CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020994, 020375/S011

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review

NDA:	**20-994**
Generic	**Estradiol Transdermal System**
(Brand®)	**Climara®**
Sponsor:	**Berlex Laboratories, Inc.** **Montville, NJ**
Submission Date:	**May 1, 1998**
Type of Submission:	**sNDA – New Indication; New Strength**
Reviewer:	**Ronald Evan Kavanagh, B.S. Pharm., Pharm.D., Ph.D.**

Synopsis

The present NDA is submitted in support of the proposed indication: 'Prevention of Osteoporosis (loss of bone mass)....' and requests approval of a new smaller patch size of 6.5 cm^2.

Berlex has studied the new 6.5 cm^2 containing 2.0 mg of estradiol in a single dose relative bioavailability trial with the 12.5 cm^2 patch, and has found them to dose proportional based upon dose adjusted relative bioavailability.

Some minor issues include:

1. The complete original assay validation report was neither provided nor referenced for the pivotal relative bioavailability study. However, prestudy assay revalidation was provided,
2. Errors in calculation of $AUC_{(0\text{-last})}$; although detected errors were minor and should not effect the conclusions.

In addition a pharmacokinetics sub-study within the phase III clinical efficacy trial for osteoporosis, suggests that accumulation is not an issue on long term multiple dosing.

The only change in the formulation is the decrease in surface area of the patch.

The proposed dissolution method is similar to the previously approved method. The only change is that the volume of media is decreased to achieve an estradiol concentration similar to that achieved with the 25 cm^2 patch. The 6.5 cm^2 patch meets all current specifications.

Recommended labeling changes include descriptions of patch application, calcium supplementation, and correction of typographical errors.

The Office of Clinical Pharmacology and Biopharmaceutics finds that Climara® 6.5 cm^2 Transdermal Patch is dose proportional to Climara® 12.5 cm^2 Transdermal Patch.

Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics recommends that Climara® 6.5 cm^2 Transdermal Patch is approvable.

Please convey recommendations and labeling comments to sponsor as appropriate.

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Appendix of Study Summaries

Protocol Number	Title of Study
97075	Study Comparing the Relative Bioavailability of 17β-Estradiol and Free Estrone Following Application of a 6.5 cm^2 Estradiol Transdermal System, Containing 2.0 mg 17β-Estradiol, with 17β-Estradiol and Free Estrone Following Application of a 12.5 cm^2 Climara® (Estradiol Transdermal Delivery System) Patch Containing 3.9 mg 17β-Estradiol.
308-03 A&B	A multicenter, double-blind, randomized, placebo-controlled study to evaluate the safety and efficacy of four doses of estradiol given by continuous transdermal administration in the prevention of osteoporosis (decrease in bone mineral density) in postmenopausal, hysterectomized women.

APPEARS THIS WAY
ON ORIGINAL

Background

Climara® is Berlex's brand of estradiol transdermal patches.

Currently Approved Indications

1. Treatment of moderate to severe vasomotor symptoms associated with the menopause. There is no adequate evidence that estrogens are effective for nervous symptoms or depression which might occur during menopause and they should not be used to treat these conditions.
2. Treatment of vulval and vaginal atrophy.
3. Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure.
4. Treatment of abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology and only when associated with a hypoplastic or atrophic endometrium.

Proposed New Indication

'Prevention of Osteoporosis (loss of bone mass). The mainstays of prevention and management of osteoporosis are estrogen, an adequate lifetime calcium intake, and exercise. Estrogen replacement therapy is the most effective single modality for the prevention of postmenopausal osteoporosis in women. Estrogen replacement therapy reduces bone resorption and retards or halts postmenopausal bone loss. Case-controlled studies have shown an approximately 60% reduction in hip and wrist fractures in women whose estrogen replacement was begun within a few years of menopause. Studies also suggest that estrogen reduces the rate of vertebral fractures. Even when started as late as 6 years after menopause, estrogen prevents further loss of bone mass for as long as treatment is continued. When estrogen therapy is discontinued, bone mass declines at a rate comparable to the immediate postmenopausal period.'

Currently only Estraderm® estradiol transdermal system (Novartis) is approved for osteoporosis, and the proposed indication is copied verbatim from the Estraderm® labeling.

Currently Approved Formulations

USP NDC Number	Surface Area (cm^2)	Estradiol Content (mg)	Delivery Rate (mg/day)
NDC 50419-451-04	12.5	3.9	0.05
NDC 50419-453-04	18.75	5.85	0.075
NDC 50419-452-04	25	7.8	0.1

Proposed New Formulation

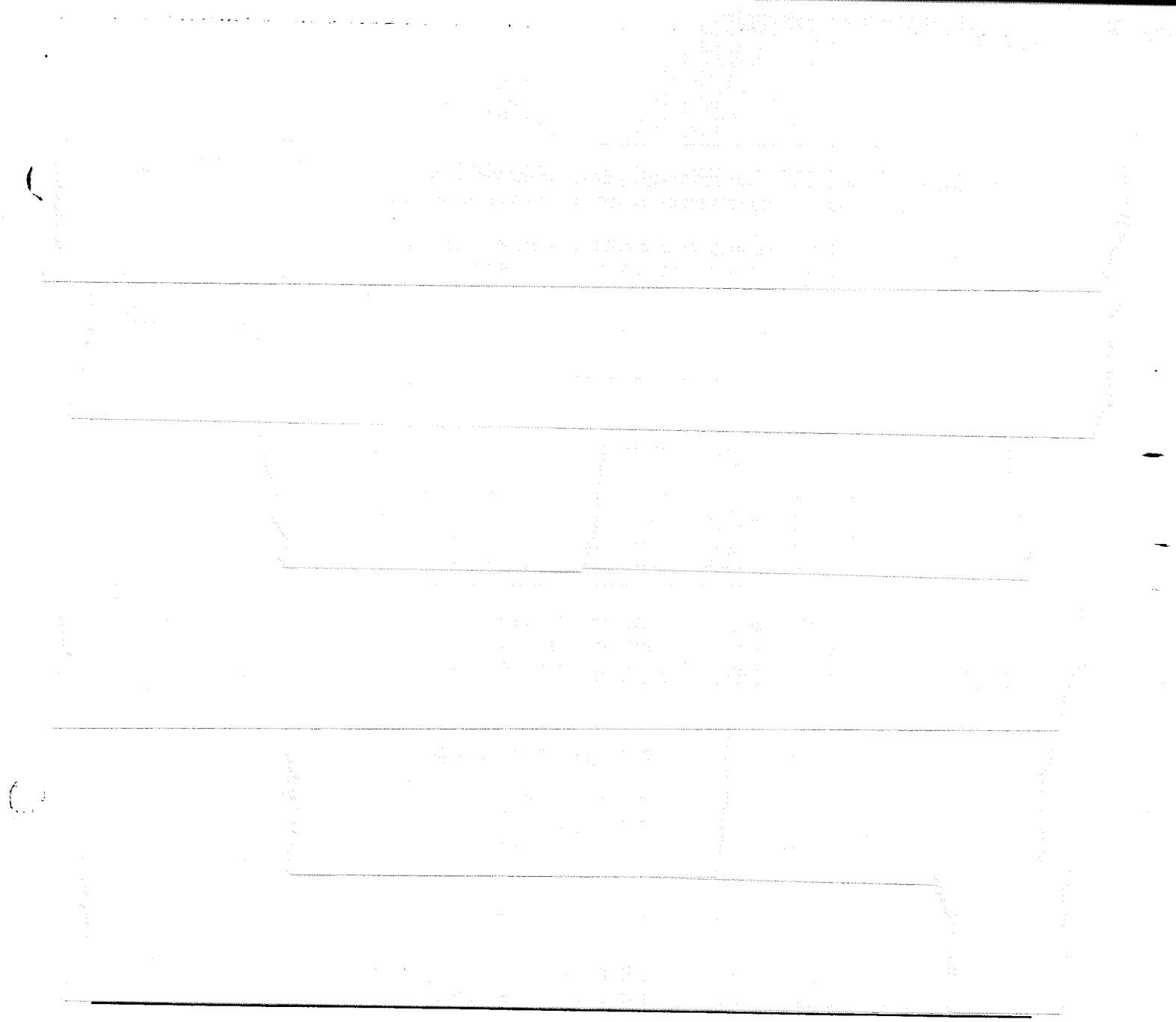
Berlex proposes a new 6.5 cm^2 formulation containing 2.0 mg of estradiol with a nominal delivery rate of 0.026 mg/day.

The relative bioavailability of his formulation was compared to the 12.5 cm^2 patch in a single dose study, and efficacy was studied in a phase III clinical efficacy trial for osteoporosis. The phase III efficacy trial also included a pharmacokinetics sub-study to evaluate accumulation on multiple dosing.

Assay Method and Validation

For the pivotal relative bioavailability study unconjugated 17β-estradiol, unconjugated estrone, and total estrone were also measured, however since unconjugated 17β-estradiol is the major determinant of relative bioavailability and the most potent active agent, only it will be discussed in this section. This assay was performed

Determination of Unconjugated Estradiol in plasma



Comments: Original assay validation data was not provided.

Calculations in sample preparation calculations show small consistent mistakes resulting in consistent bias.

In conclusion, Although there are a number of minor deficiency's with the assay and the assay validation, they do not rise to a level that would make the study results suspect.

Relative Bioavailability

The 6.5 and 12.5 cm^2 patches are bioequivalent with respect to unconjugated 17β-estradiol.

17β-estradiol is the primary compound of interest. Although other active metabolites, such as estrone, were measured, the primary determinant of relative bioavailability rests with the active parent compound, 17β-estradiol.

For 17β-estradiol when raw data is baseline corrected, log transformed (LN), and dose adjusted, the least squares means ratio and the two one-sided 90% confidence interval indicate that the 6.5 and 12.5 cm^2 patches are bioequivalent. (See Table)

2 pages

TRADE Secret

Pharmacokinetics

Accumulation:

In a pharmacokinetic sub-study of the Phase III efficacy trial, sparse samples were taken over a period of one year to assess accumulation and to perform exploratory data analysis. Unfortunately samples were obtained primarily on the day the patch was changed rather than evenly throughout the dosage interval. Consequently, the conclusions are not as strong as they might have been.

In summary, there was no difference in concentrations over time (i.e. over 1 year) for any dose level. Consequently there is no evidence for accumulation or induction.

Population Pharmacokinetics - Subpopulations

The sponsor did not report on any data exploration or if there was any relationship between demographic variables and pharmacokinetics are per the study plan as outlined in the protocol. It appears that there may have been too few samples drawn to adequately address this.

Population Pharmacokinetics – Dose Proportionality

When dose normalized concentrations are compared, there is no difference between the 6.5 and the 12.5 cm^2 patches, however the dose normalized concentrations for the 25 cm^2 patch are consistently lower than for either of the lower strength patches.

I agree with sponsor's conclusions that dose proportionality conclusions should be based on the more rigorous relative bioavailability studies.

Dosage and Administration

Patches are applied weekly. Instructions for applying patches in the clinical studies were extensive and explicit. These instructions are not reflected in the labeling, consequently the labeling will need to be changed.

Since calcium supplements were prescribed as appropriate, labeling may need to include use of calcium supplements. However per discussions with the medical reviewer the calcium intake may not have been sufficient to effect efficacy.

Formulation

The Climara transdermal system is a drug in adhesive system. The drug in adhesive along with other excipients are coated onto a liner and then backing. The is cut to different surface area to provide different strengths.

The Climara system comprises three layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are:
(1) a film
(2) an adhesive matrix containing estradiol USP.
(3) A protective liner of film that is attached to the adhesive surface and must be removed before the system can be used.

Table A provides the quantitative composition of Climara (Formulation Designation: U-4a).

TABLE A ESTRADIOL TRANSDERMAL DELIVERY SYSTEM FORMULATION
Qualitative Quantitative Composition

COMPONENTS	FUNCTION	% (w/w)	Amount (mg/cm^2)
Estradiol USP			

***In Vitro* Dissolution**

Approved Dissolution Method for 12.5, 18.75 and 25.0 cm^2

Specifications:

Dissolution methods and specifications for the 6.5 cm^2 are similar to previously approved methods and specifications for the 12.5 and 25 cm^2 patches (DMF).

The difference in the methodology is that the of the dissolution media is from ml to ml. This is a near relative to patch size and is acceptable; i.e. cm^2 is to ml as cm^2 is to ml.

6.5 cm^2 patches meet dissolution specifications. Dissolution methods and specifications are acceptable.

Comments to firm None

Labeling Comments

Most of the labeling has been previously approved and many of the changes are additions taken verbatim from the draft noncontraceptive estrogen labeling guidance.

Clinical Pharmacology Section
(Taken from draft noncontraceptive estrogen labeling guidance)

Paragraph 2 Line 4 – _____ should be _____

Paragraph 3 Line 1 – _____ should be _____

Figure 3 Title states _____ This should be _____

Figure 3 units on the X axis should be _____

Special Populations Recommend changing wording from:

_____

To:

_____

As currently worded it could be misconstrued that the issue was studied and no differences were found.

The clinical studies went to great lengths specifying the procedures regarding patch application and bathing. The major aspects of these procedures should be specified in the labeling.

In the phase III study, calcium supplements were prescribed to achieve daily calcium intake of approximately 1500 mg, and with the need for supplementation reassessed after 1 year. This should be added to the labeling.

Patient package labeling was not included for review. This will still need to be reviewed before approval.

Signatures

/S/

Ronald Evan Kavanagh, B.S. Pharm., Pharm.D., Ph.D.
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

Date: Feb 12, 1999

RD initialed by:
Hae-Young Ahn, Ph.D., Team Leader /S/

Date: 2/16/99

Clinical Pharmacology and Biopharmaceutics Briefing; February 12, 1999:
(MChen, JHunt, Zawadzki, Selen, Ahn, Kavanagh)

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17 pages

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LABELING