor symptoms. No studies of vasomotor symptoms in relation to the 0.025 mg dose have been submitted to the FDA. A single, multicenter (10 sites in the United States), 2-year, randomized, double-blind, controlled study was conducted. The study population comprised 175 hysterectomized, postmenopausal women (83 % Caucasian, ages 40-71, described as $\leq$5 years postmenopausal). A statistically significant change in the primary efficacy variable – antero-posterior view lumbar spine bone mineral density (BMD) by x-ray absorptiometry (dexa scan) as compared to placebo was noted in the four treatment groups, 6.5, 12.5, 15, 25 cm^2, which corresponded to 0.025, 0.05, 0.06, 0.1 mg estradiol/day, respectively. The percent changes in lumbosacral BMD at last observation carried forward (LOCF) or endpoint were 2.32, 3.74, 3.45, 5.20 % for the four treatment doses, respectively, as opposed to -2.33% for the placebo. Since the sponsor's intent-to-treat analysis included only subjects who had measurements of lumbar spine BMD at 6 months, two confirmatory analyses were done imputing 'zero' change and the respective 'placebo' change for the subjects without data at 6 months or subsequently. The observed change in lumbar spine BMD remained statistically significant with both imputed analyses. Changes in secondary efficacy variables (total hip BMD, femoral neck BMD, nondominant radius BMD, serum osteocalcin, urinary deoxypyridinoline/creatinine ratio, and urinary pyridinoline/creatinine ratio) helped to confirm the preservation of bone and prevention of osteoporosis suggested by the primary efficacy variable. No fractures secondary to osteoporosis were observed in the study. Of note vertebral x-rays were done at baseline and subsequently only if clinically indicated. Height was only measured at baseline. Thus, asymptomatic vertebral fractures could be missed in this protocol. By study protocol, subjects were to be discontinued if they developed osteoporosis (lumbar spine BMD < 0.9 gm/cm^2), though none were discontinued for this reason. Four subjects sustained traumatic fractures during the study.

A total of 78 subjects withdrew from the study. The reasons for withdrawal included adverse events relating to the treatment (n=20 per sponsor, 23 per medical reviewer), administrative reasons (n=55), which included relocation of subjects, loss of study drug, and withdrawal of consent. The subjects who withdrew – whether for adverse events or adninistrative reasons – were distributed throughout all five treatment groups, and thus the distribution of dropouts, *per se*, was not thought to bias the outcomes. Application site reactions affected 8/17 or 47 % of the subjects treated with estradiol who withdrew because of adverse events. This observed percentage in the clinical trial may be relatively modest, as subjects were excluded from participating in the RCT if an application site reaction occurred during a 2-4 week screening period. Other adverse events were consistent with those previously observed with estrogen therapy (emotional lability, breast pain, hot flashes, headache, depression) or with postmenopausal symptoms (hot flashes, sleeplessnes, vaginal dryness). Two withdrawals were due to serious

adverse events (colon cancer [12.5 cm^2 treatment group] and angina and hypertension [P treatment group]). There were no deaths during the study.

Factors that complicated the FDA review process included absence of clarity in the NDA submission regarding the randomization process and the intent-to-treat (ITT) analysis (e.g., there were no written explanations about the exclusion of 3 randomized subjects from the ITT analysis), the sponsor's definition of an ITT analysis, which effectively excluded 25% (12/46 in the placebo and 30/129 drug treatment group) of the randomized population, ambiguity regarding the size of the study patches vs. the size of the planned marketed patches (15 cm^2 vs 18.75 cm^2), minor inconsistencies in different volumes of the submission, and questions raised by the FDA Division of Scientific Investigation regarding the sponsor's transcription of information from one of the study sites.

In conclusion, the sponsor has shown modest efficacy of the four treatment doses of Climara estradiol transdermal drug delivery system in postmenopausal osteoporosis in one adequate, randomized, controlled double blind multicenter clinical trial, as required by the currently available draft Osteoporosis Guidance (1994), without major safety concerns. The regulatory recommendation is approval, if the labeling can cite more precisely the actual data from this clinical trial, if the question recently (2/12/99) raised by the biopharmaceutical division ("Is low-dose patch adequately effective in obese women ?") can be satisfactorily answered by the sponsor, and if the Division of Scientific Investigation has no further serious concerns regarding the study conduct.

3. Chemistry/Manufacturing Controls

The Climara system consists of two layers: (1) a translucent polyethylene film, and (2) an acrylate adhesive matrix containing estradiol USP, which is applied to the skin surface. A protective liner, consisting of siliconized or fluoropolymer-coated polyester film, must be removed before the system is applied to the skin. 17β-estradiol is the active component of this system; the other components (acrylate copolymer adhesive, fatty acid esters, polyethylene backing) are pharmacologically inactive. Only about 10 % of the 17β-estradiol in each patch is delivered during the week that the patch is applied. The specific components of the Climara system, as described in the original NDA chemistry review include the drug reservoir, consisting of estradiol USP, alcohol USP, and hydroxypropyl cellulose; the backing layer, consisting of polyester/EVA copolymer; the release membrane, consisting of ethinyl vinylacetate copolymer; the adhesive, containing polyisobutylene and light mineral oil USP; and the protective peel liner, with polyester film coated on one side with silicone. Please see the chemistry review regarding criteria for components and composition, manufacturing, processing, container, tested rate of release of estradiol and ethanol by the paddle method, and stability.

4. Animal Pharmacology/Toxicology

No animal studies were submitted in this NDA.

5. Microbiology

No microbiology studies were submitted.

6. Human Pharmacokinetics/Pharmacodynamics

A three-week bioavailability crossover study(one week on each patch with a one week of washout in between) in 24 postmenopausal women was submitted to the FDA for comparison of the bioavailability of the 6.5 and 12.5 cm^2 patches. This study was reviewed by the clinical pharmacology and biopharmaceutics team, who found the doses to be proportional based upon dose adjusted relative bioavailability. In this study, the abdomen, which previously had been shown to have a lower availability than the buttocks was used for patch placement. Thus, even greater efficacy might be achieved if the buttocks were used. In the bioavailability study, study patches were applied by the study nurse. Despite this procedure, tape needed to be applied in 9/48 (19%) applications and in 8/24 subjects (33%).

A pharmacokinetics sub-study within the Phase III clinical protocol (see below) consisted of blood samples for estradiol, estrone, and SHBG, drawn at visits 1 (week 4), visit 3 (week 24), and visit 5 (week 52). These samples were drawn mostly on days 1 and 7 of the patch application, and a smaller number were drawn inbetween (days 2-6). The concentrations obtained on active drug appeared to be above the baseline concentrations for all treatment groups, but the concentrations obtained for estradiol varied greatly, partially depending on the day the sample was drawn. Mean concentrations of the baseline corrected estradiol concentrations are summarized in the table below:

Baseline Corrected Estradiol Concentrations			
Patch size // (total n)	Week 4 (87)	Week 24 (69)	Week 52 (57)
6.5 cm^2	16.8	16.2	18.1
12.5 cm^2	30.6	33.2	30.2
25 cm^2	32	24.8	34.4
Data abstracted from clinical pharmacology review.			

No accumulation of drug was observed on long-term dosing.

Comment:

1) It is unclear if problems with adhesion were greater with the larger patch. Apparently, additional adhesion studies have been submitted by the sponsor to the HFD580 reviewing division.

2) During the clinical pharmacology and biopharmaceutics team conference review of this NDA, the question was raised whether the different patch sizes are equally effective in obese women and specifically whether the 6.5 cm^2 patch is effective in obese women. This question was referred to the sponsor for further analysis, as the SAS data set supplied to the statisticians was not accessible. From a clinical point of view, bone

mineral density is usually higher in obese women and thus prevention of osteoporosis may be a less cogent consideration.

7. Human Clinical Experience

7.1 Foreign Experience: Since this is a Type 6 NDA (essentially a supplemental NDA), no information regarding foreign experience was submitted (21 CFR 314.50(c)(1)).

7.2 Post-Marketing Experience

Post-marketing adverse events data was obtained from the Adverse Event Reporting System (AERS) and the number of prescriptions was obtained from the [redacted]. These measures are only approximations, as it is estimated only a small percentage (perhaps about 10%) of adverse events are reported, and number of prescriptions does not include the actual amount of drug dispensed or actually used. The data are summarized in the table below, and they are compared to comparable data for Estraderm:

Post-Marketing Experience with Climara and Comparison to Post Marketing Experience with Estraderm

Data Compiled Per Medical Officer
From
Adverse Event Reporting System (AERS) [redacted]

	Date Approval	Total # Prescriptions	# Prescriptions in 1998*	Total Reported AE	Serious AE	Deaths	Application Site Reactions
Climara	5/95	[redacted] (1995-8)	[redacted]	956	17 (1.8%)	0	616 (64%)
Estraderm	9/86	[redacted] (1993-8)	[redacted]	10,576	447 (4.2%)	12	3209 (30%)

Comments:

1) These data are presented only for a general comparison and conclusions must be carefully considered, as the numbers are not always precise.

2) The AERS data represent spontaneously reported events and are thought to represent only a small fraction of actual adverse events.

3) Only data since 1993 are available for computer retrieval in the [redacted] If one approximates that about [redacted] prescriptions for Estraderm were dispensed between 1986 and 1993 (extrapolated from [redacted] dispensed in 1993), then the total number of Estraderm prescriptions would approximate [redacted] Thus, the ratio of total AERS to the total number of prescriptions would be similar for Climara and Estraderm, or about one adverse event per [redacted] prescriptions.

4) The relative number of reported application site reactions appear to be twice as many for Climara (616/956 or 64%) as for Estraderm (3209/10576 or 30 %). This difference may be related to the longer duration of time the Climara patch stays in place (seven days vs. 3.5 days for the Estraderm patch). A clinical trial described by the sponsor in the label comparing Climara and Estraderm patches did not observe a significant difference in application site reactions.

8. Clinical Studies

8.1 Introduction

The 1994 draft osteoporosis guidance, "Guidelines for Preclinical and Clinical Evaluation of Agents Used in the Prevention or Treatment of Postmenopausal Osteoporosis" defines osteoporosis as "a condition in which the bone mass per unit volume (density) of normally mineralized bone is reduced" and describes postmenopausal osteoporosis as "Type I osteoporosis [which] affects women after menopause and results from an accelerated rate of bone loss (mainly trabecular) due to factors (mostly estrogen deficiency) related to menopause." (p. 7, cited FDA guidance 1994). Furthermore, the guidance notes, "if a drug has been approved for the treatment of osteoporosis [for example, estrogen] BMD may serve as an appropriate efficacy endpoint in trials for prevention of osteoporosis. Efficacy trials should be randomized, double-blind, placebo-controlled with multiple dosage arms to enable assessment of the minimumn effective dose. The study should last at least 2 years." (pp.10-11, Ibid)

The sponsor (Berlex) has followed this guidance in the preparation of Climara, an estradiol transdermal drug delivery system (ETDDS) for an application for prevention of postmenopausal osteoporosis. This NDA submission comprises one major clinical Phase III study: a randomized, double-blinded, controlled 10-site multicenter two-year clinical trial (abbreviated as RCT below) to evaluate the clinical efficacy of four doses of estradiol transdermal system versus placebo in the prevention of osteoporosis (Study 308-03B, Sponsor Report 97034) in 175 postmenopausal hysterectomized women ages 40-71. The RCT was conducted between May 17, 1994 and August 1, 1997.

A pharmacokinetic screen involving 87 subjects initially and concluding at one year with 57 subjects was incorporated as a substudy of the RCT. A relative bioavailability study, a Phase I study, in 24 postmenopausal women (Study 97075, Sponsor Report 98002) was conducted in 8/97 and consisted of a randomized crossover design, with a one week washout, comparing the patches that delivered 0.025 and 0.05 mg/day of estradiol each worn for a one week period. This study has been reviewed by Ronald E. Kavanagh PhD and discussed with him (Clinical Pharmacology and Biopharmaceutics Review). See Section 5 Human Pharmacokinetics/Pharmacodynamics above for a brief review of these findings.

Evaluability By Center/Investigator

According to Medical Officer Based on Available Lumbar BMD Data Provided as Electronic File

Center	Placebo Patch	6.5 cm^2 * Patch	12.5 cm^2 * Patch	15 cm^2 Patch	25 cm^2 * Patch	Total drug n	Total n
Time**	B,6,12,18,24 mths	B,6,12,18,24 mths	B,6,12,18,24 mths	B,6,12,18,24 mths	B,6,12,18,24 mths	B,6,12,18,24 mths	B,6,12,18,24 mths
301 Henry	7,6,4,4,4	3,3,3,3,3	4,4,4,4,4	4,2,2,2,2	4,4,4,4,4	15, 13,13,13,13	22
302 Hooper	3,2,2,2,2	2,2,2,2,2	3,3,3,3,2	3,3,3,3,3	3,3,3,3,2	11,11,11,11,9	14
304 Bath	3,2,2,1,1	2,2,1,1,2	1,1,1,1,1	2,0,0,1,0	2,2,2,1,1	7,5,4,4,4	10
305 Gordon	4,3,3,2,2	2,2,2,2,2	3,2,2,2,2	3,3,3,3,2	4,3,2,2,2	12,10,9,9,8	16
306 Smucker	2,2,0,0,0	2,2,1,0,0	1,1,0,0,0	1,1,1,0,0	2,1,1,1,1	6,5,3,1,1	8
307 Graham	3,2,2,2,1	3,2,1,1,1	3,3,3,3,3	3,2,2,2,2	2,1,1,1,1	11,8,7,7,7	14
308 Trop	5,2,1,1,1	3,2,2,2,2	2,1,1,1,0	3,3,3,3,3	3,2,2,2,2	11,8,8,8,7	16
309 Weiss	10,9,7,6,6	8,5,4,4,3	6,2,2,1,1	7,7,7,5,5	7,6,5,5,4	28,20,18,15,13	38
310 Soltes	4,3,3,0,0	3,3,2,1,1	3,3,3,3,3	3,1,1,1,1	3,2,2,2,2	12,9,8,7,7	16
311 Lenihan	5,3,2,2,2	3,2,1,0,0	4,4,2,1,1	2,2,2,2,2	4,3,2,2,2	13,11,7,5,5	18
Total	46,34,26,20,19 (41%)	31,25,19,16,16 (52%)	30,24,21,20,17 (57%)	31,24,24,22,20 (67%)	34,27,24,23,21 (62%)	126,106,103,80,74 (82%, 59%)	172
%completers @6mths	74%	81%	80%	80%	79%	84%	
%completers @12mths	56%	61%	70%	80%	71%	82%	
%completers @18mths	43%	52%	67%	73%	68%	63%	
%completers @24mths	41%	52%	57%	67%	62%	59%	

- *Three subjects (301013 (6.5 cm^2), 309006 (12.5 cm^2), 307014 (25 cm^2) had inadequate baseline lumbosacral spine BMD measurements and are excluded from th analysis. **Time refers to measurements of lumbar BMD at baseline, 6,12,18, and 24 months.

This review focuses on the Phase III randomized clinical trial . A summary of enrollment numbers for study drug and placebo for the RCT, by center, is listed in the Table "Evaluability by Center/Investigator" (page 9).

Reviewer's Comment: the sponsor uses a total n of 175; however, only 172 participants had reported baseline BMD of the lumbar spine measurement, the primary outcome measure. Apparently, a lack of communication between the central DEXA reading center and the sponsor occurred, such that the quality of these baseline scans was considered inadequate, but the information was not reported to the investigators and repeat scans were not performed. The subjects were continued in the study, and their data did not contribute to the ITT analysis, although the sponsor continued to count them.

8.2 Indication: Prevention of Postmenopausal Osteoporosis

8.2.1 Objective/Rationale

The primary objective of the RCT was to evaluate the efficacy of treatment utilizing four different doses of estradiol administered transdermally as compared to placebo, in the prevention of osteoporosis of the lumbar spine in postmenopausal, hysterectomized women. The primary efficacy parameter was the measurement of lumbar spine (AP view, L2-L4) bone mineral density by x-ray absorptiometry (DEXA). Both Lunar and Hologic equipment was used in the study, at different sites, and the results were read centrally. The sponsor reports that each patient was studied on the same equipment at baseline and subsequently.

The secondary objectives of the study included the following, as outlined by the sponsor:

(1) the effects of estradiol transdermal treatment on the bone of the midshaft of the nondominant radius and the ipsilateral proximal femoral neck;
(2) the effect of estradiol transdermal treatment on BMD of the ipsilateral total hip was added as an objective for the final analysis although it was not an objective at the start of the study;
(3) the effects of estradiol transdermal treatment on parameters of bone metabolism (serum osteocalcin, deoxypyridinoline/creatinine ratio, and pyridinoline/creatinine ratio);
(4) the safety of estradiol transdermal treatment;
(5) the population pharmacokinetics of estradiol transdermal treatment by a population screen approach.

8.2.2 Study Design

This single clinical trial was a randomized, double-blind, parallel group, placebo- controlled multicenter (10 sites). Each subject was attended by the investigator or a designated physician throughout the trial. Potential subjects had 1 – 3 screening visits before enrollment into the study. During this time, potential subjects were assessed regarding sensitivity to the transdermal estradiol delivery system, particularly if they had not used such a system previously. Women with sensitivity to the patch, described as greater than Grade 2 (i.e., moderate erythema: bright

pink or sunburned appearance), were excluded from participation. In addition, women were assessed for the presence of vasomotor symptoms in the setting of estrogen deprivation. Subjects with significant vasomotor symptoms, "too severe to be left untreated...in the opinions of the subject and investigator", were also excluded. The number of women screened was not given in the NDA. The question was addressed to the sponsor, who said that about twice as many women were screened as enrolled, though precise records were not kept.

The study was initially designed as multi-dose study, to determine the optimum dose of the 17 β-estradiol given by a transdermal delivery system, that would prevent postmenopausal osteoporosis, specifically defined as the minimum dose of estradiol transdermally which would prevent a decrease in the mean measured bone mineral density. The 6.5 cm^2 patch (0.025 mg/day dose) was selected as a no-effect dose. The lower marketed dose for vasomotor symptoms, the 12.5 cm^2 patch (0.05 mg/day dose) was expected to have approximately 60% probability of showing efficacy, based on published transdermal estradiol data. The 15 cm^2 patch (calculated to be 0.06 mg/day) was included, as an-inbetween dose to the highest marketed dose for osteoporosis, the 25 cm^2 patch (0.1 mg/day dose) which was assumed to be effective in the prevention of osteoporosis.

Subjects were randomized to the five groups by site and evaluated for up to 26 28-day cycles. See below, under population, procedures.

8.2.3 Protocol Overview

8.2.3.1 Population, procedures

The patient population in the RCT comprised 175 healthy, hysterectomized postmenopausal women ≤ 5 years postmenopausal without osteoporosis, as defined by a normal lumbar spine BMD ≥ 0.9 gm/cm^2 (Lunar scanner) and ≥ 0.805 g/cm^2 (Hologic scanner).

Inclusion criteria are listed below:

1) postmenopausal hysterectomized women ≥ 45 years old; oophorectomized women ≥ 40 years old were included;
2) natural menopause ≥ 1 - ≤ 5 years before study enrollment;
3) surgically induced menopause (bilateral oophorectomy) ≥ 4 weeks - ≤ 5 years pre-enrollment;
4) estradiol (E2) ≤ 20 pg/ml
5) FSH ≥ 50 u/l
6) BMD (lumbar spine) ≥ 0.9 gm/cm^2 (Lunar scanner) and ≥ 0.805 g/cm^2 (Hologic scanner). (Note: this specific distinction for the two different brands of x-ray absorptiometry equipment was cited only in the volume 1.20, the statistics summary, by the sponsor.)
6) Fasting total cholesterol≤ 300 mg/dl; fasting triglyceride≤ 300 mg/dl; fasting blood glucose≤ 140 mg/dl
7) Successful completion of a 2-4 week qualification period, during which tolerance of transdermal system and severity of symptoms related to estrogen deprivation was assessed. Subjects were given 4 placebo 12.5 cm^2 patches, which contained vehicle but no drug, and were asked to wear a placebo patch for one week, applying it to a site on the anterior trunk (anterior to the mid-sagittal line, above the inguinal ligaments and below the breasts). Note:

subjects with severe vasomotor symptoms were not enrolled, and subjects with skin irritation > Grade 2 (i.e., moderate erythema: bright pink or sunburned appearance) were also not enrolled.

Exclusion criteria excluded women with any of the following criteria (as listed by the sponsor):

1) Known or suspected bone disease (including osteoporosis); BMD below 0.9 gm/cm^2; hypo- or hypercalcemia; vitamin D deficiencies.
2) Fracture within 6 months prior to the start of the study.
3) Immobilization for $\geq$2 of the last 6 months prior to enrollment.
4) 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.
5) Severe systemic disease which might interfere with the conduct of the study or the interpretation of the results.
6) Abnormal baseline laboratory values that are considered clinically significant and which give suspicion of a specific organ dysfunction.
7) Hot flashes of a frequency or severity that necessitates hormone treatment.
8) History of skin irritation or allergy due to tape or other transdermal drug products; skin irritation > Grade 2 at last application during screening period.
9) Myocardial infarction within the last 6 months prior to screening or coronary heart disease severe enough to require treatment with anti-anginal drugs.
10) History of stroke or transient ischemic attacks.
11) Thrombophlebitis or thromboembolic disorders within the last 3 years that were unrelated to estrogen therapy or a history of these conditions at any time related to estrogen therapy.
12) Congestive heart failure of any degree or disturbances of cardiac rhythm requiring treatment with anti-arrhythmic drugs.
13) Uncontrolled hypertension; sitting systolic BP $\geq$ 160 mmHg or sitting diastolic BP $\geq$ 95 mm Hg.
14) Known or suspected premalignant or malignant disease or a history of these conditions.
15) History of kidney stones.
16) Insulin-dependent diabetes mellitus.
17) Uncontrolled thyroid disorders.
18) Increased frequency or severity of headaches, including migraine, during previous estrogen or oral contraceptive therapy.
19) Current or past history of clinically significant depression.
20) History of alcohol or drug abuse (within the last 2 years).
21) Treatment with anticoagulants (heparin or warfarin).
22) Systemic treatment with fluoride, calcitonin, or biphosphonates at any time.
23) Systemic treatment with corticosteroids on a chronic basis.
24) Estrogen replacement within 2 months prior to the start of the study or estrogen implants at any time.
25) Treatment with lipid-lowering drugs within the last two months.
26) Participation in another clinical trial or systemic administration of an investigational drug within the last 3 months.
27) Pendulous abdominal skin to an extent that makes patch placement difficult.

Comment: Based on the inclusion and exclusion criteria, the study population is a selected, healthier subset of the general population from which it is selected. Note – they are not osteoporotic, they are preselected to avoid application site reactions, and activity was carefully restricted during the study – no baths, swimming, or saunas while wearing the patch.

Subjects were assigned randomly to one of the five treatment groups. Because the 4 active dose levels were contained in visibly distinguishable patches, subjects were asked to wear 2 patches per week, according to a scheme which randomized each block of 11 subjects.

Randomization Scheme			
Subject	Patch A	Patch B	Treatment Assigned
1	6.5P	12.5P	Placebo
2	6.5A	12.5P	2.04 mg
3	6.5P	12.5A	3.9 mg
4	12.5P	15P	Placebo
5	12.5A	15P	3.9 mg
6	12.5P	15A	4.68 mg
7	15P	25P	Placebo
8	15A	25P	4.68 mg
9	15P	25A	7.8 mg
10	6.5P	25A	7.8 mg
11	6.5A	25P	2.04 mg
Abstracted from Appendix 16.1.1, page 13 of 54; Note 6.5, 12.5, 15, 25 refer to patch size in cm^2, and concomitant A refers to active drug vs. P for placebo			

This scheme resulted in each block of 11 subjects being assigned to the 2.04 mg, 3.9 mg, 4.68 mg, 7.8 mg and placebo groups in a ratio of 2:2:2:2:3, respectively. Randomization was done by site.

The subjects were evaluated for up to twenty-six, 28-day cycles. Transdermal systems were worn continuously for the duration of the study. A total of 11 patient visits were scheduled (screening, baseline, 4, 12, 24, 36, 52, 64, 76, 88, 104 weeks) Study evaluations were performed according to the protocol, as noted in the Study Flow Chart:

Study Flow Chart: Study Evaluations											
Visit	Screening	Baseline	1	2	3	4	5	6	7	8	9
Cycle			1	3	6	9	13	16	19	22	26
Week			4	12	24	36	52	64	76	88	104
Medical & Medication History	X										
Physical Exam (including Pelvic/Vaginal Pap Smear & Breast Exam)	X				X		X		X		X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X
Mammography	X										X
Bone Densitometry of Spine (AP view L2-L4), Femoral		X			X		X		X		X

Neck, Mid-shaft of Radius (DEXA)											
X-ray of Spine	X										
Lab. Studies, Lipid Profile	X				X		X		X		X
FSH, TSH, estradiol levels	X										
E2,E1,total E1, SHBG		X	X		X		X				
Serum osteocalcin. Urinary pyridinoline	X				X		X		X		X
Record Concomitant Medications		X	X	X	X	X	X	X	X	X	X
Adverse Events/Fractures			X	X	X	X	X	X	X	X	X
Medication Dispensed/Returned		X	X	X	X	X	X	X	X	X	X
Table abstracted from Study Flow Chart 13, page 45 of 54, appendix 16.1.1											

Comments: 1)Height and FSH were measured only once, at baseline.
2) Since the patch protocol consisted of two envelopes with the two different assigned patches to be worn each week, it is possible that the subjects would be confused and/or choose to wear only one patch, making compliance more difficcult. The sponsor, however, noted at least 75% compliance with all subjects, based on reports of which patches were worn and/or return of the patches.

At each visit, patches were distributed for the time period until the next visit. Subjects were instructed to return the used pouches and all unused medication at subsequent visits to assess compliance. Of note, women were instructed not to swim, bathe, or use a sauna while wearing the patch and not to expose the patches to sunlight. Patches were to be worn continuously, and an extra patch was provided in each packet in case a patch became dislodged.

Dietary calcium intake was assessed by a dietician at baseline, 12, and 24 months and was supplemented, if necessary, for a goal total of 1500 mg calcium per day. If necessary, the sponsor provided calcium carbonate 500 mg tablets containing 200 mg elemental calcium.

8.2.3.2 **Evaluability criteria and Defined clinical endpoints**

Specific criteria for evaluation of efficacy and safety are described by the sponsor below:

Efficacy:
1) Percent change in BMD of the lumbar spine measured by dual-energy x-ray absorptiometry (DEXA);
2) Percent change in BMD of the femoral neck measured by dual-energy x-ray absorptiometry (DEXA);
3) Percent change in BMD of the radius measured by dual-energy x-ray absorptiometry (DEXA);
4) Percent change in BMD of the total hip measured by dual-energy x-ray absorptiometry (DEXA);
5) Percent change in serum osteocalcin
6) Percent change in pyridinoline/creatinine and deoxypyridinoline/creatinine ratios.

Safety: Frequency and severity of adverse events, as assessed from physical, breast and pelvic examinations, vaginal Pap smears, vital signs, laboratory tests, x-ray of spine results, mammography, fractures, and adverse experiences.
Pharmacokinetics: Long term accumulation of estradiol and its primary metabolites.

8.2.3.3 Statistical Considerations

Assumptions in determining the sample size calculation, which resulted in an n=176, included the following:

1) Historical data on estrogen replacement therapy, indicating a monotone increasing dose-response curve over a certain domain of doses.
2) Multiple comparisons of each active dose group vs. placebo, with an alpha level of significance for each comparison of 0.0125.
3) An anticipated difference of $\geq$ 4% in BMD of lumbar spine between placebo and effective dose at 24 months of therapy, based on Ceiba-Geigy Estraderm patch study data.
4) Dropout rate of 40% for placebo and and 30% for the combined active dose groups.
5) An interim analysis was to be done when 50% (60%*) of targeted sample sizes completed 18 months of therapy, with an anticipated 0.60 (0.75*) power to detect the difference. Note original (*) goals vs. amended goals two years into the study (5/23/96). The alpha "spent" was thus changed from 0.0035 to 0.0022.

The original protocol described four sets of analyses:

(1) intent-to-treat analysis, including all subjects randomized to study and known to have taken at least one dose of drug; Note, however, the initial ITT analyses provided by the sponsor in the NDA only included subjects who had completed the 6 month visit. At FDA request, the sponsor provided analyses for all subjects for whom there was baseline data, imputing '0' or the placebo change at the missing value points for the treated subjects, for the primary efficacy variable lumbosacral spine BMD and the secondary efficacy variable, the total hip.
(2) Evaluable subjects analysis: all randomized subjects who took no prohibited medications, had a compliance of 75% or higher with the patch protocol, completed $\geq$ 13 cycles (i.e., one year), and had no major violations of exclusion/inclusion criteria.
(3) Endpoint analyses, based on subject's final visit, for all subjects.
(4) Endpoint analyses, based on subject's final visit, for completers only.

Comment: Based on "E9 Statisitical Principles for Clinical Trials" (Federal Register, Vol. 63, No. 179, 49583-98, 9/16/98), the major analysis on which the statistical team and the medical reviewer at FDA have based their conclusions has been the intent-to-treat analysis, of all randomized subjects, with data imputed for missing observations at 6 months or subsequently.

The sponsor used the following statistical methods: ANOVA/Rank ANOVA, Cochran-Mantel-Haenszel test, trend analysis.

8.2.3.4 Study Results

8.2.3.4.1 Demographics, Evaluability

The demographic characteristics of the studied population are outlined in the table below:

Demographic Characteristics							
Treatment	P	6.5	12.5	15	25	Total	Overall p-value
N	46	32	31	31	35	175	
Age (yrs)	51.5	51.9	50.9	50.3	51.3	51.2	0.6739
Range	40-60	44-59	42-62	42-60	40-71	40-71	
SD	4.3	3.9	5.4	4.9	5.8	4.9	
Race (#(%) of subjects)							
Caucasian	38 (83%)	26 (81%)	24 (77%)	26 (84%)	32 (91%)	146 (83%)	0.1993
Black	3 (7%)	5 (16 %)	2 (6%)	0	2 (6%)	12 (7%)	
Hispanic	2 (4%)	0	3 (10%)	4 (13%)	0	9 (5%)	
Others	3 (7%)	1 (3%)	2 (6%)	1 (3%)	1 (3%)	8 (5%)	
Abstracted from Berlex Text Table 11 (p.47 of 582).							

Comment: Thus the population was predominantly Caucasian, as is seen with many postmenopausal osteoporosis studies, with a mean age of 51. Based on the range of age in the 25 cm^2 active dose, it is possible that some subjects may have been more than five years postmenopausal.

The evaluable subjects for an intent-to-treat analysis for the primary efficacy variable, lumbosacral bone mineral density, are shown in Table 1, (see above, page 9.)

8.2.3.4.2 **Clinical Efficacy**

Sponsor's prespective:

The sponsor concludes that efficacy in the prevention of postmenopausal bone loss was demonstrated for all four active doses of transdermal estradiol. "Results of the primary efficacy analysis (percent change in BMD at the lumbar spine in the intent-to-treat (ITT) population) showed a statistically significant overall treatment effect at each timepoint. Mean percent change in BMD was positive (bone preservation) for all active treatment groups at all timepoints while it was negative (bone loss) for placebo at all timepoints. Furthermore, mean percent change in BMD at the lumbar spine was statistically different from placebo for all active treatment groups at all timepopints. The differences of the means at 24 months ranged from 4.86% between 6.5 cm^2 and placebo to 7.19% between 25 cm^2 and placebo.

Analysis of the individual changes in lumbar spine BMD showed that the majority of subjects receiving each active treatment dose had a response to treatment (defined as percent

change in BMD ≥ 0) at each postbaseline timepoint while the majority of placebo subjects had a decrease in BMD at each timepoint.

The findings of efficacy were supported by analyses of the results of the secondary efficacy endpoints. Most importantly, the percent change in BMD of the total hip in the ITT population showed a statistically significant overall treatment effect at each timepoint. Mean percent change in BMD was positive (bone preservation) for all active treatment groups at all timepoints while it was negative (bone loss) for placebo at all timepoints. Furthermore, mean percent change in BMD of the total hip was statistically significantly different from placebo for all active treatment groups at all timepoints. The differences of the means at 24 months ranged from 2.3% between 6.5 cm^2 and placebo to 5.09% between 15 cm^2 and placebo. The results of measurements of BMD of the femoral neck and radius were generally indicative of a treatment effect relative to placebo, although there were no statistically significant differences between the results for any treatment group and placebo. There was no evidence of loss of cortical bone."

Reviewer's Comments:

Primary Efficacy Analysis – Change in Lumbosacral BMD

The primary outcome variable in this study was the change in BMD of the lumbosacral spine as measured by x-ray absorptiometry or DEXA scan. As previously noted, the sponsor's Intent-to-Treat analysis included only subjects who had data at the 6 months visit. Since this analysis omitted about 25% of the randomized population (12/46 in the placebo group and 30/129 in the drug treatment groups), the FDA statistical reviewers asked the sponsor to perform two confirmatory analyses. The following data was imputed in the subjects who had missing data for an ITT, LOCF analysis:

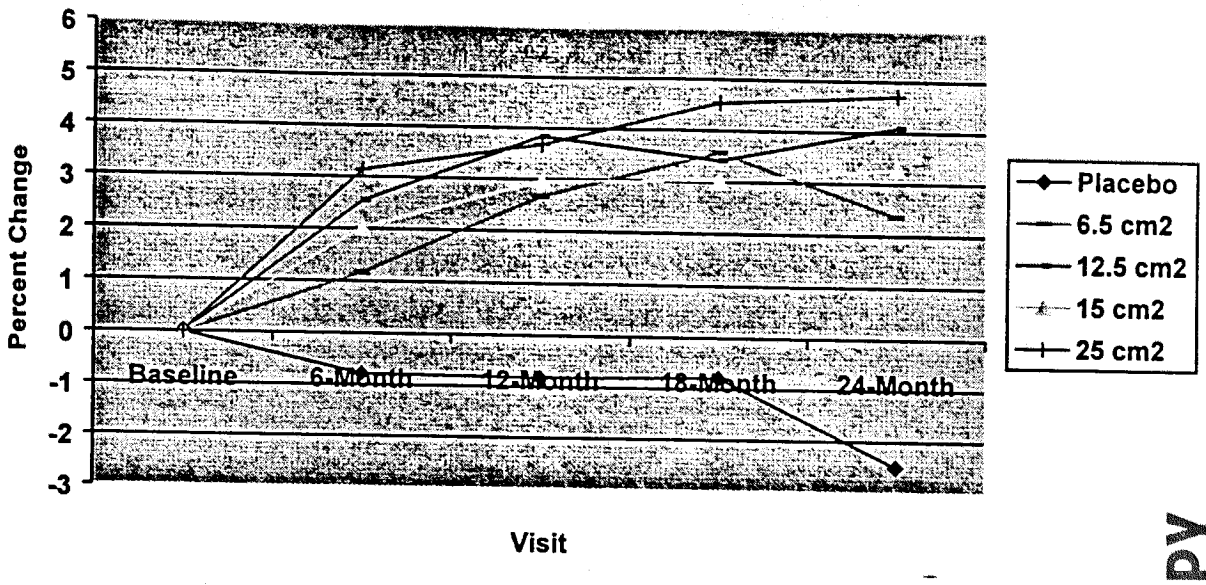
Confirmatory analysis #1: a change of zero was imputed at 6 months and at subsequent timepoints (12, 18, 24 months) for those with missing data.
Confirmatory analysis #2: The analogous placebo change was imputed for those with missing data.

These analyses were then reviewed at the FDA by the statistical reviewer Z. J. Ma, PhD.

The following graph and three tables are excerpted from Dr. Ma's review:

Note: Unlike in the sponsor's summary, where changes in the active drug groups are expressed adjusted for placebo change, in the data below the values for the changes in the placebo and active drug groups are listed separately.

Figure 1. Sponsor's Primary Efficacy Analyses



Sponsor's Primary Efficacy Analyses Mean Percent Change From Baseline in BMD (g/ cm^2) of Spine A-P View (L2-L4) by Treatment and Visit						
Treatment Group		6 months	12 months	18 months	24 months	Endpoint
Placebo	N/Mean	34/-0.78	26/-0.82	22/-0.78	21/-2.49	34/-2.33
6.5 cm^2	N/Mean	25/1.16	20/2.67	17/3.57	16/2.37	25/2.32
	p-Value	0.009	0.003	0.0009	0.0008	<0.0001
12.5 cm^2	N/Mean	23/2.54	21/3.84	18/3.41	18/4.09	23/3.74
	p-Value	<0.0001	<0.0001	0.0001	<0.0001	<0.0001
15 cm^2	N/Mean	24/2.02	24/2.97	22/3.02	20/3.28	25/3.45
	p-Value	0.0003	0.001	0.002	<0.0001	<0.0001
25 cm^2	N/Mean	27/3.14	24/3.68	23/4.53	21/4.70	27/5.20
	p-Value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Source: TT14, Vol. 20						

Revised ITT1 Analyses, Primary Efficacy Endpoint (0 change imputed) Mean Percent Change From Baseline in BMD (g/ cm^2) of Spine A-P View (L2-L4) by Treatment and Visit					
Treatment Group		6 months	12 months	18 months	24 months
Placebo	N/Mean	46/-0.58	46/-0.89	46/-0.98	46/-1.72
6.5 cm^2	N/Mean	32/0.91	32/1.98	32/2.33	32/1.81
	p-Value	0.020	0.0005	0.0002	<0.0001
12.5 cm^2	N/Mean	31/1.88	31/2.79	31/2.64	31/2.77
	p-Value	<0.0001	<0.0001	<0.0001	<0.0001
15 cm^2	N/Mean	31/1.64	31/2.46	31/2.49	31/2.78
	p-Value	0.0003	<0.0001	<0.0001	<0.0001
25 cm^2	N/Mean	35/2.42	35/3.04	35/3.56	35/4.01
	p-Value	<0.0001	<0.0001	<0.0001	<0.0001

Revised ITT2 Analysis, Primary Efficacy Endpoint (Placebo Change Imputed)					
Mean Percent Change From Baseline in BMD (g/ cm^2) of Spine A-P View (L2-L4) by Treatment and Visit					
Treatment Group		6 months	12 months	18 months	24 months
Placebo	N/Mean	46/-0.78	46/-1.12	46/-1.18	46/-2.85
6.5 cm^2	N/Mean	32/0.73	32/1.79	32/2.16	32/0.78
	p-Value	0.02	<0.0001	0.0002	0.0002
12.5 cm^2	N/Mean	31/1.68	31/2.58	31/2.54	31/1.78
	p-Value	<0.0001	<0.0001	0.0001	<0.0001
15 cm^2	N/Mean	31/1.49	31/2.30	31/2.34	31/2.01
	p-Value	0.0004	0.0006	<0.0001	<0.0001
25 cm^2	N/Mean	35/2.25	35/2.85	35/3.39	35/3.13
	p-Value	<0.0001	<0.0001	<0.0001	<0.0001

The statisticians and the medical officer concurred that these confirmatory analyses did confirm the sponsor's conclusion. Although the study was not designed to compare the different doses of estradiol, the data suggest an increased effect with the higher doses, as confirmed by the statistician's specific analyses.

Responder Analyses

However, since there was only one study submitted for this indication of postmenopausal osteoporosis, with a relatively small n, a large number of dropouts (total 78: 53 from the drug treatment groups and 25 from the placebo group), and a relatively modest effect, particularly for the 6.5 cm^2 patch, the medical officer looked at a responder analysis to further assess the significance of the sponsor's findings. The primary assumption in this analysis was the sponsor's assumption in the design of the clinical trial: i.e., that the treatment effect (difference between drug and placebo) would be $\geq$ 4% for the primary efficacy variable. Table "Responder Analysis" (page 20) outlines this analysis. Since the placebo change was –2.3% in the sponsor's analysis, "response" was defined as a change in lumbosacral BMD $\geq$ 1.7%. The analysis was done for subjects completing the 24 months also for all subjects who had data or subsequently (LOCF or endpoint) to increase the evaluable n. In this analysis, 11% in the placebo group were responders, and 42%, 50%, 54%, 67% of the 6.5, 12.5, 15, 25 cm^2 treatment groups, respectively, were responders. Of note, the likelihood of staying in the study, the continuation rate, did not differ among the drug treatment groups (81, 80, 80, 79 % for 6.5, 12.5, 15, 25 cm^2, respectively; 74% for the placebo group). There was an increase in the apparent effectiveness of the drug with increasing dose (52, 62, 67, 85% for 6.5, 12.5, 15, 25 cm^2, respectively; 15% for the placebo group), as also suggested by the sponsor's ITT analysis and as expected from prior dose-response studies in estrogen therapy.