CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 20375/S13

APPROVAL LETTER

NDA 20-375/S-013

MAY 2 0 1999

Berlex Laboratories, Inc.
Attention: Mr. Geoffrey Millington
Manager, Drug Regulatory Affairs
340 Changebridge Road
P. O. Box 1000
Montville, NJ 07045-1000

Dear Mr. Millington:

Please refer to your supplemental new drug application dated January 19, 1999, received January 22, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Climara®, (estradiol transdermal system) 0.025, 0.05, 0.075 and 0.1 mg/day.

We acknowledge receipt of your amendment dated May 5, 1999.

This supplemental new drug application provides for revising the current labeling and associated analytical methods and specifications to reflect clarification of the use of estradiol as the anhydrous form.

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted draft labeling (package insert and immediate container and carton labels submitted May 5, 1999). Accordingly, the supplemental application is approved effective on the date of this letter.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-375/S-013/S-013." Approval of this submission by FDA is not required before the labeling is used.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Ms. Diane Moore, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

/S/ 5/20/99

Lisa D. Rarick, M.D.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Archival NDA 20-375
HFD-580/Div. Files
HFD-580/D.Moore
HFD-580/LRarick/MMann/PPrice/Amitra/MRhee
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-102/ADRA (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-95/DDMS (with labeling)
HFD-820/DNDC Division Director
DISTRICT OFFICE

Drafted by: dm/April 30, 1999

Concurrence:
TRumble 05.11.99/AMitra, MRhee 05.17.99/SSlaughter, MMann LRarick 05.20.99

filename: N20375APS13.doc

APPROVAL (AP) 5/20/99

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20375/S13

FINAL PRINTED LABELING

Rx Only

PRESCRIBING INFORMATION **Climara® estradiol transdermal system**

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA IN POSTMENOPAUSAL WOMEN. Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is currently no evidence that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equi-estrogenic doses.

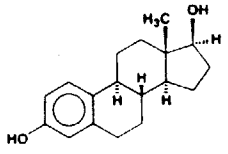
2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY
Estrogen therapy during pregnancy is associated with an increased risk of congenital defects in the reproductive organs of the fetus, and possibly other birth defects. Studies of women who received diethylstilbestrol (DES) during pregnancy have shown that female offspring have an increased risk of vaginal adenosis, squamous cell dysplasia of the uterine cervix, and clear cell vaginal cancer later in life; male offspring have an increased risk of urogenital abnormalities and possibly testicular cancer later in life. The 1985 DES Task Force concluded that use of DES during pregnancy is associated with a subsequent increased risk of breast cancer in the mothers, although a causal relationship remains unproven and the observed level of excess risk is similar to that for a number of other breast cancer risk factors.

There is no indication for estrogen therapy during pregnancy or during the immediate postpartum period. Estrogens are ineffective for the prevention or treatment of threatened or habitual abortion. Estrogens are not indicated for the prevention of postpartum breast engorgement.

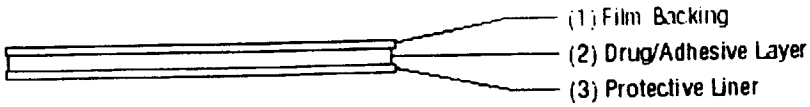
DESCRIPTION

Climara®, estradiol transdermal system, is designed to release 17β-estradiol continuously upon application to intact skin. Four (6.5, 12.5, 18.75 and 25.0 cm^2) systems are available to provide nominal *in vivo* delivery of 0.025, 0.05, 0.075 or 0.1 mg respectively of estradiol per day. The period of use is 7 days. Each system has a contact surface area of either 6.5, 12.5, 18.75 or 25.0 cm^2, and contains ~~2.04, 3.9, 5.85 or 7.8~~ 2.0, 3.8, 5.7, or 7.6 mg of estradiol USP respectively. The composition of the systems per unit area is identical.

Estradiol USP (17β-estradiol) is a white, crystalline powder, chemically described as estra-1,3,5(10)-triene-3,17β-diol. It has an empirical formula of $C_{18}H_{24}O_2$ and molecular weight of 272.37. The structural formula is:



The Climara® system comprises two layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are (1) a translucent polyethylene film, and (2) an acrylate adhesive matrix containing estradiol USP. A protective liner (3) of siliconized or fluoropolymer-coated polyester film is attached to the adhesive surface and must be removed before the system can be used.



The active component of the system is 17β-estradiol. The remaining components of the system (acrylate copolymer adhesive, fatty acid esters, and polyethylene backing) are pharmacologically inactive.

CLINICAL PHARMACOLOGY

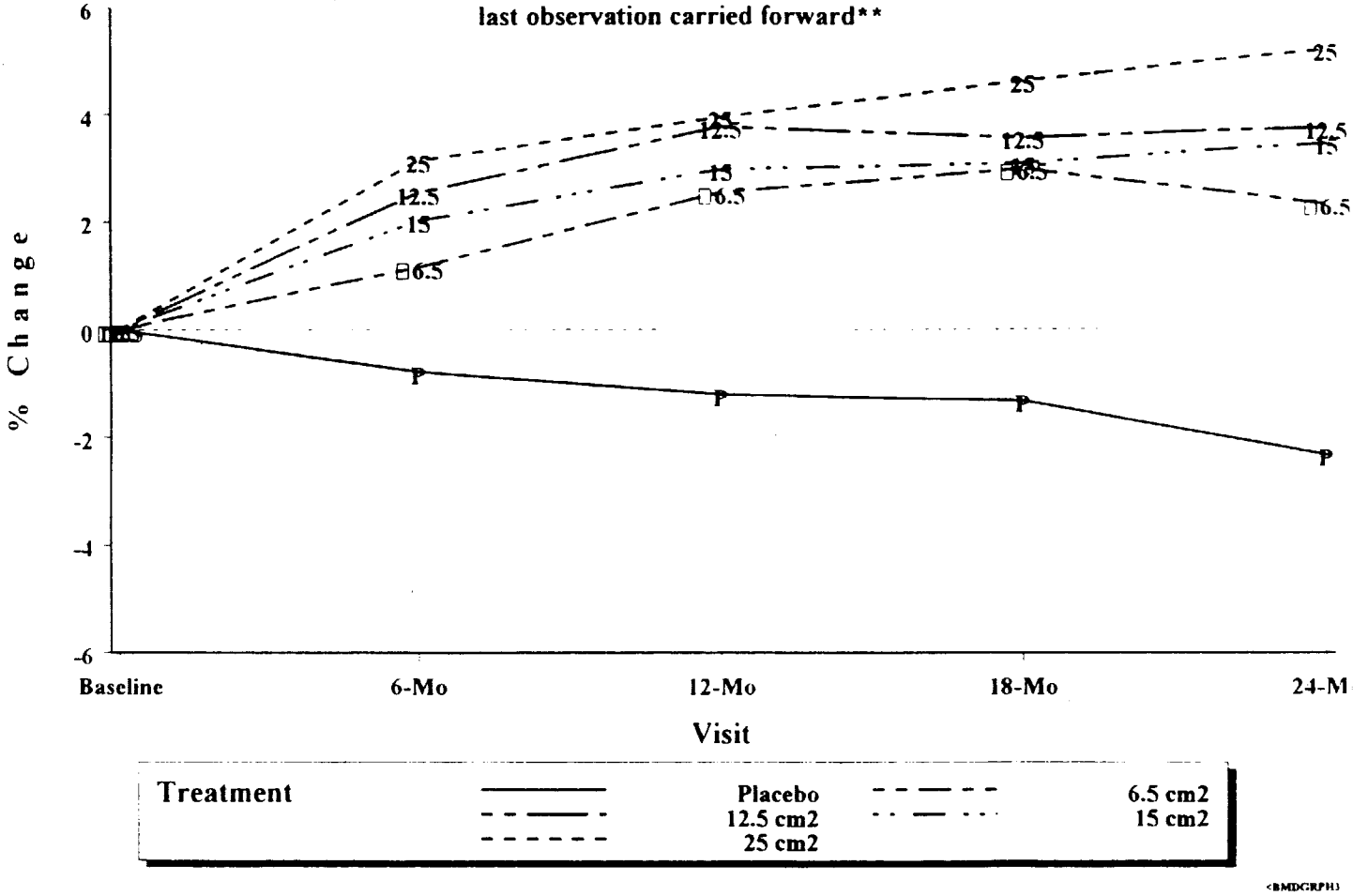
The Climara® system provides systemic estrogen replacement therapy by releasing 17β-estradiol, the major estrogenic hormone secreted by the human ovary.

Estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estriol at the receptor level. The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 μg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone and the sulfate conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.

Circulating estrogens modulate the pituitary secretion of the gonadotropins. luteininizing hormone (LH) and follicle stimulating hormone (FSH) through negative feedback mechanism and estrogen replacement therapy acts to reduce the elevated levels of these hormones seen in postmenopausal women.

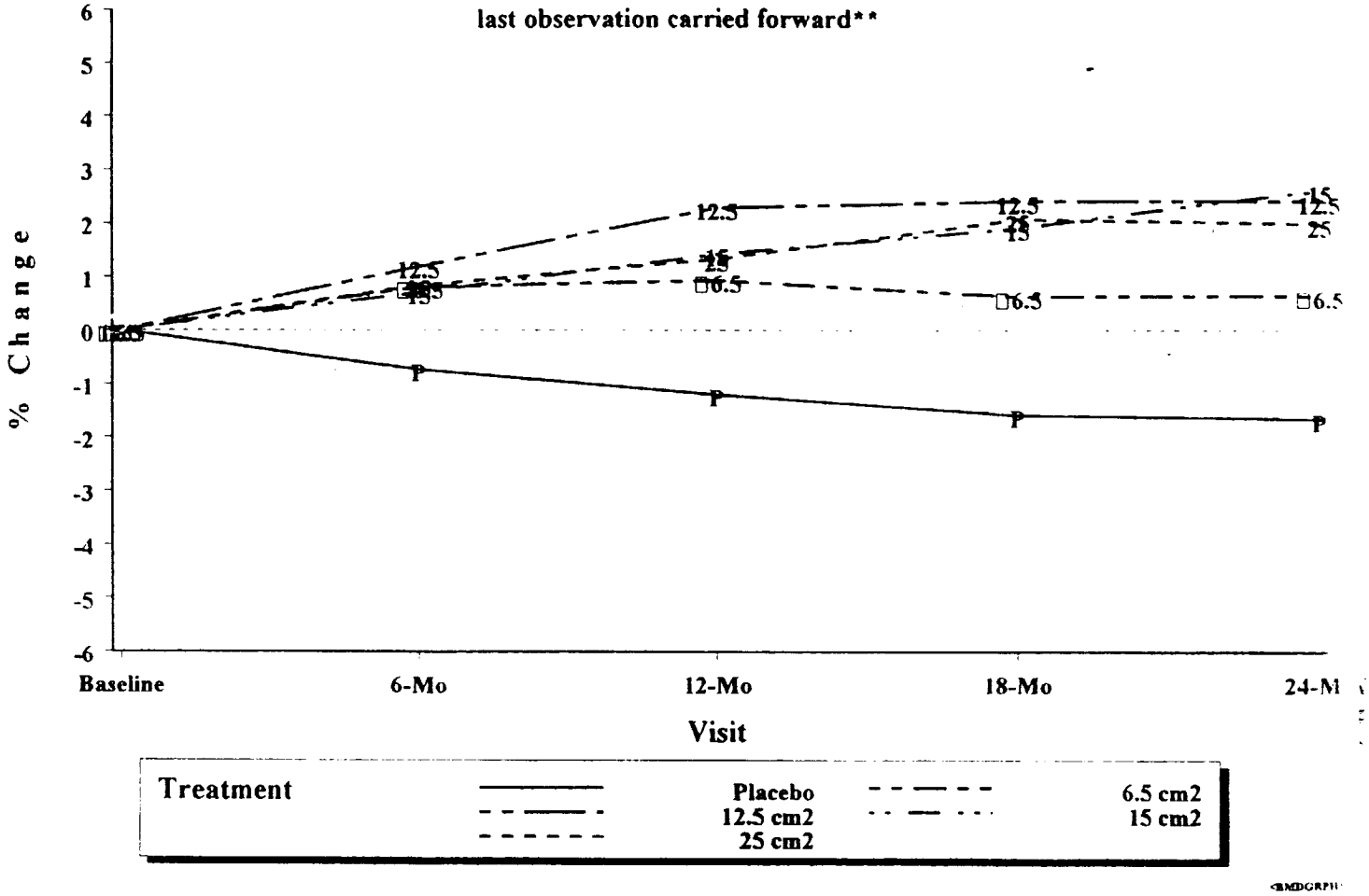
A two-year clinical trial enrolled a total of 175 healthy, hysterectomized, postmenopausal, non-osteoporotic (i.e., lumbar spine bone mineral denstiy > 0.9 gm/cm^2) women at 10 study centers in the United States[8]. 129 subjects were allocated to receive active treatment with 4 different doses of 17 β-estradiol patches (6.5, 12.5, 15, 25 cm^2) and 46 subjects were allocated to receive placebo patches. 77% of the randomized subjects (100 on active drug and 34 on placebo) contributed data to the analysis of percent change of A-P spine bone mineral density (BMD), the primary efficacy variable (see Figure 1). A statistically significant overall treatment effect at each timepoint was noted, implying bone preservation for all active treatment groups at all timepoints, as opposed to bone loss for placebo at all timepoints.

Figure 1. Mean Percent Change from Baseline in Lumbar Spine (A-P View) Bone Mineral Density By Treatment and Time last observation carried forward**



Percent change in BMD of the total hip (see Figure 2), was also statistically significantly different from placebo for all active treatment groups. The results of the measurements of biochemical markers supported the finding of efficacy for all doses of transdermal estradiol. Serum osteocalcin levels decreased, indicative of a decrease in bone formation, at all timepoints for all active treatment doses, statistically significantly different from placebo (which generally rose). Urinary deoxypyridinoline and pyridinoline changes also suggested a decrease in bone turnover for all active treatment groups.

Figure 2. Mean Percent Change from Baseline in Total Hip by Treatment and Time* last observation carried forward**



Footnote: This figure is based on 74% of the randomized subjects (95 on active drug and 34 on placebo).

PHARMACOKINETICS

Transdermal administration of Climara® produces mean serum concentrations of estradiol comparable to those produced by premenopausal women in the early follicular phase of the ovulatory cycle. The pharmacokinetics of estradiol following application of the Climara® system were investigated in 197 healthy postmenopausal women in six studies. In five of the studies Climara® system was applied to the abdomen and in a sixth study application to the buttocks and abdomen were compared.

Absorption: The Climara® transdermal delivery system continuously releases estradiol which is transported across intact skin leading to sustained circulating levels of estradiol during 7 day treatment period. The systemic availability of estradiol after transdermal administration is about 20 times higher than that after oral administration. This difference is due to the absence of first pass metabolism when estradiol is given by the transdermal route.

The bioavailability of Climara® was determined in two single dose studies after 1 week application of the Climara® system versus two consecutive 3 day and 4 day applications of the Estraderm® system. Mean estradiol serum concentrations observed during the treatment of the 25.0 and 12.5 cm^2 Climara® systems versus the 20 and 10 cm^2 Estraderm® systems are shown in Figures 3 and 4, respectively. Both sizes of Climara® maintained significantly lower peak and mean steady state estradiol levels than did the Estraderm® system; however, towards the end of each treatment period, the Climara® system maintained similar (day 6) or higher (day 7) serum estradiol levels than did the Estraderm® system. The fluctuation index with the Climara® system was ¼ to 1/3 the fluctuation index observed with Estraderm®. However, this has not been shown to be clinically significant.

Figure 3
Observed Mean (± S.E.) Estradiol Serum Concentrations for a One Week Application of the Climara® system (25 cm^2) and Consecutive Three Day and Four Day Application of the Estraderm® System (20 cm^2) in 24 postmenopausal women

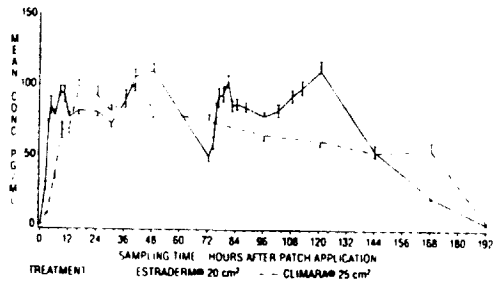
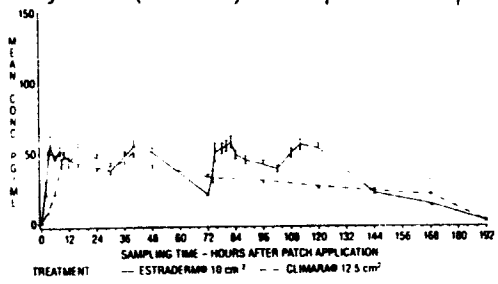


Figure 4

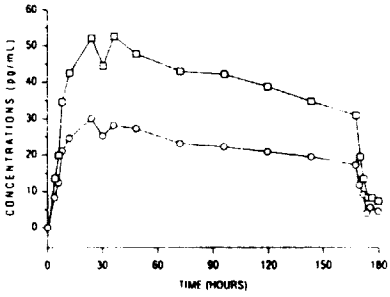
Observed Mean (± S.E.) Estradiol Serum Concentrations for a One Week Application of the Climara® system (12.5 cm^2) and Consecutive Three Day and Four Day Application of the Estraderm® System (10 cm^2) in 24 postmenopausal women



In a third bioavailability study, the Climara 6.5 cm^2 was studied with the Climara 12.5 cm^2 as reference. The mean estradiol levels in serum from the 2 sizes are shown in Figure 5.

Figure 5

Mean Serum 17β-Estradiol Concentrations vs. Time Profile following Application of a 6.5 cm^2 Transdermal Patch and Application of a 12.5 cm^2 Climara patch.



Time in (hrs)

Legend ○ 6.5 cm^2 Climara patch
□ 12.5 cm^2 Climara patch

Dose proportionality was demonstrated for the Climara 6.5 cm^2 patch as compared to the Climara 12.5 cm^2 patch in a 2 week crossover study with a one week washout period between the two patches in 24 postmenopausal women.

Dose proportionality was also demonstrated for the Climara® system (12.5 cm^2 and 25 cm^2) in a 1week study conducted in 54 postmenopausal women. The mean steady state levels (Cavg) of the estradiol during the application of Climara 25 cm^2 and 12.5 cm^2 on the abdomen were about 80 and 40 pg/mL, respectively.

In a 3 week multiple application study in 24 postmenopausal women, the 25.0 sq cm Climara® system produced average peak estradiol concentrations (Cmax) of approximately 100 pg/mL. Trough values at the end of each wear interval (Cmin) were approximately 35 pg/mL. Nearly identical serum curves were seen each week, indicating little or no accumulation of estradiol in the body. Serum estrone peak and trough levels were 60 and 40 pg/mL, respectively.

In a single dose randomized crossover study conducted to compare the effect of site of application, 38 postmenopausal women wore a single Climara® 25 sq cm system for 1 week on the abdomen and buttocks. The estradiol serum concentration profiles are shown in Figure 6. Cmax and Cavg values were, respectively, 25% and 17% higher with the buttock application than with the abdomen application.

Figure 6.
Observed Mean (± S.E.) Estradiol Serum Concentrations for a One Week Application of the Climara® system (25 cm^2) to the abdomen and buttocks of 38 postmenopausal women.

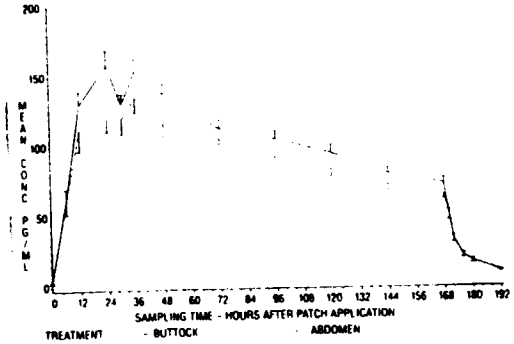


Table 1 provides a summary of estradiol pharmacokinetic parameters determined during evaluation of Climara®.

Table 1
Pharmacokinetic Summary
(Mean Estradiol Values)

Climara® Delivery Rate	Surface Area (cm^2)	Application Site	No. of Subjects	Dosing	Cmax (pg/mL)	Cmin (pg/mL)	Cavg (pg/mL)
0.025	6.5	Abdomen	24	Single	32	17	22
0.05	12.5	Abdomen	102	Single	71	29	41
0.1	25	Abdomen	139	Single	147	60	87
0.1	25	Buttock	38	Single	174	71	106

The relative standard deviation of each pharmacokinetic parameter after application to the abdomen averaged 50%, which is indicative of the considerable intersubject variability associated with transdermal drug delivery. The relative standard deviation of each pharmacokinetic parameter after application to the buttock was lower than that after application to the abdomen (e.g., for Cmax 39% vs 62%, and for Cavg 35% vs 48%).

Distribution: The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Estradiol and other naturally occurring estrogens are bound mainly to sex hormone binding globulin (SHBG), and to lesser degree to albumin.

Metabolism: Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is the major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the gut followed by reabsorption. In postmenopausal women a significant portion of the circulating estrogens exist as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens.

Excretion: Estradiol, estrone and estriol are excreted in the urine along with glucuronide and sulfate conjugates. After removal of the Climara® system, serum estradiol levels decline in about 12 hours to preapplication levels with an apparent half life of approximately 4 hours.

Special populations:

Race: There is no available information to establish the relevance of race for the absorption and pharmacokinetics of estradiol following transdermal application.

Patients with Renal Impairment: Total estradiol serum levels are higher in postmenopausal women with end stage renal disease (ESRD) receiving maintenance hemodialysis than in normal subjects at baseline and following oral doses of estradiol. Therefore, conventional transdermal estradiol doses used in individuals with normal renal function may be excessive for postmenopausal women with ESRD receiving maintenance hemodialysis.

Patients with Hepatic Impairment: Estrogens may be poorly metabolized in patients with impaired liver function and should be administered with caution.

INDICATIONS AND USAGE

Climara® is indicated in the:

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.

5. Prevention of Postmenopausal Osteoporosis (loss of bone mass). The mainstays of prevention of postmenopausal osteoporosis are estrogen, an adequate lifetime calcium and vitamin D intake, and exercise.

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.

CONTRAINDICATIONS

Estrogens should not be used in individuals with any of the following conditions:

1. Known or suspected pregnancy (see Boxed Warning). Estrogens may cause fetal harm when administered to a pregnant woman.

2. Undiagnosed abnormal genital bleeding.

3. Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease.

4. Known or suspected estrogen-dependent neoplasia.

5. Active thrombophlebitis or thromboembolic disorders.

WARNINGS

1. **Induction of malignant neoplasms.**

Endometrial cancer. The reported endometrial cancer risk among unopposed estrogen users is about 2 to 12 fold greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than one year. The greatest risk appears associated with prolonged use — with increased risks of 15- to 24-fold for five to ten years or more. In three studies, persistence of risk was demonstrated for 8 to over 15 years after cessation of estrogen treatment. In one study a significant decrease in the incidence of endometrial cancer occurred six months after estrogen withdrawal. Concurrent progestin therapy may offset this risk but the overall health impact in postmenopausal women is not known (see Precautions).

Breast Cancer. While the majority of studies have not shown an increased risk of breast cancer in women who have ever used estrogen replacement therapy, some have reported a moderately increased risk (relative risks of 1.3-2.0) in those taking higher doses or those taking lower doses for prolonged periods of time, especially in excess of 10 years.

Congenital lesions with malignant potential. Estrogen therapy during pregnancy is associated with an increased risk of fetal congenital reproductive tract disorders, and possibly other birth defects. Studies of women who received DES during pregnancy have shown that female offspring have an increased risk of vaginal adenosis, squamous cell dysplasia of the uterine cervix, and clear cell vaginal cancer later in life; male offspring have an increased risk of urogenital abnormalities and possibly testicular cancer later in life. Although some of these changes are benign, others are precursors of malignancy.

2. **Gallbladder disease**. Two studies have reported a 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in women receiving postmenopausal estrogens.

3. **Cardiovascular disease**. Large doses of estrogen (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men to increase the risks of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis. These risks cannot necessarily be extrapolated from men to women. However, to avoid the theoretical cardiovascular risk to women caused by high estrogen doses, the dose for estrogen replacement therapy should not exceed the lowest effective dose.

4 **Elevated blood pressure**. Occasional blood pressure increases during estrogen replacement therapy have been attributed to idiosyncratic reactions to estrogens. More often, blood pressure has remained the same or has dropped. One study showed that postmenopausal estrogen users have higher blood pressure than nonusers. Two other studies showed slightly lower blood pressure among estrogen users compared to nonusers. Postmenopausal estrogen use does not increase the risk of stroke. Nonetheless, blood pressure should be monitored at regular intervals with estrogen use. Ethinyl estradiol and conjugated estrogens have been shown to increase renin substrate. In contrast to these oral estrogens, transdermally administered estradiol has been reported not to affect renin substrate.

5. **Hypercalcemia**. Administration of estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If this occurs, the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

PRECAUTIONS

A. General

1. **Addition of a progestin**. Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Morphological and biochemical studies of endometria suggest that 10 to 14 days of progestin are needed to provide maximal maturation of the endometrium and to reduce the likelihood of hyperplastic changes.

There are, however, possible risks that may be associated with the use of progestins in estrogen replacement regimens. These include: (1) adverse effects on lipoprotein metabolism (lowering HDL and raising LDL) which could diminish the purported cardioprotective effect of estrogen therapy (see Precautions D.4., below); (2) impairment of glucose tolerance; and (3) possible enhancement of mitotic activity in breast epithelial tissue, although few epidemiological data are available to address this point (see Precautions below). The choice of progestin, its dose, and its regimen may be important in minimizing these adverse effects, but these issues will require further study before they are clarified.

2. **Cardiovascular risk**. *A causal relationship between estrogen replacement therapy and reduction of cardiovascular disease in postmenopausal women has not been proven. Furthermore, the effect of added progestins on this putative benefit is not yet known.*

In recent years many published studies have suggested that there may be a cause-effect relationship between postmenopausal oral estrogen replacement therapy *without added progestins* and a decrease in cardiovascular disease in women. Although most of the observational studies that assessed this statistical association have reported a 20% to 50% reduction in coronary heart disease risk and associated mortality in estrogen takers, the following should be considered when interpreting these reports: (1) Because only one of these studies was randomized and it was too small to yield statistically significant results, all relevant studies were subject to selection bias. Thus, the apparently reduced risk of coronary artery disease cannot be attributed with certainty to estrogen replacement therapy. It may instead have been caused by life-style and medical characteristics of the women studied with the result that healthier women were selected for estrogen therapy. In general, treated women were of a higher socioeconomic and educational status, more slender, more physically active, more likely to have undergone

surgical menopause, and less likely to have diabetes than the untreated women. Although some studies attempted to control for these selection factors, it is common for properly designed randomized trials to fail to confirm benefits suggested by less rigorous study designs. (2) Current medical practice often includes the use of concomitant progestin therapy with intact uteri (see Precautions and Warnings). While the effects of added progestins on the risk of ischemic heart disease are not known, all available progestins reverse at least some of the favorable effects of estrogens on HDL and LDL levels. (3) While the effects of added progestins on the risk of breast cancer are also unknown, available epidemiological evidence suggests that progestins do not reduce, and may enhance, the moderately increased breast cancer incidence that has been reported with prolonged estrogen replacement therapy (see WARNINGS above).

Because relatively long-term use of estrogens by a woman with a uterus has been shown to induce endometrial cancer, physicians often recommend that women who are deemed candidates for hormone replacement should take progestins as well as estrogens. When considering prescribing concomitant estrogens and progestins for hormone replacement therapy, physicians and patients are advised to carefully weigh the potential benefits and risks of the added progestin. Large-scale randomized, placebo-controlled, prospective clinical trials are required to clarify these issues.

3. **Physical examination**. A complete medical and family history should be taken prior to the initiation of any estrogen therapy. The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolaou smear. As a general rule, estrogen should not be prescribed for longer than one year without reexamining the patient.

4. **Hypercoagulability**. Some studies have shown that women taking estrogen replacement therapy have hypercoagulability, primarily related to decreased antithrombin activity. This effect appears dose- and duration-dependent and is less pronounced than that associated with oral contraceptive use. Also, postmenopausal women tend to have increased coagulation parameters at baseline compared to premenopausal women. There is some suggestion that low dose postmenopausal mestranol may increase the risk of thromboembolism, although the majority of studies (of primarily conjugated estrogens users) report no such increase. There is insufficient information on hypercoagulability in women who have had previous thromboembolic disease.

5. **Familial hyperlipoproteinemia**. Estrogen therapy may be associated with massive elevations of plasma triglycerides leading to pancreatitis and other complications in patients with familial defects of lipoprotein metabolism.

6. **Fluid retention**. Because estrogens may cause some degree of fluid retention, conditions that might be exacerbated by this factor, such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation.

7. **Uterine bleeding and mastodynia**. Certain patients may develop undesirable manifestations of estrogenic stimulation, such as abnormal uterine bleeding and mastodynia.

8. **Impaired liver function**. Estrogens may be poorly metabolized in patients with impaired liver function and should be administered with caution.

B **Information for the Patient**. See text of Patient Package Insert after the How Supplied section

C. **Laboratory Tests**. Estrogen administration should generally be guided by clinical response at the smallest dose, rather than laboratory monitoring, for relief of symptoms for those indications in which symptoms are observable.

D. **Drug/Laboratory Test Interactions**.

1. Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and betathromboglobulin; decreased levels of anti-factor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.

2. Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 levels (by column or by radioimmunoassay) or T3 levels by radioimmunoassay. T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered.

3. Other binding proteins may be elevated in serum, i.e., corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased circulating corticosteroids and sex steroids respectively. Free or biologically active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

4. Increased plasma HDL and HDL-2 subfraction concentrations, reduced LDL cholesterol concentration, increased triglycerides levels.

5. Impaired glucose tolerance.

6. Reduced response to metyrapone test.

7. Reduced serum folate concentration.

E. **Carcinogenesis, Mutagenesis, and Impairment of Fertility**. See Contraindications and Warnings. Long term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver.

F **Pregnancy Category X**. See Contraindications and Boxed Warning. Estrogens should not be used during pregnancy.

G. **Nursing Mothers**. As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk. In addition, estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk.

ADVERSE REACTIONS

See WARNINGS and Boxed Warning regarding induction of neoplasia, adverse effects on the fetus, increased incidence of gallbladder disease, cardiovascular disease, elevated blood pressure, and hypercalcemia.

The most commonly reported adverse reaction to the Climara® system in clinical trials was skin irritation at the application site. In two well-controlled clinical studies, the overall rate of discontinuation due to skin irritation at the application site was 6.8%: 7.9% for the 12.5 cm^2 system and 5.3% for the 25.0 cm^2 system compared with 11.5% for the placebo system. Patients with known skin irritation to the patch were excluded from participation in the studies. In a 3-week comparative skin irritation study with the Estraderm® system, in 95 subjects, no statistically significant differences in irritation were observed. Some degree of irritation at the end of week three was seen in 25% of Estraderm® and 31% of Climara® subjects. Clinically significant irritation (mild erythema associated with symptoms or moderate to severe erythema) was evident at the end of week three in 11% of Estraderm® and 9% of Climara® subjects. The following additional adverse reactions have been reported with estrogen therapy:

1. **Genitourinary system**.
Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow, breakthrough bleeding, spotting. Increase in size of uterine leiomyomata. Vaginal candidiasis. Change in amount of cervical secretion

2. **Breasts**.
Tenderness, enlargement.

3. **Gastrointestinal**.
Nausea, vomiting. Abdominal cramps, bloating. Cholestatic jaundice. Increased incidence of gallbladder disease.

4. **Skin**.
Chloasma or melasma that may persist when drug is discontinued. Erythema multiforme. Erythema nodosum. Hemorrhagic eruption. Loss of scalp hair. Hirsutism.

5. **Eyes**.
Steepening of corneal curvature. Intolerance to contact lenses.

6. **Central Nervous System**.
Headache, migraine, dizziness. Mental depression. Chorea.

7. **Miscellaneous**.
Increase or decrease in weight. Reduced carbohydrate tolerance. Aggravation of porphyria. Edema. Changes in libido.

OVERDOSAGE

Serious ill effects have not been reported following acute ingestion of large doses of estrogen-containing oral contraceptives by young children. Overdosage of estrogen may cause nausea and vomiting, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION

The adhesive side of the Climara® system should be placed on a clean, dry area of the lower abdomen or the upper quadrant of the buttock. *The Climara® system should not be applied to the breasts.* The sites of application must be rotated, with an interval of at least 1week allowed between applications to a particular site. The area selected should not be oily, damaged, or irritated. The waistline should be avoided, since tight clothing may rub and remove the system. Application to areas where sitting would dislodge the system should also be avoided. The system should be applied immediately after opening the pouch and removing the protective liner The system should be pressed firmly in place with the fingers for about 10 seconds, making sure there is good contact, especially around the edges. If the system lifts, apply pressure to maintain adhesion. In the event that a system should fall off, a new system should be applied for the remainder of the 7-day dosing interval. Only one system should be worn at any one time during the 7-day dosing interval. Swimming, bathing, or using a sauna while using the Climara® system has not been studied, and these activities may decrease the adhesion of the system and the delivery of estradiol.

Initiation of Therapy

Four (6.5, 12.5, 18.75 and 25.0 cm^2) Climara® systems are available.

For the treatment of vasomotor symptoms, treatment is usually initiated with the 12.5 cm^2 (0.05 mg/day) Climara® system applied to the skin once-weekly. The dose should be adjusted as necessary to control symptoms. Clinical responses (relief of symptoms) at the lowest effective dose should be the guide for establishing administration of the Climara® system, especially in women with an intact uterus. Attempts to taper or discontinue the medication should be made at 3- to 6-month intervals. In women who are not currently taking oral estrogens, treatment with the Climara® system can be initiated at once.

In women who are currently taking oral estrogen, treatment with the Climara® system can be initiated 1 week after withdrawal of oral therapy or sooner if symptoms reappear in less than 1 week.

For the prevention of postmenopausal osteoporosis, the minimum dose that has been shown to be effective is the 6.5 cm^2 (0.025 mg/day) Climara® system. Response to therapy can be assessed by biochemical markers and measurement of bone mineral density.

HOW SUPPLIED

Climara® (estradiol transdermal system), 0.025 mg/day - each 6.5 cm^2 system contains ~~2.04~~ 2.0 mg of estradiol USP NDC 50419- 450-04
Individual Carton of 4 systems
Shelf Pack Carton of 6 Individual Cartons of 4 systems

Climara® (estradiol transdermal system), 0.05 mg/day - each 12.5 cm^2 system contains ~~3.9~~ 3.8 mg of estradiol USP NDC 50419-451-04
Individual Carton of 4 systems
Shelf Pack Carton of 6 Individual Cartons of 4 systems

Climara® (estradiol transdermal system), 0.075 mg/day - each 18.75 cm^2 system contains ~~5.85~~ 5.7 mg of estradiol USP NDC 50419-453-04
Individual Carton of 4 systems
Shelf Pack Carton of 6 Individual Cartons of 4 systems

Climara® (estradiol transdermal system), 0.1 mg/day - each 25.0 cm^2 system contains ~~7.8~~ 7.6 mg of estradiol USP NDC 50419-452-04
Individual Carton of 4 systems
Shelf Pack Carton of 6 Individual Cartons of 4 systems

Do not store above 86° F (30° C). Do not store unpouched. Apply immediately upon removal from the protective pouch.

Manufactured for Berlex Laboratories, Wayne, NJ 07470
Manufactured by 3M Pharmaceuticals, St. Paul, MN 55144

Berlex code number ~~March~~ May 1999

Fda510b.doc

NDC 50419-451-01

Climara®

estradiol transdermal system

0.05 mg/day

Contents:
One 12.5 cm^2 system containing 3.8 mg estradiol USP to provide 0.05 mg of estradiol per day. The inactive components are acrylate copolymer adhesive, fatty acid esters, and polyethylene backing.

Rx only

BERLEX®

Do not store unpouched. Do not store above 86°F (30°C).

See patient instructions for application. Apply immediately upon removal from pouch. Each Climara® estradiol transdermal system is intended to be worn for 7 days.

Keep this and all drugs out of the reach of children.

Mfd for:
Berlex Laboratories, Wayne, NJ 07470
Mfd by:
3M Pharmaceuticals, St. Paul, MN 55144-1000

LOT

EXP

1

453200

NDC 50419-453-01

Climara®

estradiol transdermal system

0.075 mg/day

Contents:
One 18.75 cm² system containing 5.7 mg estradiol USP to provide 0.075 mg of estradiol per day. The inactive components are acrylate copolymer adhesive, fatty acid esters, and polyethylene backing.

Rx only

BERLEX®

Do not store unpouched. Do not store above 86°F (30°C).

See patient instructions for application. Apply immediately upon removal from pouch. Each Climara® estradiol transdermal system is intended to be worn for 7 days.

Keep this and all drugs out of the reach of children.

Mfd for:
Berlex Laboratories, Wayne, NJ 07470
Mfd by:
3M Pharmaceuticals, St. Paul, MN 55144-1000

LOT

EXP

453100

NDC 50419-452-01

Climara®

estradiol transdermal system

0.1 mg/day

Contents:
One 25 cm^2 system containing 7.6 mg estradiol USP to provide 0.1 mg of estradiol per day. The inactive components are acrylate copolymer adhesive, fatty acid esters, and polyethylene backing.

Rx only

BERLEX®

Do not store unpouched. Do not store above 86°F (30°C).

See patient instructions for application. Apply immediately upon removal from pouch. Each Climara® estradiol transdermal system is intended to be worn for 7 days.

Keep this and all drugs out of the reach of children.

Mfd for:
Berlex Laboratories, Wayne, NJ 07470
Mfd by:
3M Pharmaceuticals, St. Paul, MN 55144-1000

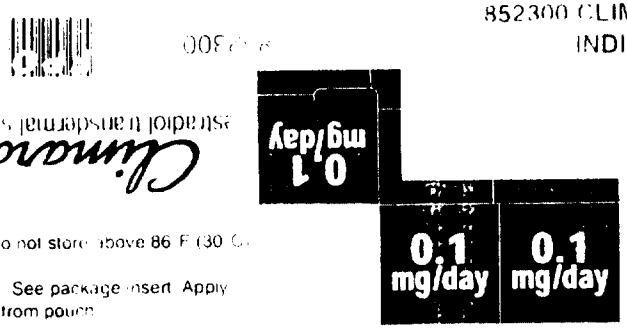
LOT

EXP

1

453300

852300 CLIMARA® TRANSDERMAL SYSTEMS 0.1 MG/DAY
INDIVIDUAL (4 SYSTEMS) TRADE CARTON



NDC 50419-452-04
4 systems

Climara®
estradiol transdermal system
0.1 mg/day

Contents
Each 25 cm² system contains 7.6 mg estradiol USP to provide 0.1 mg of estradiol per day. The active components are acrylate copolymer adhesive, fatty acid esters, and polyethylene backing.

For transdermal use only

Keep this and all drugs out of the reach of children

Rx only

BERLEX®

Climara
estradiol transdermal system
0.1 mg/day

Climara
estradiol transdermal system
0.1 mg/day

Do not store unpouched. Do not store above 86°F (30°C).

Dosage and Administration: See package insert. Apply immediately upon removal from pouch.

Each Climara estradiol transdermal system is intended to be worn for 7 days.

50419-452-04

Mfd for
Berlex Laboratories
Wayne, NJ 07470

Mfd by
3M Pharmaceuticals
St. Paul, MN 55144-1000

PRINTING
1. BACKGROUND - PANTONE 203C PINK
2. BRAND STROKE & RX LABEL BOX - WHITE
3. COPY BLOCKS - REVERSE WHITE ON PINK
4. COPY - BLACK

853400 CLIMARA® TRANSDERMAL SYSTEMS 0.075 MG/DAY
INDIVIDUAL (4 SYSTEMS) TRADE CARTON

853400

Climara® 0.075 mg/day
estradiol transdermal system

Do not store unpouched. Do not store above 86°F (30°C).

Dosage and Administration: See package insert. Apply immediately upon removal from pouch.

Each Climara® estradiol transdermal system is intended to be worn for 7 days.

FPO

N 3 50419-453-04 2

Mfd for:
Berlex Laboratories
Wayne, NJ 07470

Mfd by:
3M Pharmaceuticals
St. Paul, MN 55144-1000

853400

FPO

NDC 50419-453-04
4 systems

Climara®
estradiol transdermal system
0.075 mg/day

Contents:
Each 18.75 cm^2 system contains 5.7 mg estradiol USP to provide 0.075 mg of estradiol per day. The inactive components are acrylate copolymer adhesive, fatty acid esters, and polyethylene backing.

For transdermal use only.

Keep this and all drugs out of the reach of children.

Rx only

BERLEX®

Climara estradiol transdermal system 0.075 mg/day

Climara® 0.075 mg/day
estradiol transdermal system

PRINTING
1) BACKGROUND - PANTONE 196C LIGHT PINK
2) BRUSH STROKE & RX LABEL BOX - PANTONE 204C DARK PINK
3) COLOR BLOCKS - PANTONE 204C DARK PINK OVER WHITE
4) TEXT BLACK

852100

0.05 mg/day

Climara®

estradiol transdermal system

0.05 mg/day

Do not store unpouched. Do not store above 86°F (30°C).

Dosage and Administration: See package insert. Apply immediately upon removal from pouch.

Each Climara® estradiol transdermal system is intended to be worn for 7 days.

50419-451-04

Mfd for
Berlex Laboratories
Wayne, NJ 07470

Mfd by:
3M Pharmaceuticals
St. Paul, MN 55144-1000

852100

3M PHARMACEUTICALS,Special
3-1/8 X 5/8 X 3-7/8
PRINT SIDE

0.05 mg/day | 0.05 mg/day

Climara®

estradiol transdermal system

0.05 mg/day

NDC 50419-451-04
4 systems

Climara®

estradiol transdermal system

0.05 mg/day

Contents

Each 12.5 cm^2 system contains 3.8 mg estradiol USP to provide 0.05 mg of estradiol per day. The inactive components are acrylate copolymer adhesive, fatty acid esters, and polyethylene backing.

For transdermal use only.

Keep this and all drugs out of the reach of children.

Rx only

BERLEX®

Climara® 0.05 mg/day

estradiol transdermal system

852100 CLIMARA® TRANSDERMAL SYSTEMS 0.05 MG/DAY INDIVIDUAL (4 SYSTEMS) TRADE CARTON

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20375/S13

CHEMISTRY REVIEW(S)

APR 28

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS

REVIEW OF CHEMISTRY MANUFACTURING AND CONTROLS
CHEMIST'S REVIEW

1. NDA NUMBER: 20-375

2. NAME AND ADDRESS OF APPLICANT
Berlex Laboratories, Inc.
340 Changebridge Road
P.O Box 1000
Montville, NJ 07045-1000

3. SUPPLEMENT NUMBER/DATE/DATE ASSIGNED
NDA 20-375 SLR-013/1-19-99/1-22-99

NDA 20-375 SLR-014BL/2-09-99/2-10-99

4. NAME OF THE DRUG:Climara ^{R} (estradiol transdermal system)
5. NONPROPRIETARY NAME: Estradiol Transdermal System
6. NDA PROVIDES FOR: Changing the current labeling and associated analytical methods and specifications to reflect clarification of the use of estradiol as the anhydrous form.
7. AMENDMENTS/REPORTS/ DATE: None
8. PHARMACOLOGICAL CATEGORY
Estrogen

9. HOW DISPENSED
Prescription

10. RELATED IND/NDA/DMF/SUPPLEMENT
DMF

11. DOSAGE FORM : Transdermal
12. POTENCY
2.04, 3.9, 5.85, 7.8 mg per patch delivering
0.025, 0.05 , 0.075 and 0.1 mg/day (6.5, 12.5, 18.75, and 25 cm^2) respectively

13. CHEMICAL NAME AND STRUCTURE
$C_{18}H_{24}O_2$ ½ H_2O
MW = 281.4

Estra-1,3,5(10)-triene-3,17β-diol, hemi hydrate

14. COMMENTS

Climara is manufactured by [redacted] as a drug-in-adhesive formulation. The formulations are manufactured using the drug substance, estradiol hemihydrate. The labeled content (3.9, 5.9, 7.8 mg estradiol, USP for the 12.5, 18.75 or 25 Cm^2 systems respectively) is actually the content of estradiol in hemihydrate form. The USP reference standard for routine analysis of the drug product is estradiol in its hemihydrate form. The data generated for generated for the drug product is quantitated in terms of estradiol hemihydrate.

The current labeling lists three (12.5, 18.75 or 25 Cm^2 systems) systems containing (3.9, 5.9, 7.8 mg estradiol). The proposed labeling for the 12.5, 18.75 or 25 Cm^2 would be corrected to reflect estradiol anhydrous with the content of 3.8, 5.7, and 7.6 mg respectively. The 6.5 Cm^2 patch approved under S-011 would be proposed to be labeled at 2.0 mg estradiol anhydrous per patch instead of 2.04 mg estradiol, as approved. The labeling change for the 6.5 Cm^2 patch was provided in the NDA 20-375, SLR-014, dated 1-28-99 with adhesion data for 6.5 Cm^2 system, and it was reviewed by the MO (Dr. P. Price). No Chemistry review of the supplement is necessary. The labeling change for the pouch, carton and revised patient insert which reflects four sizes instead of three were provided in an amendment to the labeling supplement 20-375, SLR-014BL. The pouch and the carton labels reflect the change in the estradiol content from 2.04 to 2.0 mg, and it is satisfactory.

3M Pharamceutical manufactures and releases the drug product under DMF [redacted] and it was cross referenced reflecting the change in calculation into anhydrous form. The DMF was reviewed separately and found adequate to support this change.

The following changes were made:

Changing the current labeling and associated analytical methods and specifications to reflect clarification of the use of estradiol as the anhydrous form.

15. CONCLUSIONS AND RECOMMENDATIONS The supplement SLR-013 can be approved with respect to CMC.

/S/

Reviewed By: Amit K. Mitra, Ph.D, 4-23-99

/S/ 4/28/99

R/D INIT BY: Moo-Jhong Rhee, Ph.D

CC: A. K. MITRA/HFD-580
M.J.RHEE/HFD-580
D. Moore/HFD-580
NDA 20-375

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20375/S13

ADMINISTRATIVE DOCUMENTS

MAY 20

NDA 20-375/S-013
Climara®
Physician's labeling
Date received: January 19, 1999
Date amended: May 5, 1999

Currently Approved Labeling	Proposed Revisions	Medical Officer Comments
DESCRIPTION Climara®, estradiol transdermal system, is designed to release 17β-estradiol continuously upon application to intact skin. Four (6.5, 12.5, 18.75 and 25.0 cm^2) systems are available to provide nominal *in vivo* delivery of 0.025, 0.05, 0.075 or 0.1 mg respectively of estradiol per day. The period of use is 7 days. Each system has a contact surface area of either 6.5, 12.5, 18.75 or 25.0 cm2, and contains 2.04, 3.9, 5.85 or 7.8 mg of estradiol USP respectively. The composition of the systems per unit area is identical.	**DESCRIPTION** Climara®, estradiol transdermal system, is designed to release 17β-estradiol continuously upon application to intact skin. Four (6.5, 12.5, 18.75 and 25.0 cm^2) systems are available to provide nominal *in vivo* delivery of 0.025, 0.05, 0.075 or 0.1 mg respectively of estradiol per day. The period of use is 7 days. Each system has a contact surface area of either 6.5, 12.5, 18.75 or 25.0 cm2, and contains 2.0, 3.8, 5.7 or 7.6 mg of estradiol USP respectively. The composition of the systems per unit area is identical.	Previous analyses of the amount of estradiol in the system used formulations manufactured using the drug substance, estradiol hemihydrate, Ph. Eur./estradiol, USP with no compensation for water content made. The changes in the amount of estradiol contained in each system reflect clarification of the use of estradiol as the anhydrous form.
CLINICAL PHARMACOLOGY	**CLINICAL PHARMACOLOGY** NC	
INDICATIONS AND USAGE	**INDICATIONS AND USAGE** NC	
CONTRAINDICATIONS	**CONTRAINDICATIONS** NC	
WARNINGS	**WARNINGS** NC	
PRECAUTIONS	**PRECAUTIONS** NC	
ADVERSE REACTIONS	**ADVERSE REACTIONS** NC	
DRUG ABUSE AND DEPENDENCE	**DRUG ABUSE AND DEPENDENCE** NC	
OVERDOSAGE	**OVERDOSAGE** NC	
DOSAGE AND ADMINISTRATION	**DOSAGE AND ADMINISTRATION** NC	
HOW SUPPLIED Climara® (estradiol transdermal system), 0.05 mg/day – each 12.5 cm^2 system contains 3.9 mg of estradiol USP NDC 50419-451-04	**HOW SUPPLIED** Climara® (estradiol transdermal system), 0.05 mg/day – each 12.5 cm^2 system contains 3.8 mg of estradiol USP NDC 50419-451-04	

Individual Carton of 4 systems Shelf Pack Carton of 6 Individual Cartons of 4 systems Climara® (estradiol transdermal system), 0.075 mg/day – each 18.75 cm^2 system contains 5.85 mg of estradiol USP NDC 50419-453-04 Individual Carton of 4 systems Shelf Pack Carton of 6 Individual Cartons of 4 systems Climara® (estradiol transdermal system), 0.1 mg/day – each 25.0 cm^2 system contains 7.8 mg of estradiol USP NDC 50419-452-04 Individual Carton of 4 systems Shelf Pack Carton of 6 Individual Cartons of 4 systems	Individual Carton of 4 systems Shelf Pack Carton of 6 Individual Cartons of 4 systems Climara® (estradiol transdermal system), 0.075 mg/day – each 18.75 cm^2 system contains 5.7 mg of estradiol USP NDC 50419-453-04 Individual Carton of 4 systems Shelf Pack Carton of 6 Individual Cartons of 4 systems Climara® (estradiol transdermal system), 0.1 mg/day – each 25.0 cm^2 system contains 7.6 mg of estradiol USP NDC 50419-452-04 Individual Carton of 4 systems Shelf Pack Carton of 6 Individual Cartons of 4 system	
OTHER		

Note: The labeling submitted on May 5, 1999, is identical to the labeling approved in Supplement S-011 associated with NDA 20-994 in which the osteoporosis indication was approved with the additional changes from Supplement 013 in the **DESCRIPTION** and **HOW SUPPLIED** sections.

This supplement pertains to the physician's labeling and the carton and container labeling. The patient package labeling was unchanged during review of supplement S-011. This labeling contained the black box warning. However, the patient package insert included in the original submission to Supplement 013 did not include the black box warning. Also, in the **DOSAGE AND ADMINISTRATION** section of the patient package labeling, the word, "unlikely" should have been removed from the sentence, "In the unlikely event that a system should fall off, a new system should be applied for the remainder of the 7-day dosing interval." This word was not removed in either labeling supplement. No patient package insert was included in the May 5, 1999, amendment to the labeling.

See next page

Proposed Regulatory Action (MO to complete):

Approval
Approvable with the following modifications:

Not Approvable (provide rationale)

/S/ 5/20/99
CSO/PM signature Date

/S/ for Dr. Price 5/20/99
Medical Officer Signature Date

Chemist Date

/S/ 5/20/99
Chemistry Team Leader Date

/S/ 5/21/99
Deputy Director Concurrence Date

cc:
HFD-580/Div file
HFD-580/LRarick/MMann/SSlaughter/PPrice/AMitra/MRhee/KRaheja/AJordan
HFD-580/DMoore/TRumble

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20375/S13

CORRESPONDENCE

DF

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-375/S-013

FEB - 3 1999

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

Attention: Geoffrey Millington
Manager, Drug Regulatory Affairs

Dear Mr. Millington:

We acknowledge receipt of your supplemental application for the following:

Name of Drug:	Climara® (estradiol trandermal systems)
NDA Number:	20-375
Supplement Number:	S-013
Date of Supplement:	January 19, 1999
Date of Receipt:	January 22, 1999

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on March 13, 1999, in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Office of Drug Evaluation II
Attention: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

/S/

for Lana Pauls
Chief, Project Management Staff
Division of Reproductive and Urologic
Drug Products, HFD-580
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20-375/S-013
HFD-580/Div. Files
HFD-580/CSO/D. Moore

SUPPLEMENT ACKNOWLEDGEMENT