CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-182

Approval Letter

ANDA 75-182

FEB 24 2000

Mylan Technologies, Inc.
Attention: Elizabeth Ash
110 Lake Street
St. Albans, VT 05478

Dear Madam:

This is in reference to your abbreviated new drug application dated August 6, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Estradiol Transdermal System, 0.1 mg/day, (Once-a-Week Formulation).

Reference is also made to your amendments dated February 24, March 12, May 28, and October 28, 1998; and April 14, July 26, September 3, and October 27, 1999.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Estradiol Transdermal System, 0.1 mg/day, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Climara® Transdermal System, 0.1 mg/day of Berlex Laboratories, Inc.).

The dissolution testing should be incorporated into your manufacturing controls and stability program. The "interim" dissolution test and tolerances are:

> The dissolution testing should be conducted in 500 mL of 0.3% sodium lauryl sulfate in 0.005 N NaH_2PO_4, pH 5.5, at 32° C using USP 23 apparatus 5 (paddle over disk) at 100 rpm. These percentages of the labeled amount of estradiol in the dosage form should be released within the following time periods:

The "interim" dissolution test and tolerances should be finalized by submitting dissolution data for the first three production size batches in a supplemental application. The supplemental application should be submitted under Section 505(j) of the Act as a "Changes Being Effected (CBE-0)" supplement when there are no revisions to the interim specifications or when the final specifications are tighter than the interim specifications. In all other instances the supplement should be submitted under Section 505(j) of the Act as a prior approval supplement.

We note that the listed drug (RLD) referenced in your application, Climara Transdermal System of Berlex Laboratories, is subject to a period of patent protection which expires on June 29, 2010, (U.S. Patent No. 5,223,261). Your application contains a patent certification under Section 505(j)(2)(A)(vii)(IV) of the Act stating that your manufacture, use, sale, offer for sale, or importation of this drug product will not infringe on this patent, or that the patent is invalid or unenforceable. Section 505(j)(5)(B)(iii) of the Act provides that approval of an abbreviated application shall be made effective immediately, unless an infringement action is brought against you before the expiration of forty-five days from the receipt date of the notice provided under paragraph (2)(B)(i). You have notified FDA that Mylan Technologies, Inc. (Mylan) has complied with the requirements of Section 505(j)(2)(B) of the Act and that no action for patent infringement was brought against Mylan within the statutory forty-five day period.

Under Section 506(A) of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy that you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug

Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-182

FINAL PRINTED LABELING

Estradiol Transdermal System (Once a Week Formulation) Continuous Delivery for Once-Weekly Application

Rx only

PRESCRIBING INFORMATION

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.

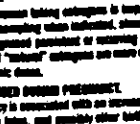
Estrogen therapy during pregnancy is associated with an increased risk of congenital defects in the reproductive organs of the fetus, and possibly other birth defects. Studies of women who received diethylstilbestrol (DES) during pregnancy have shown that female offspring have an increased risk of vaginal 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 established 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 abortion. Estrogens are not indicated for the prevention of postpartum breast engorgement.

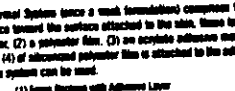
DESCRIPTION

Estradiol Transdermal System (once a week formulation), is designed to release 17β-estradiol continuously upon application to intact skin. Two (15.5 and 31 sq cm active area) systems are available to provide nominal *in vivo* delivery of 0.05 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 15.5 or 31 sq cm, and contains 1.94 or 3.86 mg of estradiol USP respectively.

Estradiol USP (17β-estradiol) is a white, crystalline powder, chemically described as Estra-1,3,5(10)-triene-3,17β-diol. It has a molecular formula of $C_{18}H_{24}O_2$ and molecular weight of 272.39. The structural formula is:



The Estradiol Transdermal System (once a week formulation) comprises three layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are (1) foam backing with adhesive layer, (2) a polyester film, (3) an acrylate adhesive matrix containing estradiol USP. A protective liner (4) of siliconized 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 (propylene glycol, povidone, anhydrous colloidal silicon dioxide, pressure sensitive acrylic adhesive, copolymer foam, polyester film, and brown ink) are pharmacologically inactive.

CLINICAL PHARMACOLOGY

The Estradiol Transdermal System (once a week formulation) provides systemic estrogen replacement therapy by releasing 17β-estradiol, the major estrogenic hormone secreted by the human ovary.

Estrogens are important in the development and maintenance of the female reproductive system and secondary sex characteristics. By a direct action, they cause growth and development of the uterus, fallopian tubes, and vagina. With other hormones, such as pituitary hormones and progesterone, they cause enlargement of the breasts through promotion of ductal growth, stromal development, and the accretion of fat. Estrogens are clinically marked with other hormones, especially progesterone, in the processes of the ovulatory menstrual cycle and pregnancy, and affect the release of pituitary gonadotropins. They also contribute to the shaping of the skeleton, maintenance of tone and elasticity of urogenital structures, changes in the epiphyses of the long bones that allow for the pubertal growth spurt and its termination, and pigmentation of the nipples and genitals.

Estrogens occur naturally in several forms. The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 micrograms of estradiol daily, depending on the phase of the menstrual cycle. This is converted primarily to estrone, which circulates in roughly equal proportion to estradiol, and to small amounts of estriol. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone - especially in its sulfate ester form - is the most abundant circulating estrogen in postmenopausal women. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than estrone or estriol at the receptor.

Estrogen drug products act by regulating the transcription of a limited number of genes. Estrogens diffuse through cell membranes, distribute themselves throughout the cell, and bind to and activate the nuclear estrogen receptor, a DNA-binding protein which is found in estrogen-responsive tissues. The activated estrogen receptor binds to specific DNA sequences, or hormone-response elements, which enhance the transcription of adjacent genes and in turn lead to the observed effects. Estrogen receptors have been identified in tissues of the reproductive tract, breast, pituitary, hypothalamus, liver, and bone of women.

Estrogens used in therapy are well absorbed through the skin, mucous membranes, and gastrointestinal tract. Administered estrogens and their esters are handled within the body essentially the same as the endogenous hormones. Metabolic conversion of estrogens occurs primarily in the liver (first pass effect), but also at local target tissue sites. Complex metabolic processes result in a dynamic equilibrium of circulating conjugated and unconjugated estrogenic forms, which are continually interconverted, especially between estrone and estradiol and between unsulfated and sulfated forms. Although naturally-occurring estrogens circulate in the blood largely bound to sex hormone-binding globulin and albumin, only unbound estrogens enter target tissue cells. A significant proportion of the circulating estrogen exists as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogenic species. A certain proportion of the estrogen is excreted into the bile and then reabsorbed from the intestine. During the enterohepatic recirculation, estrogens are deconjugated and transported and undergo degradation through conversion to less active estrogens (estriol and other estrogens), oxidation to nonestrogenic substances (catecholestrogens, which interact with catecholamine metabolism, especially in the central nervous system), and conjugation with glucuronic acids (which are then rapidly excreted in the urine).

When given orally, naturally-occurring estrogens and their esters are extensively metabolized (first pass effect) and circulate primarily as estrone sulfate, with smaller amounts of other conjugated and unconjugated estrogenic species. This results in limited oral potency. In contrast, the skin metabolizes estradiol only to a small extent. Therefore, transdermal administration produces therapeutic serum levels of estradiol with lower circulating levels of estrone and estrone conjugates, and requires smaller total doses than does oral therapy. Because estradiol has a short half-life, transdermal administration of estradiol allows a rapid decline in blood levels after the Estradiol Transdermal System (once a week formulation) is removed.

Pharmacokinetics

Transdermal administration of estradiol is reported to produce mean serum concentrations of estradiol comparable to those produced by daily oral administration of estradiol at about 20 times the daily transdermal dose.

In a 3-week multiple-application study in 24 postmenopausal women, the 0.1 mg/day Estradiol Transdermal System (once a week formulation) produced average peak estradiol concentrations of approximately 100 pg/mL. Trough values at the end of each wear interval vary 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. Because estradiol has a short half-life (approximately 1 hour), serum concentrations of estradiol and estrone returned to preapplication levels within 6 to 24 hours after removal of the last system. No more than 17 pg/mL of estradiol and 35 pg/mL estrone.

Linear pharmacokinetics have been demonstrated for the Estradiol Transdermal System (once a week formulation). In a 1-week application study in 54 postmenopausal women, the 0.1 mg/day system produced estradiol serum level profiles and pharmacokinetic parameters that were twice as high as the 0.05 mg/day system. Statistical analyses confirmed the 2:1 dose proportionality.

On average, the Estradiol Transdermal System, 0.1 mg/day (once a week formulation) maintained mean steady-state serum estradiol levels of approximately 70 pg/mL, and the Estradiol Transdermal System, 0.05 mg/day (once a week formulation) maintained mean steady-state serum estradiol levels of approximately 35 pg/mL.

Table 1 summarizes the mean results from four pharmacokinetic studies. All systems were applied on the abdomen for a single 1-week period. C_{max} occurred at approximately 30 hours.

Table 1
Pharmacokinetic Summary

Surface Area (sq cm)	Delivery Rate (mg/day)	C_{ave} (pg/mL)	C_{max} (pg/mL)	C_{min} (pg/mL)
15.5	0.05	56-82	70-92	33-45
31	0.1	98-172	98-61	53-93

The relative standard deviation of each pharmacokinetic parameter averaged 30%, which is indicative of the considerable intersubject variability associated with transdermal drug delivery.

Two studies compared a single, 1-week application of the Estradiol Transdermal System (once a week formulation) with consecutive 3-day and 4-day applications of Estradiol Transdermal System (twice a week formulation). The Estradiol Transdermal System, 0.1 mg/day (once a week formulation) was compared with the Estradiol Transdermal System (twice a week formulation) 0.1 mg/day system (see Figure 1); the Estradiol Transdermal System, 0.05 mg/day (once a week formulation) was compared to the Estradiol Transdermal System (twice a week formulation) 0.05 mg/day system (see Figure 2). For a 1-week treatment period, both sizes of Estradiol Transdermal Systems (once a week formulation) maintained significantly lower peak and mean steady-state levels than did the Estradiol Transdermal System (twice a week formulation); however, towards the end of each treatment period, the Estradiol Transdermal Systems (once a week formulation) maintained similar (day 6) or higher (day 7) serum estradiol levels than did the Estradiol Transdermal System (twice a week formulation). As a result, the peak-to-end of application interval trough level fluctuations were 3- to 4- times less with the Estradiol Transdermal System (once a week formulation).

Figure 1
Mean Serum Levels for a One-Week Application of the Estradiol Transdermal System (Once a Week Formulation) (0.1 mg/day) and Consecutive Three-Day and Four-Day Applications of the Estradiol Transdermal System (Twice a Week Formulation) (0.1 mg/day)

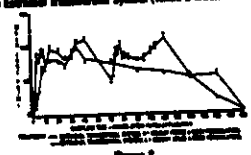


Figure 2
Mean Serum Levels for a One-Week Application of the Estradiol Transdermal System (Once a Week Formulation) (0.05 mg/day) and Consecutive Three-Day and Four-Day Applications of the Estradiol Transdermal System (Twice a Week Formulation) (0.05 mg/day)

INDICATIONS AND USAGE

Estradiol Transdermal System (once a week formulation) 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.

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 ratio of 1.3 to 2.0) in those taking higher doses or those taking lower doses for prolonged periods of time, especially in excess of 10 years. Other studies have not shown this relationship.

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 prostrate 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 in 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. Clinical estradiol and conjugated estrogens have been shown to increase serum triglycerides. In contrast to these oral estrogens, transdermally administered estradiol has been reported not to affect serum triglycerides.

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 lessened incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Morphological and biochemical studies of endometrium 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 which 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 B.4., below); (2) impairment of glucose tolerance; and (3) possible enhancement of allergic activity in treated epileptic women, although how 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 delay in cardiovascular disease in women. Although most of the observational studies which demonstrated this statistical association have reported a 30% to 50% reduction in coronary heart disease risk and associated mortality in estrogen takers, the following should be considered when evaluating 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 caused, 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 educated, 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. Thus, ongoing and future large-scale randomized trials may fail to confirm this apparent benefit. (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 risk evidence 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 long-term 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 progestins. 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. Hypersensitivity. Some studies have shown that women taking estrogen replacement therapy have hypersensitivity, presumably 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 or heparins compared to premenopausal women. There is some suggestion that low dose postmenopausal menotropins 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 hypertriglyceridemia. 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 which 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.

9. 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, VII coagulant activity IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; 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, 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 in the Estradiol Transdermal System (once a week formulation) 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 6.6%; 7.9% for the 0.05 mg/day system and 5.3% for the 0.1 mg/day system compared with 11.5% for the placebo system. In a 3-week comparative skin irritation study with Estradiol Transdermal System (twice a week formulation), 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

Estradiol Transdermal System (once a week formulation) and 37% of Estradiol Transdermal System (once a week formulation) subjects. Clinically significant irritation (mild erythema associated with symptoms or moderate to severe erythema) was evident at the end of wear time in 17% of Estradiol Transdermal System (once a week formulation) and 9% of Estradiol Transdermal System (once a week formulation) 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 Estradiol Transdermal System (once a week formulation) should be placed on a clean, dry area of the abdomen or the upper quadrant of the buttock. *Estradiol Transdermal System (once a week formulation) should not be applied to the breasts.* The sites of application must be rotated, with an interval of at least 1 week 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 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 Estradiol Transdermal System (once a week formulation) has not been studied, and these activities may decrease the adhesion of the system and the delivery of estradiol.

Initiation of Therapy

Treatment is usually initiated with the 15.5 sq cm (0.05 mg/day) Estradiol Transdermal System (once a week formulation) 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 Estradiol Transdermal System (once a week formulation), 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 Estradiol Transdermal System (once a week formulation) can be initiated at once. In women who are currently taking oral estrogen, treatment with the Estradiol Transdermal System (once a week formulation) can be initiated 1 week after withdrawal of oral therapy or sooner if symptoms reappear in less than 1 week.

HOW SUPPLIED

Estradiol Transdermal System, 0.05 mg/day (Once a Week Formulation) - each 15.5 sq cm system contains 1.94 mg of estradiol USP .... NDC 0378-3350-99
Individual Carton of 4 systems

Estradiol Transdermal System, 0.1 mg/day (Once a Week Formulation) - each 31 sq cm system contains 3.88 mg of estradiol USP .... NDC 0378-3352-99
Individual Carton of 4 systems

Store at 15° - 30°C (59° - 86°F). Do not store unpouched. Apply immediately upon removal from the protective pouch.

MYLAN®

MYLAN PHARMACEUTICALS INC.
Morgantown, WV 26505

REVISED MAY 1999
ETS:R2

PATIENT INFORMATION
Estradiol Transdermal System (Once a Week Formulation)
Continuous Delivery for Once-Weekly Application

℞ only

INFORMATION FOR THE PATIENT

INTRODUCTION

The Estradiol Transdermal System (once a week formulation) that your doctor has prescribed for you releases small amounts of estradiol through the skin in a continuous way. Estradiol is the same hormone that your ovaries produce abundantly before menopause. The dose of estradiol you require will depend upon your individual response. The dose is adjusted by the size of the Estradiol Transdermal System (once a week formulation) used; the systems are available in two sizes.

This leaflet describes when and how to use estrogens, and the risks and benefits of estrogen treatment.

Estrogens have important benefits but also some risks. You must decide, with your doctor, whether the risks to you of estrogen use are acceptable because of their benefits. If you use estrogens, check with your doctor to be sure you are using the lowest possible dose that works, and that you don't use them longer than necessary. How long you need to use estrogens will depend on the reason for use.

1. ESTROGENS INCREASE THE RISK OF CANCER OF THE UTERUS IN WOMEN WHO HAVE HAD THEIR MENOPAUSE ("CHANGE OF LIFE").
If you use any estrogen-containing drug, it is important to visit your doctor regularly and report any unusual vaginal bleeding right away. Vaginal bleeding after menopause may be a warning sign of uterine cancer. Your doctor should evaluate any unusual vaginal bleeding to find out the cause.

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.
Estrogens do not prevent miscarriage (spontaneous abortion) and are not needed in the days following childbirth. If you take estrogens during pregnancy, your unborn child has a greater than usual chance of having birth defects. The risk of developing these defects is small, but clearly larger than the risk in children whose mothers did not take estrogens during pregnancy. These birth defects may affect the baby's urinary system and sex organs. Daughters born to mothers who took DES (an estrogen drug) have a higher than usual chance of developing cancer of the vagina or cervix when they become teenagers or young adults. Sons may have a higher than usual chance of developing cancer of the testicles when they become teenagers or young adults.

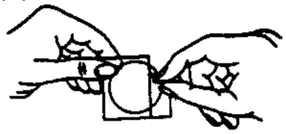
INFORMATION ABOUT ESTRADIOL TRANSDERMAL SYSTEM (ONCE A WEEK FORMULATION)

How The Estradiol Transdermal System (Once a Week Formulation) Works

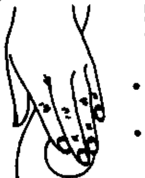
The Estradiol Transdermal System (once a week formulation) contains 17β-estradiol. When applied to the skin as directed below, the Estradiol Transdermal System (once a week formulation) releases 17β-estradiol, which flows through the skin into the bloodstream.

How and Where to Apply the Estradiol Transdermal System (Once a Week Formulation)

Each Estradiol Transdermal System (once a week formulation) is individually sealed in a protective pouch. Tear open this pouch at the indentation (do not use scissors) and remove the system.



A protective liner covers the adhesive side of the system - the side that will be placed against your skin. This liner must be removed before applying the system. Remove the protective liner and discard it. Try to avoid touching the adhesive. Apply the adhesive side of the system to a clean, dry area of the skin on the abdomen. *Do not apply the Estradiol Transdermal System (once a week formulation) to your breasts.*



The sites of application must be rotated, with an interval of at least 1 week allowed between applications to a particular site on the abdomen or the upper quadrant of the buttock. The area selected should not be oily, damaged, or irritated. Avoid the waistline, since tight clothing may rub and remove the system. Application to areas where sitting would dislodge the system should be avoided. Apply the system immediately after opening the pouch and removing the protective liner. Press the system firmly in place with the fingers for about 10 seconds, making sure there is a good contact, especially around the edges.

The Estradiol Transdermal System (once a week formulation) should be worn continuously for one week. You may wish to experiment with different locations when applying a new system, to find ones that are most comfortable for you and where clothing will not rub on the system.

When to Apply the Estradiol Transdermal System (Once a Week Formulation)

The Estradiol Transdermal System (once a week formulation) should be changed once weekly. When changing the system, remove the used Estradiol Transdermal System (once a week formulation) and discard it. Any adhesive that might remain on your skin can be easily rubbed off. Then place the new Estradiol Transdermal System (once a week formulation) on a different skin site. (The same skin site should not be used again for at least 1 week after removal of the system.)

Contact with water when you are bathing, swimming, or showering may affect the system. In the event that a system should fall off, a new system should be applied for the remainder of the 7-day dosing interval.

USES OF ESTROGEN

(Not every estrogen drug is approved for every use listed in this section. If you want to know which of these possible uses are approved for the medicine prescribed for you, ask your doctor or pharmacist to show you the professional labeling. You can also look up the specific estrogen product in a book called the "Physicians' Desk Reference", which is available in many book stores and public libraries. Generic drugs carry virtually the same labeling information as their brand name versions.)

- **To reduce moderate or severe menopausal symptoms.** Estrogens are hormones made by the ovaries of normal women. Between ages 45 and 55, the ovaries normally stop making estrogens. This leads to a drop in body estrogen levels which causes the "change of life" or menopause (the end of monthly menstrual periods). If both ovaries are removed during an operation before natural menopause takes place, the sudden drop in estrogen levels causes "surgical menopause".
  When the estrogen levels begin dropping, some women develop very uncomfortable symptoms, such as feelings of warmth in the face, neck, and chest, or sudden intense episodes of heat and sweating ("hot flashes" or "hot flushes"). Using estrogen drugs can help the body adjust to lower estrogen levels and reduce these symptoms. Most women have only mild menopausal symptoms or none at all and do not need to use estrogen drugs for these symptoms. Others may need to take estrogens for a few months while their bodies adjust to lower estrogen levels. The majority of women do not need estrogen replacement for longer than six months for these symptoms.
- **To treat vulval and vaginal atrophy** (itching, burning, dryness in or around the vagina, difficulty or burning on urination) associated with menopause.
- **To treat certain conditions in which a young woman's ovaries do not produce enough estrogen naturally.**
- **To treat certain types of abnormal vaginal bleeding due to hormonal imbalance when your doctor has found no serious cause of the bleeding.**
- **To treat certain cancers in special situations, in men and women.**
- **To prevent thinning of bones.**
  Osteoporosis is a thinning of the bones that makes them weaker and allows them to break more easily. The bones of the spine, wrists and hips break most often in osteoporosis. Both men and women start to lose bone mass after about age 40, but women lose bone mass faster after the menopause. Using estrogens after the menopause slows down bone thinning and may prevent bones from breaking. Lifelong adequate calcium intake, either in the diet (such as dairy products) or by calcium supplements (to reach a total daily intake of 1000 milligrams per day before menopause or 1500 milligrams per day after menopause), may help to prevent osteoporosis. Regular weight-bearing exercise (like walking and running for an hour, two or three times a week) may also help to prevent osteoporosis. Before you change your calcium intake or exercise habits, it is important to discuss these lifestyle changes with your doctor to find out if they are safe for you.
  Since estrogen use has some risks, only women who are likely to develop osteoporosis should use estrogens for prevention. Women who are likely to develop osteoporosis often have the following characteristics: white or Asian race, slim, cigarette smokers, and a family history of osteoporosis in a mother, sister, or aunt. Women who have relatively early menopause, often because their ovaries were removed during an operation ("surgical menopause"), are more likely to develop osteoporosis than women whose menopause happens at the average age.

WHO SHOULD NOT USE ESTROGENS

Estrogens should not be used:

- **During pregnancy (see Boxed Warning).**
  If you think you may be pregnant, do not use any form of estrogen-containing drug. Using estrogens while you are pregnant may cause your unborn child to have birth defects. Estrogens do not prevent miscarriage.
- **If you have unusual vaginal bleeding which has not been evaluated by your doctor (see Boxed Warning).**
  Unusual vaginal bleeding can be a warning sign of cancer of the uterus, especially if it happens after menopause. Your doctor must find out the cause of the bleeding so that he or she can recommend the proper treatment. Taking estrogens without visiting your doctor can cause you serious harm if your vaginal bleeding is caused by cancer of the uterus.
- **If you have had cancer.**
  Since estrogens increase the risk of certain types of cancer, you should not use estrogens if you have ever had cancer of the breast or uterus, unless your doctor recommends that the drug may help in the cancer treatment. (For certain patients with breast or prostate cancer, estrogens may help.)
- **If you have any circulation problems.**
  Estrogen drugs should not be used except in unusually special situations in which your doctor judges that you need estrogen therapy so much that the risks are acceptable. Men and women with abnormal blood clotting conditions should avoid estrogen use (see DANGERS OF ESTROGENS, below).
- **When they do not work.**
  During menopause, some women develop nervous symptoms or depression. Estrogens do not relieve these symptoms. You may have heard that taking estrogens for years after menopause will keep your skin soft and supple and keep you feeling young. There is no evidence for these claims and such long-term estrogen use may have serious risks.
- **After childbirth or when breastfeeding a baby.**
  Estrogens should not be used to try to stop the breasts from filling with milk after a baby is born. Such treatment may increase the risk of developing blood clots (see DANGERS OF ESTROGENS, below).
  If you are breastfeeding, you should avoid using any drugs because many drugs pass through to the baby in the milk. While nursing a baby, you should take drugs only on the advice of your health care provider.

DANGERS OF ESTROGENS

- **Cancer of the uterus.**
  Your risk of developing cancer of the uterus gets higher the longer you use estrogens and the larger doses you use. One study showed that after women stop taking estrogens, this higher cancer risk quickly returns to the usual level of risk (as if you had never used estrogen therapy). Three other studies showed that the cancer risk stayed high for 8 to more than 15 years after stopping estrogen treatment. Because of this risk, IT IS IMPORTANT TO TAKE THE LOWEST DOSE THAT WORKS AND TO TAKE IT ONLY AS LONG AS YOU NEED IT.
  Using progestin therapy together with estrogen therapy may reduce the higher risk of uterine cancer related to estrogen use (but see OTHER INFORMATION below).
  If you have had your uterus removed (total hysterectomy), there is no danger of developing cancer of the uterus.
- **Cancer of the breast.**
  Most studies have not shown a higher risk of breast cancer in women who have ever used estrogens. However, some studies have reported that breast cancer developed more often (up to twice the usual rate) in women who used estrogens for long periods of time (especially more than 10 years), or who used higher doses for shorter time periods.
  Regular breast examinations by a health professional and monthly self-examination are recommended for all women.
- **Gallbladder disease.**
  Women who use estrogens after menopause are more likely to develop gallbladder disease needing surgery than women who do not use estrogens.
- **Abnormal blood clotting.**
  Taking estrogens may cause changes in your blood clotting system. These changes allow the blood to clot more easily, possibly allowing clots to form in your bloodstream. If blood clots do form in your bloodstream, they can cut off the blood supply to vital organs, causing serious problems. These problems may include a stroke (by cutting off blood to the brain), a heart attack (by cutting off blood to the heart), a pulmonary embolus (by cutting off blood to the lungs), or other problems. Any of these conditions may cause death or serious long term disability. However, most studies of low dose estrogen usage by women do not show an increased risk of these complications.

SIDE EFFECTS

In addition to the risks listed above, the following side effects have been reported with estrogen use:

- Nausea and vomiting.
- Breast tenderness or enlargement.
- Enlargement of benign tumors ("fibroids") of the uterus.
- Retention of excess fluid. This may make some conditions worsen, such as asthma, epilepsy, migraine, heart disease, or kidney disease.
- A spotty darkening of the skin, particularly on the face.

REDUCING RISK OF ESTROGEN USE

If you use estrogens, you can reduce your risks by doing these things:

- **See your doctor regularly.**
  While you are using estrogens, it is important to visit your doctor at least once a year for a check-up. If you develop vaginal bleeding while taking estrogens, you may need further evaluation. If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram (breast x-ray), you may need to have more frequent breast examinations.
- **Reassess your need for estrogens.**
  You and your doctor should reevaluate whether or not you still need estrogens at least every six months.
- **Be alert for signs of trouble.**
  If any of these warning signals (or any other unusual symptoms) happen while you are using estrogens, call your doctor immediately:
  Abnormal bleeding from the vagina (possible uterine cancer)
  Pains in the calves or chest, sudden shortness of breath, or coughing blood (possible clot in the legs, heart, or lungs)
  Severe headache or vomiting, dizziness, faintness, changes in vision or speech, weakness or numbness of an arm or leg (possible clot in the brain or eye)
  Breast lumps (possible breast cancer; ask your doctor or health professional to show you how to examine your breasts monthly)
  Yellowing of the skin or eyes (possible liver problem)
  Pain, swelling, or tenderness in the abdomen (possible gallbladder problem)

OTHER INFORMATION

1. Estrogens increase the risk of developing a condition (endometrial hyperplasia) that may lead to cancer of the lining of the uterus. Taking progestins, another hormone drug, with estrogens lowers the risk of developing this condition. Therefore, if your uterus has not been removed, your doctor may prescribe a progestin for you to take together with your estrogen.
You should know, however, that taking estrogens with progestins may have additional risks. These include:
- unhealthy effects on blood fats (especially a lowering of HDL blood cholesterol, the "good" blood fat which protects against heart disease);
- unhealthy effects on blood sugar (which might make a diabetic condition worse); and
- a possible further increase in breast cancer risk which may be associated with long-term estrogen use.

Some research has shown that estrogens taken without progestins may protect women against developing heart disease. However, this is not certain. The protection shown may have been caused by the characteristics of the estrogen-treated women, and not by the estrogen treatment itself. In general, treated women were slimmer, more physically active, and were less likely to have diabetes than the untreated women. These characteristics are known to protect against heart disease.

You are cautioned to discuss very carefully with your doctor or health care provider all the possible risks and benefits of long-term estrogen and progestin treatments as they affect you personally.

2. Your doctor has prescribed this drug for you and you alone. Do not give the drug to anyone else.
3. If you will be taking calcium supplements as part of the treatment to help prevent osteoporosis, check with your doctor about how much to take.
4. Keep this and all drugs out of the reach of children. In case of overdose, call your doctor, hospital or poison control center immediately.
5. This leaflet provides a summary of the most important information about estrogens. If you want more information, ask your doctor or pharmacist to show you the professional labeling. The professional labeling is also published in a book called the "Physicians' Desk Reference," which is available in book stores and public libraries. Generic drugs carry virtually the same labeling information as their brand name versions.

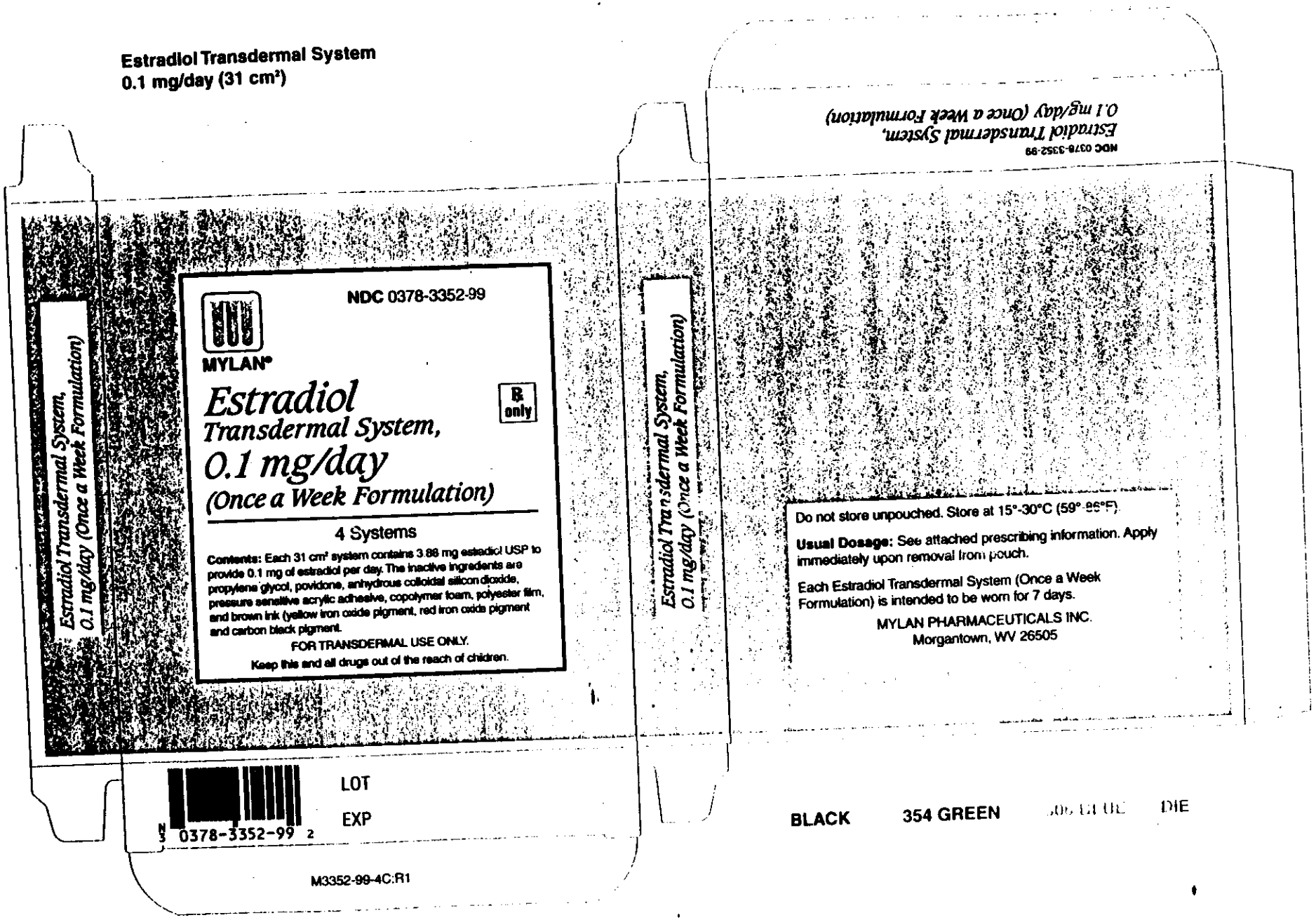
Store at 15° - 30°C (59° - 86°F). Do not store unpouched. Apply immediately upon removal from the protective pouch.

MYLAN®

MYLAN PHARMACEUTICALS INC.
Morgantown, WV 26505

REVISED MAY 99
PL:ETS

Estradiol Transdermal System
0.1 mg/day (31 cm²)



NDC 0378-3352-16

B only

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MYLAN®

Estradiol
Transdermal System,
0.1 mg/day
(Once a Week Formulation)

Contents:

One 31cm^2 system containing 3.86 mg estradiol USP to provide 0.1 mg of estradiol per day. The inactive components are propylene glycol, povidone, anhydrous colloidal silicon dioxide, pressure sensitive acrylic adhesive, copolymer foam, polyester film, and brown ink (yellow iron oxide pigment, red iron oxide pigment and carbon black pigment.)

Do not store unpouched. Store at 15°-30°C (59°-86°F).

MYLAN PHARMACEUTICALS INC.
Morgantown, WV 26505

Face prints PMS 306 Blue, PMS 354 Green, and Black.
110 mm x 110 mm - 6 mm Heat Seal.
Keylines and Heat Seal do not print.

3352:1

Usual Dosage: See patient instructions for application. Apply immediately upon removal from pouch.

Each system is intended to be worn for 7 days.

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

Back prints Black.

"SPECIMEN"

Estradiol Transdermal System
(Once a Week Formulation)
Continuous Delivery for Once-Weekly Application

Rx only

PRESCRIBING INFORMATION

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 in the case of breakthrough or escape 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.

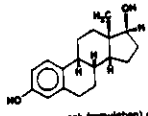
Estrogen therapy during pregnancy is associated with an increased risk of congenital defects in the reproductive organs of the fetus, and possibly other birth defects. Studies of women who received diethylstilbestrol (DES) during pregnancy have shown that female offspring have an increased risk of vaginal 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.

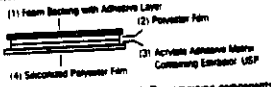
DESCRIPTION

Estradiol Transdermal System (once a week formulation), is designed to release 17β-estradiol continuously upon application to intact skin. Two (15.5 and 31 sq cm active area) systems are available to provide nominal *in vivo* delivery of 0.05 or 0.1 mg respectively, of estradiol per day. The period of use is 7 days. Each system has a contact surface area of 15.5 or 31 sq cm, and contains 1.94 or 3.88 mg of estradiol USP respectively.

Estradiol USP (17β-estradiol) is a white, crystalline powder, chemically described as Estra-1,3,5(10)-triene-3,17β-diol. It has a molecular formula of $C_{18}H_{24}O_2$ and molecular weight of 272.39. The structural formula is:



The Estradiol Transdermal System (once a week formulation) comprises three layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are (1) foam backing with adhesive layer, (2) a polyester film, (3) an acrylate adhesive matrix containing estradiol USP. A protective liner (4) of siliconized 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 (propylene glycol, povidone, anhydrous colloidal silicon dioxide, pressure sensitive acrylic adhesive copolymer foam, polyester film, and brown ink) are pharmacologically inactive.

CLINICAL PHARMACOLOGY

The Estradiol Transdermal System (once a week formulation) provides systemic estrogen replacement therapy by releasing 17β-estradiol, the major estrogenic hormone secreted by the human ovary.

Estrogens are important in the development and maintenance of the female reproductive system and secondary sex characteristics. By a direct action, they cause growth and development of the uterus, fallopian tubes, and vagina. With other hormones, such as pituitary hormones and progesterone, they cause enlargement of the breasts through promotion of ductal growth, stromal development, and the accretion of fat. Estrogens are intricately involved with other hormones, especially progesterone, in the processes of the ovulatory menstrual cycle and pregnancy, and affect the release of pituitary gonadotropins. They also contribute to the shaping of the skeleton, maintenance of tone and elasticity of urogenital structures, changes in the complexion of the long bones that allow for the pubertal growth spurt and its termination, and pigmentation of the nipples and genitals.

Estrogens occur naturally in several forms. The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 micrograms of estradiol daily, depending on the phase of the menstrual cycle. This is converted primarily to estrone, which circulates in roughly equal proportion to estradiol and to small amounts of estriol. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus estrone - especially in its sulfate ester form - is the most abundant circulating estrogen in postmenopausal women. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than estrone or estriol at the receptor.

Estrogen drug products act by regulating the transcription of a limited number of genes. Estrogens diffuse through cell membranes, distribute themselves throughout the cell, and bind to and activate the nuclear estrogen receptor, a DNA-binding protein which is found in estrogen-responsive tissues. The activated estrogen receptor binds to specific DNA sequences, or hormone-response elements, which enhance the transcription of adjacent genes and in turn lead to the observed effects. Estrogen receptors have been identified in tissues of the reproductive tract, breast, pituitary, hypothalamus, liver, and bone of women.

Estrogens used in therapy are well absorbed through the skin, mucous membranes, and gastrointestinal tract. Administered estrogens and their esters are handled within the body essentially the same as the endogenous hormones. Metabolic conversion of estrogens occurs primarily in the liver (first pass effect), but also at local target tissue sites. Complex metabolic processes result in a dynamic equilibrium of circulating conjugated and unconjugated estrogenic forms, which are continually interconverted, especially between estrone and estradiol and between esterified and unesterified forms. Although naturally-occurring estrogens circulate in the blood largely bound to sex hormone-binding globulin and albumin, only unbound estrogens enter target tissue cells. A significant proportion of the circulating estrogen exists as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogenic species. A certain proportion of the estrogen is excreted into the bile and then reabsorbed from the intestine. During this enterohepatic recirculation, estrogens are desulfated and resulfated and undergo degradation through conversion to less active estrogens (estriol and other estrogens), oxidation to nonestrogenic substances (catecholestrogens, which interact with catecholamine metabolism, especially in the central nervous system), and conjugation with glucuronic acids (which are then rapidly excreted in the urine).

When given orally, naturally-occurring estrogens and their esters are extensively metabolized (first pass effect) and circulate primarily as estrone sulfate, with smaller amounts of other conjugated and unconjugated estrogenic species. This results in limited oral potency. In contrast, the skin metabolizes estradiol only to a small extent. Therefore, transdermal administration produces therapeutic serum levels of estradiol with lower circulating levels of estrone and estrone conjugates, and requires smaller total doses than does oral therapy. Because estradiol has a short half-life, transdermal administration of estradiol allows a rapid decline in blood levels after the Estradiol Transdermal System (once a week formulation) is removed.

Pharmacokinetics

Transdermal administration of estradiol is reported to produce mean serum concentrations of estradiol comparable to those produced by daily oral administration of estradiol at about 20 times the daily transdermal dose.

In a 3-week multiple-application study in 24 postmenopausal women, the 0.1 mg/day Estradiol Transdermal System (once a week formulation) produced average peak estradiol concentrations of approximately 100 pg/mL. Trough values at the end of each wear interval 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 80 and 40 pg/mL, respectively. Because estradiol has a short half-life (approximately 1 hour), serum concentrations of estradiol and estrone returned to preapplication levels within 6 to 24 hours after removal of the test system (in less than 17 pg/mL of estradiol and 30 pg/mL estrone).

Linear pharmacokinetics have been demonstrated for the Estradiol Transdermal System (once a week formulation), in a 3-week application study in 54 postmenopausal women, the 0.1 mg/day system produced estradiol serum level profiles and pharmacokinetic parameters that were twice as high as the 0.05 mg/day system. Statistical analyses confirmed the 2:1 dose proportionality.

On average, the Estradiol Transdermal System, 0.1 mg/day (once a week formulation) maintained mean steady-state serum estradiol levels of approximately 70 pg/mL, and the Estradiol Transdermal System, 0.05 mg/day (once a week formulation) maintained mean steady-state serum estradiol levels of approximately 35 pg/mL.

Table 1 summarizes the mean results from four pharmacokinetic studies. All systems were applied on the abdomen for a single 1-week period. C_{max} occurred at approximately 30 hours.

Table 1
Pharmacokinetic Summary

Surface Area) (sq cm)	Delivery Rate (mg/day)	C_{max} (pg/mL)	C_{min} (pg/mL)	C_{avg} (pg/mL)
15.5	0.05	58-82	20-32	33-45
31	0.1	96-172	39-61	53-93

The relative standard deviation of each pharmacokinetic parameter averaged 50%, which is indicative of the considerable intersubject variability associated with transdermal drug delivery.

Two studies compared a single, 1-week application of the Estradiol Transdermal System (once a week formulation) with consecutive 3-day and 4-day applications of Estradiol Transdermal System (twice a week formulation). The Estradiol Transdermal System, 0.1 mg/day (once a week formulation) was compared with the Estradiol Transdermal System (twice a week formulation) 0.1 mg/day system (see Figure 1); the Estradiol Transdermal System, 0.05 mg/day (once a week formulation) was compared to the Estradiol Transdermal System (twice a week formulation) 0.05 mg/day system (see Figure 2). For a 1-week treatment period, both doses of Estradiol Transdermal Systems (once a week formulation) maintained significantly lower peak and mean steady-state levels than did the Estradiol Transdermal System (twice a week formulation); however, towards the end of each treatment period, the Estradiol Transdermal Systems (once a week formulation) maintained similar (day 6) or higher (day 7) serum estradiol levels than did the Estradiol Transdermal System (twice a week formulation). As a result, the peak-to-end of application interval trough level fluctuations were 3- to 4- times less with the Estradiol Transdermal System (once a week formulation).

Figure 1
Mean Serum Levels for a One-Week Application of The Estradiol Transdermal System (Once a Week Formulation) (0.1 mg/day) and Consecutive Three-Day and Four-Day Applications of the Estradiol Transdermal System (Twice a Week Formulation) (0.1 mg/day)

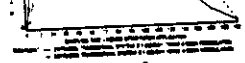


Figure 2
Mean Serum Levels for a One-Week Application of the Estradiol Transdermal System (Once a Week Formulation) (0.05 mg/day) and Consecutive Three-Day and Four-Day Applications of the Estradiol Transdermal System (Twice a Week Formulation) (0.05 mg/day)

INDICATIONS AND USAGE

Estradiol Transdermal System (once a week formulation) 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.

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 to 2.0) in those taking higher doses or those taking lower doses for prolonged periods of time, especially in excess of 10 years. Other studies have not shown this relationship.

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 prostrate 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 lessened 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 progestins are needed to provide maximal maturation of the endometrium and to reduce the likelihood of hyperplastic changes.

There are, however, possible risks which 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 reduced risk of cardiovascular disease in postmenopausal women has not been proven. Furthermore, the risk of cardiovascular disease in postmenopausal women has not been proven to be an estrogen deficiency 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 which espoused 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. Thus, ongoing and future large-scale randomized trials may fail to confirm this apparent benefit. (2) Current medical practice often includes the use of concomitant progestin therapy with most often (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 estrogen 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 hypertriglyceridemia.** 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 which 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 beta-thromboglobulin; 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, 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 Estradiol Transdermal System (once a week formulation) 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 0.05 mg/day system and 5.3% for the 0.1 mg/day system compared with 11.5% for the placebo system. In a 3-week comparative skin irritation study with Estradiol Transdermal System (twice a week formulation), 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

Estradiol Transdermal System (once a week formulation) and 31% of Estradiol Transdermal System (once a week formulation) subjects. Clinically significant erythema (mild erythema associated with symptoms or moderate to severe erythema) was evident at the end of week three in 11% of Estradiol Transdermal System (once a week formulation) and 9% of Estradiol Transdermal System (once a week formulation) 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 Estradiol Transdermal System (once a week formulation) should be placed on a clean, dry area of the abdomen. *Estradiol Transdermal System (once a week formulation) should not be applied to the breasts.* The sites of application must be rotated, with an interval of at least 1 week 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. 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. 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. Only one system should be worn at any one time during the 7-day dosing interval.

Initiation of Therapy

Treatment is usually initiated with the 15.5 sq cm (0.05 mg/day) Estradiol Transdermal System (once a week formulation) 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 Estradiol Transdermal System (once a week formulation), 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 Estradiol Transdermal System (once a week formulation) can be initiated at once. In women who are currently taking oral estrogen, treatment with the Estradiol Transdermal System (once a week formulation) can be initiated 1 week after withdrawal of oral therapy or sooner if symptoms reappear in less than 1 week.

Therapeutic Regimen

Therapy with the Estradiol Transdermal System (once a week formulation) is usually administered on a cyclic schedule (e.g., 3 weeks of therapy followed by 1 week without), especially in women with an intact uterus, who are not using concomitant progestin therapy.

HOW SUPPLIED

Description

Estradiol Transdermal System (once a week formulation) is designed to release 17β-estradiol continuously upon application to intact skin. Two (15.5 and 31 sq cm active area) systems are available to provide nominal *in vivo* delivery of 0.05 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 15.5 or 31 sq cm, and contains 1.94 or 3.88 mg of estradiol USP respectively.

Estradiol Transdermal System, 0.05 mg/day (Once a Week Formulation) - each 15.5 sq cm system contains 1.94 mg of estradiol USP — NDC 0378-3350-99
Individual Carton of 4 systems

Estradiol Transdermal System, 0.1 mg/day (Once a Week Formulation) - each 31 sq cm system contains 3.88 mg of estradiol USP — NDC 0378-3352-99
Individual Carton of 4 systems

Store at 15° - 30°C (59° - 86°F). Do not store unpouched. Apply immediately upon removal from the protective pouch.

MYLAN®

MYLAN PHARMACEUTICALS INC
Morgantown WV 26505

REVISED June 1998
ETS R1

PATIENT INFORMATION
Estradiol Transdermal System (Once a Week Formulation)
Continuous Delivery for Once-Weekly Application

Rx only

INFORMATION FOR THE PATIENT

INTRODUCTION

The Estradiol Transdermal System (once a week formulation) that your doctor has prescribed for you releases small amounts of estradiol through the skin in a continuous way. Estradiol is the same hormone that your ovaries produce abundantly before menopause. The dose of estradiol you require will depend upon your individual response. The dose is adjusted by the size of the Estradiol Transdermal System (once a week formulation) used. The systems are available in two sizes.

This leaflet describes when and how to use estrogens, and the risks and benefits of estrogen treatment.

Estrogens have important benefits but also some risks. You must decide, with your doctor, whether the risks to you of estrogen use are acceptable because of their benefits. If you use estrogens, check with your doctor to be sure you are using the lowest possible dose that works, and that you don't use them longer than necessary. How long you need to use estrogens will depend on the reason for use.

1. ESTROGENS INCREASE THE RISK OF CANCER OF THE UTERUS IN WOMEN WHO HAVE HAD THEIR MENOPAUSE ("CHANGE OF LIFE").
If you use any estrogen-containing drug, it is important to visit your doctor regularly and report any unusual vaginal bleeding right away. Vaginal bleeding after menopause may be a warning sign of uterine cancer. Your doctor should evaluate any unusual vaginal bleeding to find out the cause.

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.
Estrogens do not prevent miscarriage (spontaneous abortion) and are not needed in the days following childbirth. If you take estrogens during pregnancy, your unborn child has a greater than usual chance of having birth defects. The risk of developing these defects is small, but clearly larger than the risk in children whose mothers did not take estrogens during pregnancy. These birth defects may affect the baby's urinary system and sex organs. Daughters born to mothers who took DES (an estrogen drug) have a higher than usual chance of developing cancer of the vagina or cervix when they become teenagers or young adults. Sons may have a higher than usual chance of developing cancer of the testicles when they become teenagers or young adults.

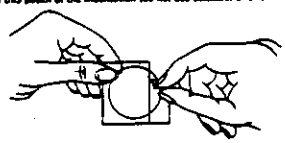
INFORMATION ABOUT ESTRADIOL TRANSDERMAL SYSTEM (ONCE A WEEK FORMULATION)

How The Estradiol Transdermal System (Once a Week Formulation) Works

The Estradiol Transdermal System (once a week formulation) contains 17β-estradiol. When applied to the skin as directed below, the Estradiol Transdermal System (once a week formulation) releases 17β-estradiol, which flows through the skin into the bloodstream.

How and Where to Apply the Estradiol Transdermal System (Once a Week Formulation)

Each Estradiol Transdermal System (once a week formulation) is individually sealed in a protective pouch. Tear open this pouch at the indentation (do not use scissors) and remove the system.



A protective liner covers the adhesive side of the system - the side that will be placed against your skin. This liner must be removed before applying the system. Remove the protective liner and discard it. Try to avoid touching the adhesive.

Apply the adhesive side of the system to a clean, dry area of skin on the abdomen. *Do not apply the Estradiol Transdermal System (once a week formulation) to your breasts.* The sites of application must be rotated, with an interval of at least 1 week allowed between applications to a particular site. The area selected should not be oily, damaged, or irritated. Avoid the waistline, since tight clothing may rub and remove the system. Apply the system immediately after opening the pouch and removing the protective liner. Press the system firmly in place with the fingers for about 10 seconds, making sure there is a good contact, especially around the edges.

The Estradiol Transdermal System (once a week formulation) should be worn continuously for one week. You may wish to experiment with different locations when applying a new system, to find ones that are most comfortable for you and where clothing will not rub on the system.

When to Apply the Estradiol Transdermal System (Once a Week Formulation)

The Estradiol Transdermal System (once a week formulation) should be changed once weekly.

When changing the system, remove the used Estradiol Transdermal System (once a week formulation) and discard it. Any adhesive that might remain on your skin can be easily rubbed off. Then place the new Estradiol Transdermal System (once a week formulation) on a different skin site. (The same skin site should not be used again for at least 1 week after removal of the system.)

Contact with water when you are bathing, swimming, or showering will not affect the system. 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.

USES OF ESTROGENS

(Not every estrogen drug is approved for every use listed in this section. If you want to know which of these possible uses are approved for the medicine prescribed for you, ask your doctor or pharmacist to show you the professional labeling. You can also look up the specific estrogen product in a book called the "Physicians' Desk Reference", which is available in many book stores and public libraries. Generic drugs carry virtually the same labeling information as their brand name versions.)

- **To reduce moderate or severe menopausal symptoms.**
  Estrogens are hormones made by the ovaries of normal women. Between ages 45 and 55, the ovaries normally stop making estrogens. This leads to a drop in body estrogen levels which causes the "change of life" or menopause (the end of monthly menstrual periods). If both ovaries are removed during an operation before natural menopause takes place, the sudden drop in estrogen levels causes "surgical menopause".
  When the estrogen levels begin dropping, some women develop very uncomfortable symptoms, such as feelings of warmth in the face, neck, and chest, or sudden intense episodes of heat and sweating ("hot flashes" or "hot flushes"). Using estrogen drugs can help the body adjust to lower estrogen levels and reduce these symptoms. Most women have only mild menopausal symptoms or none at all and do not need to use estrogen drugs for these symptoms. Others may need to take estrogens for a few months while their bodies adjust to lower estrogen levels. The majority of women do not need estrogen replacement for longer than six months for these symptoms.
- **To treat vulval and vaginal atrophy** (itching, burning, dryness in or around the vagina, difficulty or burning on urination) associated with menopause.
- **To treat certain conditions in which a young woman's ovaries do not produce enough estrogen naturally.**
- **To treat certain types of abnormal vaginal bleeding due to hormonal imbalance when your doctor has found no serious cause of the bleeding.**
- **To treat certain cancers in special situations, in men and women.**
- **To prevent thinning of bones.**
  Osteoporosis is a thinning of the bones that makes them weaker and allows them to break more easily. The bones of the spine, wrists and hips break most often in osteoporosis. Both men and women start to lose bone mass after about age 40, but women lose bone mass faster after the menopause. Using estrogens after the menopause slows down bone thinning and may prevent bones from breaking. Lifelong adequate calcium intake, either in the diet (such as dairy products) or by calcium supplements (to reach a total daily intake of 1000 milligrams per day before menopause or 1500 milligrams per day after menopause), may help to prevent osteoporosis. Regular weight-bearing exercise (like walking and running for an hour, two or three times a week) may also help to prevent osteoporosis. Before you change your calcium intake or exercise habits, it is important to discuss these lifestyle changes with your doctor to find out if they are safe for you.
  Since estrogen use has some risks, only women who are likely to develop osteoporosis should use estrogens for prevention. Women who are likely to develop osteoporosis often have the following characteristics: white or Asian race, slim, cigarette smokers, and a family history of osteoporosis in a mother, sister, or aunt. Women who have relatively early menopause, often because their ovaries were removed during an operation ("surgical menopause"), are more likely to develop osteoporosis than women whose menopause happens at the average age.

WHO SHOULD NOT USE ESTROGENS

Estrogens should not be used:

- **During pregnancy (see Boxed Warning).**
  If you think you may be pregnant, do not use any form of estrogen-containing drug. Using estrogens while you are pregnant may cause your unborn child to have birth defects. Estrogens do not prevent miscarriage.
- **If you have unusual vaginal bleeding which has been evaluated by your doctor (see Boxed Warning).**
  Unusual vaginal bleeding can be a warning sign of cancer of the uterus, especially if it happens after menopause. Your doctor must find out the cause of the bleeding so that he or she can recommend the proper treatment. Taking estrogens without visiting your doctor can cause you serious harm if your vaginal bleeding is caused by cancer of the uterus.
- **If you have had cancer.**
  Since estrogens increase the risk of certain types of cancer, you should not use estrogens if you have ever had cancer of the breast or uterus, unless your doctor recommends that the drug may help in the cancer treatment. (For certain patients with breast or prostate cancer, estrogens may help.)
- **If you have any circulatory problems.**
  Estrogen drugs should not be used except in unusually special situations in which your doctor judges that you need estrogen therapy so much that the risks are acceptable. Men and women with abnormal blood clotting conditions should avoid estrogen use (see DANGERS OF ESTROGENS, below).
- **When they do not work.**
  During menopause, some women develop nervous symptoms or depression. Estrogens do not relieve these symptoms. You may have heard that taking estrogens for years after menopause will keep your skin soft and supple and keep you feeling young. There is no evidence for these claims and such long-term estrogen use may have serious risks.
- **After childbirth or when breastfeeding a baby.**
  Estrogens should not be used to try to stop the breasts from filling with milk after a baby is born. Such treatment may increase the risk of developing blood clots (see DANGERS OF ESTROGENS, below).

If you are breastfeeding, you should avoid using any drugs because many drugs pass through to the baby in the milk. While nursing a baby, you should take drugs only on the advice of your health care provider.

DANGERS OF ESTROGENS

- **Cancer of the uterus.**
  Your risk of developing cancer of the uterus gets higher the longer you use estrogens and the larger the doses you use. One study showed that after women stop taking estrogens, this high cancer risk quickly returns to the usual level of risk (as if you had never used estrogen therapy). Three other studies showed that the cancer risk stayed high for 5 to more than 15 years after stopping estrogen treatment. Because of this risk, **IT IS IMPORTANT TO TAKE THE LOWEST DOSE THAT WORKS AND TO TAKE IT ONLY AS LONG AS YOU NEED IT.**
  Using progestin therapy together with estrogen therapy may reduce the higher risk of uterine cancer related to estrogen use (but see OTHER INFORMATION below).
  If you have had your uterus removed (total hysterectomy), there is no danger of developing cancer of the uterus.
- **Cancer of the breast.**
  Most studies have not shown a higher risk of breast cancer in women who have ever used estrogens. However, some studies have reported that breast cancer developed more often (up to twice the usual rate) in women who used estrogens for long periods of time (especially more than 10 years), or who used higher doses for shorter time periods.
  Regular breast examinations by a health professional and monthly self-examination are recommended for all women.
- **Gallbladder disease.**
  Women who use estrogens after menopause are more likely to develop gallbladder disease needing surgery than women who do not use estrogens.
- **Abnormal blood clotting.**
  Taking estrogens may cause changes in your blood clotting system. These changes allow the blood to clot more easily, possibly allowing clots to form in your bloodstream. If blood clots do form in your bloodstream, they can cut off the blood supply to vital organs, causing serious problems. These problems may include a stroke (by cutting off blood to the brain), a heart attack (by cutting off blood to the heart), a pulmonary embolus (by cutting off blood to the lungs), or other problems. Any of these conditions may cause death or serious long term disability. However, most studies of low dose estrogen usage by women do not show an increased risk of these complications.

SIDE EFFECTS

In addition to the risks listed above, the following side effects have been reported with estrogen use:

- Nausea and vomiting
- Breast tenderness or enlargement
- Enlargement of benign tumors ("fibroids") of the uterus
- Retention of excess fluid. This may make some conditions worsen, such as asthma, epilepsy, migraine, heart disease, or kidney disease.
- A spotty darkening of the skin, particularly on the face

REDUCING RISK OF ESTROGEN USE

If you use estrogens, you can reduce your risks by doing these things:

- **See your doctor regularly.**
  While you are using estrogens, it is important to visit your doctor at least once a year for a check-up. If you develop vaginal bleeding while taking estrogens, you may need further evaluation. If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram (breast x-ray), you may need to have more frequent breast examinations.
- **Reassess your need for estrogens.**
  You and your doctor should reevaluate whether or not you still need estrogens at least every six months.
- **Be alert for signs of trouble.**
  If any of these warning signals (or any other unusual symptoms) happen while you are using estrogens, call your doctor immediately:
  Abnormal bleeding from the vagina (possible uterine cancer)
  Pains in the calves or chest, sudden shortness of breath, or coughing blood (possible clot in the legs, heart, or lungs)
  Severe headache or vomiting, dizziness, faintness, changes in vision or speech, weakness or numbness of an arm or leg (possible clot in the brain or eye)
  Breast lumps (possible breast cancer; ask your doctor or health professional to show you how to examine your breasts monthly)
  Yellowing of the skin or eyes (possible liver problem)
  Pain, swelling, or tenderness in the abdomen (possible gallbladder problem)

OTHER INFORMATION

1. Estrogens increase the risk of developing a condition (endometrial hyperplasia) that may lead to cancer of the lining of the uterus. Taking progestins, another hormone drug, with estrogens lowers the risk of developing this condition. Therefore, if your uterus has not been removed, your doctors may prescribe a progestin for you to take together with your estrogen.
   You should know, however, that taking estrogens *with* progestins may have additional risks. These include:
   - unhealthy effects on blood fats (especially a lowering of HDL blood cholesterol, the "good" blood fat which protects against heart disease);
   - unhealthy effects on blood sugar (which might make a diabetic condition worse), and
   - a possible further increase in breast cancer risk which may be associated with long-term estrogen use.

   Some research has shown that estrogens taken *without* progestins may protect women against developing heart disease. However, this is not certain. The protection shown may have been caused by the characteristics of the estrogen-treated women, and not by the estrogen treatment itself. In general, treated women were slimmer, more physically active, and were less likely to have diabetes than the untreated women. These characteristics are known to protect against heart disease.
   You are cautioned to discuss very carefully with your doctor or health care provider all the possible risks and benefits of long-term estrogen and progestin treatments as they affect you personally.
2. Your doctor has prescribed this drug for you and you alone. Do not give the drug to anyone else.
3. If you will be taking calcium supplements as part of the treatment to help prevent osteoporosis, check with your doctor about how much to take.
4. Keep this and all drugs out of the reach of children. In case of overdose, call your doctor, hospital or poison control center immediately.
5. This leaflet provides a summary of the most important information about estrogens. If you want more information, ask your doctor or pharmacist to show you the professional labeling. The professional labeling is also published in a book called the "Physicians' Desk Reference", which is available in book stores and public libraries. Generic drugs carry virtually the same labeling information as their brand name versions.

Store at 15° - 30°C (59° - 86°F). Do not store unpouched. Apply immediately upon removal from the protective pouch.

MYLAN®

MYLAN PHARMACEUTICALS INC
Morgantown WV 26505

REVISED June 1998
PL ETS R1

FEB 24

0190-R1 0.1 mg/day 4-12-99.

"SPECIMEN"

Estradiol 0.1 mg/day (Once Weekly)

CENTER FOR DRUG EVALUATION AND RESARCH

Application Number 75-182

MEDICAL REVIEW(S)

ATTACHMENT 2

MEDICAL OFFICER REVIEW

May 7, 1999

ANDA 75-182
75-233

Drug Product: Estradiol Transdermal System, 0.1 mg/day and 0.05 mg/day
Sponsor: Bertek Inc.

Reference Listed Drug: Climara Estradiol Transdermal System (Berlex, Inc.)

Regulatory History

In correspondence dated February 24, 1998, the Office of Generic Drugs recommended that Mylan/Bertek conduct a 21-day cumulative irritation study on this product. This was the usual requirement for transdermal products and was particularly important because the Bertek product contains a greater amount of propylene glycol (21%) than was present in other transdermal products. Bertek sent an amendment to their original application on May 28, 1998. This amendment included two studies: a primary dermal irritation study (test vs. reference for a single application) and a repeat insult study (test vs. placebo for 21 days with subsequent evaluation for contact sensitization). These studies were found to establish similar patterns of adhesion of the test and reference products and acceptable contact sensitization for the test product. The requirement for cumulative skin irritation comparing test vs. reference was not addressed adequately, however. The sponsor was in touch with the Office of Generic Drugs to discuss this in April 1999. They had completed a 21-day skin irritation study that compared test vs. reference, and they wanted to know if it would be necessary to submit it. It was agreed that they would submit it for review to complete the requirements for skin irritation studies.

Title

A 21-Day Evaluation of Cumulative Skin Irritation Potential in Humans for a 0.05 mg/day Estradiol Transdermal Patch

CRO: Hilltop Research, Inc.

Study Objective

To evaluate the cumulative irritation potential of Estradiol Transdermal Systems, manufactured by Bertek, Inc., relative to that of the reference product, Climara (Berlex, Inc.) following repetitive topical application over a 21-day period.

Study Design

This was a blinded (to scorer) study comparing the skin irritation of three test articles:

1. Estradiol Transdermal System 0.05 mg/day
2. Climara Transdermal System 0.05 mg/day
3. Estradiol Transdermal System placebo

The transdermal patches were applied for 7 days each for a total of 3 consecutive applications. Scoring for irritation was done prior to re-application of a new patch and after removal of the last patch. Any site reaching maximum irritation (score of 3 or greater) was not re-patched but it continued to be scored until the end of the study. The study

enrollment was set to have 25 "completers" – subjects who satisfied all entry criteria and completed all required visits. Patients who withdrew were not replaced.

Inclusion and Exclusion Criteria

Inclusion Criteria

1. Females, 18 years of age or older.
2. Absence of menses for one year for post-menopausal subjects, or at least 6 weeks for oophorectomized subjects. For oophorectomized subjects, an operative report documenting bilateral oophorectomy and a surgical pathology report documenting the absence of malignant disease must be available for review.
3. Signed informed consent.
4. Minor deviations in normal medical history, physical examination and clinical laboratory results, considered to be clinically insignificant by the Investigator/Sub-Investigator and the Mylan monitor will be permitted.
5. Baseline 17-beta-estradiol plasma serum level </= 20 pg/ml.
6. Baseline FSH serum levels > 40 mIU/ml.

Exclusion Criteria

1. Male; premenopausal, perimenopausal or pregnant, lactating females.
2. History of any significant chronic disease or medical condition which, in the Investigator's judgement, makes the subject ineligible or places the subject at undue risk as determined by a prestudy medical evaluation performed within 14 days of the initial dose of study medication:
    a. Physical examination
    b. Breast examination
    c. Pelvic examination consistent with hypoestrogenism
    d. Mammogram – if not done in the last 12 months
    e. Papanicolaou smear – if not done in the last 12 months
    f. Clinical laboratory evaluation (chemistry/hematology/urinalysis)
    g. 12-lead EKG
3. Active clinically significant skin diseases which may contraindicate participation, including eczema, psoriasis and atopic dermatitis.
4. Any acute illness or surgery within the past four weeks.
5. Participation in a patch test for irritation or sensitization within the last 30 days.
6. Topical drugs used at patch site.
7. Damaged skin in or around test sites which include sunburn, uneven skin tones, tattoos, scars or other disfiguration of the test site.
8. Allergy or hypersensitivity to any of the components of the transdermal system (i.e., adhesive dressings, medical tape, band-aids), estradiol or other hormonal products.
9. History of drug and/or alcohol abuse.
10. Subjects who have received an investigational drug within the last 30 days of the initiation of this study or who are currently participating in or plan to enter a clinical study.
11. Use of any systemic antibiotic, estrogens, or hormone within a minimum of 4 weeks prior to the initial dose of study medication.
12. Unwillingness or inability to sign consent.
13. Known or suspected breast cancer.
14. Known or suspected estrogen-dependent neoplasia.
15. Active thrombophlebitis or thromboembolic disorders.
16. Any undiagnosed vaginal bleeding.
17. Insulin-dependent diabetes.
18. Asthma that requires prescribed medication.
19. Immunological disorders such as HIV positive, AIDS and systemic lupus erythematosus.
20. Use of any prescribed anti-inflammatory drug, immunosuppressive drugs or prescription or non prescription antihistamine medication (steroid nose drops and/or eye drops are permitted) within 14 days of dosing and

throughout the study. Any over-the-counter pain medication that is ingested in quantities exceeding label instructions within 14-days of dosing and throughout the study.

Study Conduct

Sixty-six individuals were screened. A medical history, physical examination, and laboratory testing was completed and subjects' eligibility was determined according to the inclusion/exclusion criteria listed above. Thirty subjects were enrolled in the study and 29 completed the study. Transdermal patches were applied to the abdomen at the same site for the duration of the study unless the maximum allowable irritation limit was reached (a score of 3 or greater or a letter grade of F, G, or H).

The primary measurement was the evaluation of irritation using a validated scoring system. Skin evaluations were conducted 30 minutes after removal of the first, second, and third patch by trained blinded scorers. Scoring was done by trained individuals. The protocol states that all attempts would be made to have a single individual do all the scoring but the final report does not specify if this was the case or not. The scorer was blinded to the treatment assignments and all prior scores. The following scale was used to quantify irritation:

0 = No evidence of irritation
1 = Minimal erythema, barely perceptible
2 = Definite erythema, readily visible; or minimal edema; or minimal papular response
3 = Erythema and papules
4 = Definite edema
5 = Erythema, edema and papules
6 = Vesicular eruption
7 = Strong reaction spreading beyond the test site

Effects on the superficial layers of the skin were scored as follows:

A = Slight glazed appearance
B = Marked glazing
C = Glazing with peeling and cracking
F = Glazing with fissures
G = Film of dried serous exudate covering all or portion of patch site
H = Small petechial erosions and/or scabs

Several maximum limits were defined for these scores. When a numerical score of 3, 4, 5, 6, or 7 was reached or any numerical score was appended with the letter grade of F, G, or H, no further applications of test material were made. However, this site continued to be scored to the end of the 21-day study period. In this situation, a score of 3 was entered for all scores through the remainder of the study. The letter grades were converted to numerical scores as follows: A = 0, B = 1, C = 2, and F, G, and H = 3. These numerical equivalents were considered additive to the numerical score (e.g., 2C = 2 + 2 = 4). They were added in the calculation of the total irritancy score for the entire cohort. The upper limit individual score selected was 3. All scores were calculated and those above this were entered as 3 in order to maintain the focus on evaluation of mild irritation expected for these products. Statistical analysis was carried out on the total irritation for each test day and overall, ranked within each subject, and analyzed using the Friedman rank sum method. The hypotheses for this test were as follows:

Ho: The rank sums of the three test articles are identical.
Ho: At least two of the rank sums differ.

Fisher's LSD test was performed if significant differences ($p</=0.05$) were observed with the Friedman rank sum test.

Concomitant medications and adverse events were recorded at each visit. The Investigator determined the severity and relatedness of adverse events to the test material.

Study Results

All primary data was provided by the Applicant and reviewed by the Medical Officer in tandem with review of the mean and cumulative data presented by the Applicant.

Thirty subjects were enrolled and patched between July 7, 1998 and July 28, 1998. One subject withdrew from the study because they were "going out town". There were 11 protocol violations. In 4 subjects the patch contact time of 8 patches at one application was reduced to 15, 36, 49, 76, and 167 hours. This involved 2 Estradiol, 3 Climara, and 3 placebo patches. Three subjects had laboratory values that were slightly out of the range specified in the Inclusion criteria (FSH level of 39.1 instead of >40 mIU/ml, FSH level of 38.3 instead of >40 mIU/ml, and Estradiol level of 21 instead of </= 20 pg/ml). In three subjects patches were reapplied after being "lost". This occurred on Day 2 (1) and Day 4 (2), patches were reapplied within 11 to 18 hours, and all three patches applied per subject were involved. One subject was erroneously patched using the incorrect randomization scheme.

Demographics

Twenty-six subjects (87%) were Caucasian and four were African-American (13%). The age distribution of the Caucasian subjects was 45 to 81 and the African-American subjects ranged in age from 52 to 74 years old.

Concomitant Medications

Twenty subjects who had not had a hysterectomy were also treated with Provera 10 mg following the final patch to minimize the risks of unopposed estradiol administration. In addition, 7 subjects took concomitant medications for hypertension, blood thinning, reduction of cholesterol, arthritis pain (Advil), yeast infection, kidney infection and associated pain, and headache. None of these medications were forbidden by the study protocol.

Adverse Events

Thirteen subjects experienced 27 events involving 18 different adverse events. Of these, 8 events in 9 subjects were determined to have a Possible, Probable, or Highly Probable relationship to the study drug. Only one of these events was a local reaction to the transdermal patch and/or its active drug product. These events are presented in the Table below.

Table I
Adverse events with a Possible, Probable, or Highly Probable relationship to the study drug.

	# of subjects	Mild	Moderate	Severe	# of occurrences
Highly Probable					
Itching on site B	1	0	1	0	1
Probable					
Breast Tenderness	2	1	1	0	2
Breast Soreness	3	2	2	0	4
Soreness in Nipples	3	1	3	0	4
Possible	**# of subjects**	**Mild**	**Moderate**	**Severe**	**# of occurrences**
Moodiness	1	0	0	1	1
Headache	1	0	1	0	1
Cramping (intermittent)	1	0	1	0	1
Cramping	1	1	0	0	1

Mean Irritation Scores

The mean scores for each evaluation day were calculated. Cumulative irritation was noted for all the patch types characterized as minimal to definite erythema. The mean scores are summarized in the table below (Table II).

Table II
Mean Irritation Scores

Test Article	Day 8 (n=29)	Day 15 (n=28)	Day 22 (n=29)	Overall (n=28)
Estradiol	0.793	0.964	1.172	2.857
Climara	0.862	0.821	1.000	2.750
Placebo	0.621	0.643	0.966	2.214
p-values	0.1935	0.0121	0.2050	0.0222
Significant LSD comparisons	None	Estradiol vs. placebo	None	Estradiol vs. placebo

The Estradiol transdermal system was significantly more irritating overall and at Day 15 than its placebo indicating that the active drug product contributed to the irritation. The mean scores did not differ on Day 22 and the scores for Estradiol and Climara were similar at all evaluations. Letter scores were assigned to one subject in each group: glazing and fissures, Estradiol and Placebo patches and papules, Climara patch.

Total Cumulative Irritation

Total cumulative irritation was similar for the two active patches and a little less in the placebo patch group. These figures were adjusted because of differences in sample size in each group at each visit to a base of 10 subjects. These results are similar to overall cumulative irritation and are displayed in Table III.

Table III
Cumulative Irritation Scores

	Cumulative Irritation	Base 10 Cumulative Irritation
Estradiol	87	30
Climara	77	27
Placebo	65	22

The distribution of scores at each evaluation day is shown in Table IV below. The majority of the scores for all groups were 1+. One-third of subjects in the placebo group had with scores of 0 throughout the application period.

Table IV
Proportion of subjects with individual scores of 0, 1+, 2+, and 3+ at each evaluation time

Score	Day 8			Day 15			Day 22		
	E	C	P	E	C	P	E	C	P
0	8	9	13	3	7	13	2	5	13
1	19	16	14	23	20	14	21	20	21
2	2	3	2	3	0	2	6	3	3
3	0	1	0	0	1	0	0	1	0

E – Estradiol C – Climara P – Placebo

0 = No evidence of irritation
1 = Minimal erythema, barely perceptible
2 = Definite erythema, readily visible; or minimal edema; or minimal papular response
3 = Erythema and papules

Only three subjects required patch site changes because of irritation: Day 8, Climara, score 3+; Day 15, Estradiol, score 2F (glazing and fissures); Day 15, Placebo, score 2F (glazing and fissures).

Conclusion

There was no significant difference in the mean or cumulative irritation scores of the Bertek Estradiol transdermal patch and the Climara patch. The Estradiol patch was found to be more irritating than its placebo patch at the Day 15 evaluation and overall. One subject experienced moderate itching on one occasion at the site of the Climara patch. There were no other patch site adverse events reported.

In combination with the studies reviewed previously that found similar patterns of adhesion of the test and reference products and acceptable contact sensitization for the test product, this study confirms that the test and reference products are similar in their skin irritation potential.

Mary M. Fanning, M.D., Ph.D.
Associate Director of Medical Affairs
Office of Generic Drugs

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-182

CHEMISTRY REVIEW(S)

1. ***CHEMIST's REVIEW #5*** [Courier New 12]

2. **ANDA 75-182**
ANDA 75-233

3. APPLICANT, Name/Address/Telephone/Fax:
Mylan Technologies, Inc. (formerly Bertek, Inc.)
Attention: Elizabeth Ash
110 Lake Street
St. Albans, VT 05478
☎802 527-7792/*fax* 802 527-0486

4. LEGAL BASIS FOR ANDA SUBMISSION: *505(j)*

5. Supplement: n/a

6. PROPRIETARY NAME: none

7. **Non-PROPRIETARY NAME**: **Estradiol Transdermal System** (TDS)

Innovator's Product Name: *Climara®* Estradiol Transdermal System (*Berlex Labs*)

8. Supplement Provides For: n/a

9. AMENDMENTS & Other DATES.

A. **FIRM**:
08-06-97 Orig. application (75-182)
10-21-97 Orig. application (75-233)
07-26-99 Minor amendment
07-29-99 new correspondance

B. **FDA**:
06-07-99 labeling review (sat.)
06-15-99 BIOEQUIVALENCY status sat. (Located in vol. 5.1)
09-02-99 telacon between Ms Ash and Drs. Rudman & Trimmer.
09-03-99 tel amendment

10. PHARMACOLOGICAL CATEGORY: treatment of moderate to severe vasomotor symptoms associated with menopause, treatment of vulval & vaginal atrophy, treatment of hypoestrogenism, treatment of abnormal uterine bleeding.

11. Rx or OTC: R_x

12. RELATED ANDA's: none

13. DOSAGE Form: transdermal patches

14. POTENCY: 75-182 0.1 mg/day
75-233 0.05 "

15. CHEMICAL Name: Estradiol

16. Records & Reports: n/a

17. COMMENTS.

A. General Comments:
Not a USP drug product but is a USP drug substance.
MV sat. EER sat. Bio sat. CMC sat. DMF adequate.

18. CONCLUSIONS & RECOMMENDATIONS:
For approval

19. Reviewer/Branch Chief:
Robert W. Trimmer, Ph.D.
BRANCH IV, DIV. OF CHEMISTRY I, OGD

Davinder S. Gill, Ph.D.
TEAM LEADER

Date Started: 08-25-99
Date Completed: 08-26-99
revised: 09-08-99

Page(s) 15

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

Chemistry Review #5

9/8/99

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-182.

Statistical
~~MEDICAL~~ REVIEW(S)

3.1

Statistical Report: Estradiol Patches 0.1 mg/day (31 cm^2); Office of Generic Drugs: ANDA 75-182, Mylan Pharmaceuticals Inc. (manufactured by Bertek, Inc.)

OGD reviewer: Lin Whei Chuang, Ph.D.

In this trial, 32 fasted healthy post-menopausal female volunteers were dosed in an open-label randomized single-application, three-period, 4 sequence, two-way crossover bioequivalence wear study to evaluate the relative bioavailability of estradiol 0.1 mg/day Mylan patches manufactured by Bertek to Climara® 0.1 mg/day patches manufactured by Berlex. An additional goal was to compare the adhesion and acute irritation of the two products. The patches were worn for 7 days (168 hours). The washout period between treatments was 2 weeks. All 32 treated subjects successfully completed the study.

Study Design and Model:

Open-label, randomized, single-application, crossover bioequivalence study.

Experimental Treatment:

Reference: A = Climara® Estradiol Transdermal System - 25 cm^2 (Berlex)

Test: B = Mylan Estradiol Transdermal Systems - 31 cm^2

Experimental Design: three Periods, four Sequences

Sequence 1: ABA (7 subjects)

Sequence 2: BAB (8 subjects)

Sequence 3: BAA (8 subjects)

Sequence 4: ABB (9 subjects)

Subjects entered the study in three separate Groups: Group A (subjects 1-11) received treatment in weeks 1, 4 and 7; Group B (subjects 12-17) in weeks 2, 5 and 8; and Group C (subjects 18-34) in weeks 3, 6 and 9. One subject (#15) was unable to arrive for the first treatment, for reasons unrelated to the study, and was given a different number, #33, and enrolled in Group C. Subject #25 was discontinued due to abnormal laboratory values prior to first treatment.

Skin irritation was evaluated after patch removal, and patch adhesion was assessed at 8 time points during each period.

Plasma concentrations of estradiol and its metabolites, estrone and estrone sulfate, were evaluated. The plasma concentrations were adjusted by the Sponsor by subtracting out the average of the baseline concentrations (at times -48, -24, 0 hours). The following primary pharmacokinetic parameters derived from the adjusted plasma concentration-time curves were statistically analyzed to assess bioequivalence of the two products:

lauct = log(auct)
laucinf = log(aucinf)
lcmax = log(cmax)

In addition, $t_{1/2}$, tmax and kel were evaluated, in the original units, and on the log scale because of marked positive skewness indicating non-normality on the original scale of measurement.

Basic model for bioequivalence assessment

For a given primary endpoint, for example, lauct, in the absence of carryover, the following statistical model was used: Let Y_{jklmq} be a measurement of this endpoint for subject k in sequence j in week l at which time treatment m was received; then

where

and

μ = mean response
α_j = sequence effect
s_{jk} = subject effect (nested within sequence)
ω_l = week effect
τ_m = treatment effect
τs_{jkm} = subject * treatment interaction
ϵ_{jklm} = random error

The variable "week" was used instead of the usual "period" to account for the staggered entry of the 3 groups.

SAS® code

The following SAS® code was used to carry out a mixed model analysis with random subject and subject*treatment interaction and all other effects assumed fixed.

```
proc mixed;
classes seq subj week trt;
model y = seq week trt;
random subj(seq) subj*trt(seq);
lsmeans trt/cl pdiff alpha=0.1;
run;
```

The assumed covariance structure is block diagonal with a random effect for each subject, that is, subject-by-treatment was modeled. This corresponds to the assumption that the random effects covariance matrix *G* is block diagonal and the random error covariance matrix *R* is simple diagonal.

Carryover.

The OGD guidance document: Conjugated Estrogens Tablets *in vivo* Bioequivalence and *in vitro* Drug Release (8/1991) indicated that tests for bias due to carryover should be carried out. If such tests were significant at the 0.10 level in preliminary analyses, then the estimated treatment difference was adjusted for bias due to carryover in the final statistical model.

Carryover due to first-order residual effects was modeled as a categorical variable, with values "0" for period 1, and "1" or "2" for periods 2 and 3, according as the current treatment is A or B, respectively. For this design, after the basic model is fitted, there is only one degree of freedom for this variable, and in the analysis, a continuous variable, FOC (first-order carryover), was used, with value 0.5 if the previous treatment was A, -0.5 if the previous treatment was B, and 0 if period=1.

Carryover due to treatment-by-residual effects was modeled as a categorical variable, called CARRY, with values "0" for period 1, "11" if the current and previous treatments are A, "22" is the current and previous treatments are B, "12" if the current treatment is B and the previous one A, and "21" if the current treatment is A and the previous one B. After adjusting for the other factors in the basic model, CARRY has 3 degrees of freedom. The one degree-of-freedom component corresponding to possible bias in the estimated treatment effect due to the presence of treatment-by-residual carryover was modeled by the continuous variable, called

TRC (treatment-by-residual carryover). TRC takes the value 0 if CARRY="0", -0.125 if CARRY="11", 0.125 if CARRY="22", 0.5 if CARRY="12" and -0.5 if CARRY="21".

In preliminary screening, first-order and treatment-by-residual effects were explored by addition of the relevant factors to the basic model. If FOC was significant, at the 0.10 level, then the adjusted estimate of the treatment difference was obtained from this model, i.e., the basic model plus FOC. If TRC was significant at the 0.1 level, with CARRY in the model, then the adjusted estimate of the treatment difference was obtained from this model, that is, basic model plus CARRY. This is in accord with the customary OGD practice.

Definition of Bioequivalence

Bioequivalence of compounds is concluded if each of the 90% confidence intervals for the ratios (T/R) of each of the endpoints lies entirely in the interval (0.80, 1.25).

Results

There were complete measurements, i.e. 96, for lauct and lcmax for estradiol, estrone and estrone sulfate. However, only 71/96 measurements were available for lauci for estradiol, 57/96 for lauci for estrone, and 56/96 for lauci for estrone sulfate. The (non-missing) lauci's were closely similar to the corresponding lauct's. This suggests that any substantial differences between the lauct and lauci results might be a consequence of missing data..

1. **Estradiol**

There was no evidence of first-order residual or residual-by-treatment carryover, for lauct, lauci, or lcmax. Table 1 gives the results for auct, auci, and cmax. All analyses were carried out on the log scale, and the least squares means and confidence limits transformed back to the original scale of measurement.

Table 1.

Endpoint	Model	Mean Ref.	Mean Test	DDF	Ratio Test/Ref	90%CI Lower	90% CI Upper
auct	basic	15750.5	17015.6	31	1.0803	1.0135	1.1517
auci	basic	15202.0	16795.8	20	1.1048	1.0290	1.1863
cmax	basic	172.2	162.8	31	0.9451	0.8784	1.0168

The bioequivalence standard is met for auct, auci, and cmax.

Table 2 gives least squares means and 90% confidence intervals for the test-reference differences from analyses of tmax, $t_{1/2}$ and kel on the original scale, together with the (back-transformed) least squares means and 90% confidence intervals for the test/reference ratios from analyses on the log scale, i.e. of ltmax, $lt_{1/2}$ and lkel. All analyses were done using the basic model.

Table 2.

Endpoint	Model	Mean Ref.	Mean Test	DDF	Difference and Ratio Test/Ref.	90%CI Lower	90% CI Upper
tmax (orig.)	basic	22.9459	31.3921	31	8.4462	1.9549	14.9375
tmax (log)		20.1467	25.4508	31	1.2633	1.0773	1.4813
$t_{1/2}$ (orig.)	basic	8.7395	6.7521	20	-1.9874	-4.7344	0.7596
$lt_{1/2}$ (log)		8.5209	4.8195	20	0.7391	0.5480	0.9968
kel (orig.)	basic	0.1344	0.1933	20	0.0590	0.0091	0.1088
kel (log)		0.1063	0.1438	20	1.3531	1.0032	1.8249

Tmax and kel are substantially greater for the test than the reference products (and $t_{1/2}$ being proportional to 1/kel is much less), and the bioequivalence standard is not met for tmax, kel or $t_{1/2}$.

2. **Estrone**

There was no evidence of first-order residual or residual-by-treatment carryover, for lauct, lauci, or lcmax. Table 3 gives the results for auct, auci, and cmax. All analyses were carried out on the log scale, and the means and confidence limits transformed back to the origin scale of measurement.

Table 3.

Endpoint	Model	Mean Ref.	Mean Test	DDF	Ratio Test/Ref	90%CI Lower	90% CI Upper
auct	basic	8336.3	7968.2	31	0.9558	0.8859	1.0312
auci	basic	8979.9	9380.1	20	1.0446	0.9345	1.1675
cmax	basic	72.5	68.2	31	0.9408	0.8637	1.0248

The bioequivalence standard is met for auct, auci, and cmax.

Table 4 gives least squares means and 90% confidence intervals for the test-reference differences from analyses of tmax, $t_{1/2}$ and kel on the original scale, together with the (back-transformed) least squares means and 90% confidence intervals for the test/reference ratios from analyses on the log scale, i.e. of ltmax, $lt_{1/2}$ and lkel. All analyses were done using the basic model.

Table 4.

Endpoint	Model	Mean Ref.	Mean Test	DDF	Difference and Ratio Test/Ref	90%CI Lower	90% CI Upper
tmax (orig.)	basic	47.6520	64.3514	31	16.6994	8.0329	25.3658
tmax (log)		43.0158	57.2943	31	1.3319	1.1146	1.5917
$t_{1/2}$ (orig.)	basic	14.3782	13.9101	14	-0.4681	-6.6882	5.7520
$lt_{1/2}$ (log)		11.9732	10.1999	14	0.8519	0.5757	1.2606
kel (orig.)	basic	0.0695	0.0914	14	0.0219	-0.0134	0.0572
kel (log)		0.0579	0.0680	14	1.1743	0.7936	1.7376

Tmax and kel are substantially greater for the test than the reference products (and $t_{1/2}$ is much less), and the bioequivalence standard is not met for tmax, kel or $t_{1/2}$.

3. Estrone sulfate

There was no evidence of a first-order residual carryover effect for lauct, lauci, or lcmax, or treatment-by-residual carryover for lauci. However, for lauct and lcmax, the estimate of the bias due to treatment-by-residual carryover, TRC, was significant (p-value = 0.0047 and 0.0281, respectively) with CARRY in the model, and thus the estimated treatment difference was obtained from the basic model plus CARRY to adjust for this bias. On a technical note, in both instances, the 3 degrees of freedom of CARRY could be separated as one due to TRC, another due to FOC (both significant), and a third unimportant component which was far from significance. Table 5 gives the results for auct, auci, and cmax. All analyses were carried out on the log scale, and the means and confidence limits transformed back to the original scale of measurement.

Table 5.

Endpoint	Model	Mean Ref.	Mean Test	DDF	Ratio Test/Ref	90%CI Lower	90% CI Upper
auct	basic + CARRY	139823.0	175964.0	30	1.2585	1.0816	1.4643
auci	basic	173121.3	170310.1	15	0.9838	0.8428	1.1482
cmax	basic + CARRY	1281.36	1534.08	30	1.1972	0.9962	1.4388

The bioequivalence standard is met for auci, but not for auct or cmax.

Table 6 gives least squares means and 90% confidence intervals for the test-reference differences from analyses of tmax, $t_{1/2}$ and kel on the original scale, together with the (back-transformed) least squares means and 90% confidence intervals for the test/reference ratios from analyses on the log scale, i.e. of ltmax, $lt_{1/2}$ and lkel. All analyses were done using the basic model.

Table 6.

Endpoint	Model	Mean Ref.	Mean Test	DDF	Difference and Ratio Test/Ref	90%CI Lower	90% CI Upper
tmax (orig)	basic	47.6520	64.3514	31	16.6994	8.0329	25.3658
tmax (log)		43.0158	57.2943	31	1.3319	1.1146	1.5917
$t_{1/2}$ (orig.)	basic	14.3782	13.9101	15	-0.4681	-6.6882	5.7520
$lt_{1/2}$ (log)		11.9732	10.1999	15	0.8519	0.5757	1.2606
kel (orig.)	basic	0.0695	0.0914	15	0.0219	-0.0134	0.0572
kel (log)		0.0579	0.0680	15	1.1743	0.7936	1.7376

Tmax and kel are substantially greater for the test than the reference products (and $t_{1/2}$ is much less), and the bioequivalence standard is not met for tmax, kel or $t_{1/2}$.

Adhesion and irritability

The following table gives, for the 8 time periods examined, the number of patches out of 96 (47 on A, 49 on B) which were not perfectly (100%) attached.

Trt/time	1	2	3	4	5	6	7	8
Trt A	0	0	0	0	0	0	0	0
Trt. B	0	0	0	1	1	2	2	2

The test product B is not quite as perfect as the reference product A, but the difference in the proportion perfectly attached is not significant (Fisher's exact test p-value = 0.258).

The following table shows the irritation scores (0 = no problem, 0.5 = slight redness, 1 = erythema, 2 = erythema and elevation) at three time points for the two products.

	Treatment	0	0.5	1	2
time=0	A	31	12	4	0
	B	23	19	5	2
time=30mins.	A	36	10	1	0
	B	31	15	1	2
time=60mins.	A	41	5	1	0
	B	38	8	3	0

The test product B appears slightly more irritating than the reference product A. Using Fisher's exact test to compare the treatments in terms of score 0 versus score > 0, treatment B was significantly more irritating than A at time 0 (p-value = 0.047) but not at 30 minutes and 60 minutes (p-values 0.115 and 0.135, respectively).

Comments on the Company's Analyses

The Sponsor assessed bioequivalence using SAS® PROC GLM with the following terms in the model: sequence, subject(sequence), treatment, and period. Our analysis using SAS® PROC MIXED is similar (ignoring carryover and group) to that using SAS® PROC GLM with the following terms in the model: sequence, subject(sequence), treatment, period, and the treatment*subject interaction. Since the subject-by-treatment interaction forms the basis for the estimated standard error of the estimate of the mean treatment difference, we consider the model used by the Sponsor to be inappropriate. In addition, the Sponsor did not take into account possible group differences. Nor did they explain how the first order carryover effect (RESID1) was defined.

Conclusion

The analyses of the data from this study support the bioequivalence of the test and reference treatments for the three endpoints auct, auci, and cmax for the components **estradiol** and **estrone**. Bioequivalence is not supported for **estrone sulfate**, since the 90% confidence intervals for the ratio of the test/reference means for auct and cmax fail to fall within the interval (0.80, 1.25). The bioequivalence standard was not met for tmax, kel, or $t_{1/2}$, for any of the three components. The irritation score dichotomized as "no problem" versus "some problem" for the test product was significantly greater than that of the reference product at patch removal, but not at 30 minutes or 60 minutes later.

Stella G. Machado 6/5/98

Stella G. Machado, Ph.D. 6/5/98
Mathematical Statistician

Original:	ANDA 75-182
HFD-705	QMR Chron
HFD-705	Yi Tsong
HFD-705	Donald Schuirmann
HFD-700	Charles Anello
HFD-652	Lin Whei Chuang
HFD-650	Dale Conner
HFD-652	Yih Chain Huang
HFD-615	Harvey Greenberg
HFD-651	Rabindra Patnaik
HFD-600	Doug Spom

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-182

BIOEQUIVALENCE REVIEW(S)

BERTEK

APR 14 1999

A3

Office of Generic Drugs, CDER, FDA
Douglas L. Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

BIOEQUIVALENCE AMENDMENT
(Submission of Additional Skin Irritation Study)

RE: ESTRADIOL TRANSDERMAL SYSTEM, 0.1MG/DAY - ANDA 75-182
ESTRADIOL TRANSDERMAL SYSTEM, 0.05MG/DAY - ANDA 75-233

Dear Mr. Sporn:

Reference is made to the Abbreviated New Drug Applications identified above, which are currently under review and to an April 13, 1999, telephone conversation which took place between Dr. Mary Fanning of your Office and Dr. John O'Donnell of Mylan regarding the skin irritation studies that were submitted to the Agency on May 28, 1998. As a result of this telephone conversation Bertek wishes to amend these applications with the enclosed report of an additional skin irritation study entitled, "*A 21-Day Evaluation of Cumulative Skin Irritation Potential in Humans for a 0.05mg/day Estradiol Transdermal Patch*" (ESTR-9842). This study was designed to evaluate the cumulative irritation potential of Bertek's Estradiol Transdermal System relative to that of the reference product, Climara® (Berlex, Inc.) following repetitive topical application over a 21-day period. The design of this study follows the recommendations provided in the Agency's correspondence dated February 24, 1998.

The enclosed study report demonstrates that there were no significant differences in the irritation resulting from treatment with the Bertek Estradiol Transdermal System and Climara®. This data confirms the conclusion reached from the two irritation studies, primary dermal irritation and the repeat insult study, submitted in the May 28, 1998, amendment. The data from the three skin irritation studies demonstrates that Bertek's Estradiol Transdermal System is equally safe with the innovator product, showing no potential of being more irritating than the innovator product.

Bertek Inc. is a fully owned subsidiary of Mylan Laboratories, Inc. and the referenced product will be marketed under the Mylan Pharmaceuticals label. For this reason the product is referred to as Bertek's patch and as Mylan's patch interchangeably throughout the study report. This study report is being submitted in duplicate to ANDA 75-182 only, and is incorporated by reference in ANDA 75-233. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (802) 527-7792 or via facsimile at (802) 527-0466.

Sincerely,

Frank A. Tedo for

Lamont Fulton
Manager of Regulatory Affairs

/tlr

enclosures

RECEIVED
APR 16 1999
GENERIC DRUGS

BERTEK, INC., 110 LAKE STREET, ST. ALBANS, VT 05478, 802-527-7792, FAX 802-527-0486, TELEX 11 710-991-8483

Estradiol
Transdermal System,
ANDA #75-182 (0.1 mg/day)
ANDA #75-233 (0.05 mg/day)
Reviewer : Lin-Whei Chuang

Bertek, Inc.
St. Albans, VT

Submission Date:
October 28, 1998

Review of an Amendment to a Bioequivalence Study

The bioequivalence study conducted on the 0.1 mg/day strength submitted on 8/6/97 under ANDA #75-182 was reviewed within the Division of Bioequivalence and by the mathematical statistician of QMR staff. It was found to be incomplete due to 7 deficiencies (see review of 7/10/98 and 6/5/98).

As noted in the review of 6/8/98 by the QMR staff, using SAS PROC MIXED model with carryover effects, the data of non-conjugated estradiol and non-conjugated estrone supported bioequivalence between the test and reference drugs. However, using the same SAS model, bioequivalence was not supported by the estrone sulfate data since the 90% confidence intervals for LNAUCT and LNCMAX fail to fall within the acceptable range.

The firm's response to these deficiencies are reviewed below. Response to deficiencies 1-3 are also reviewed by the expert mathematical statistician of QMR staff (Attachment 1).

#1. *Please conduct statistical analysis (with and without carryover effects) on the total estrone data; because the method of calculation from which the concentration of estrone sulfate was derived, i.e. subtracting free estrone concentration from total estrone concentration, involved two sets (total estrone and of free estrone) of intra-subject variabilities.*

Firm's Response:
a. Total estrone data are presented in Figure 1 and Tables 1-2.

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releasable.

figure 1 - data

TABLE 1: MEAN PLASMA CONCENTRATIONS OF TOTAL ESTRONE

TIME	TEST MEAN	SD	REF. MEAN	SD	TEST/REF.
TIME HR	14.28	41.13	7.14	24.69	2.00
-48	7.22	15.03	8.14	24.56	0.89
-24	18.47	39.63	16.22	30.90	1.14
0	255.02	182.58	277.60	272.63	0.92
6	536.15	266.19	551.00	271.00	0.97
12	673.16	389.80	730.51	377.40	0.92
18	979.33	571.40	1120.22	691.72	0.87
24	1261.36	766.14	1346.63	907.01	0.94
48	1260.24	876.13	1255.81	823.76	1.00
72	1155.39	915.15	1088.46	761.25	1.06
96	975.40	719.70	1003.06	767.80	0.97
120	806.28	541.83	809.16	648.37	1.00
144	678.08	495.32	694.72	496.03	0.98
168	638.67	475.83	659.90	480.77	0.97
169	610.45	448.55	639.35	411.45	0.95
170	508.29	401.11	553.44	438.08	0.92
176	293.54	279.97	358.37	311.22	0.82
182	187.54	186.77	240.76	258.53	0.78
190	137.46	146.92	216.45	276.61	0.64
200					

TABLE 2: ARITHMETIC MEANS OF PK PARAMETERS OF TOTAL ESTRONE

	TEST MEAN	SD	REF. MEAN	SD	TEST/REF.
PARAMETER	200348.39	128746.40	177610.10	89296.17	1.13
AUCI	173187.54	108649.06	178859.74	116764.78	0.97
AUCT	1492.42	952.76	1538.94	891.29	0.97
CMAX	0.09	0.11	0.07	0.08	1.22
KE	11.114809	0.61	11.954930	0.55	1.07a
LAUCI	11.883914	0.61	11.924549	0.60	0.96a
LAUCT	7.146000	0.56	7.205984	0.52	0.94a
LCMAX	16.34	21.11	15.16	8.75	1.08
THALF	72.45	40.31	62.30	29.46	1.16
TMAX					

a = RATIO OF GEOMETRIC MEANS

b. ANOVA was conducted on the above data using SAS PROC GLM model with and without carryover effect. No significant effect for the factor of "treatment*residual 1" at alpha level of 0.05 was found by the firm. The p value of this factor for LNAUCL was 0.0766. Following are results obtained by the firm with various SAS models.

TABLE 3: STATISTICAL ANALYSIS OF TOTAL ESTRONE - USING SAS PROC GLM									
	WITH FULL CARRYOVER			WITH RESIDUAL 1 ONLY			WITHOUT CARRYOVER		
	TEST LSM	REF. LSM	90% CI	TEST LSM	REF. LSM	90% CI	TEST LSM	REF. LSM	90% CI
AUCT	168281	177481	0.84-1.05	176790	175057	0.91-1.11	175738	176153	0.90-1.09
AUCI	193397	186995	0.85-1.21	193820	183948	0.89-1.21	194955	183613	0.91-1.21
CMAX	1465.9	1533.5	0.83-1.08	1526.9	1503.0	0.90-1.14	1513.0	1517.5	0.88-1.10
LNAUCT	11.88	11.92	0.88-1.04	11.90	11.90	0.92-1.09	11.90	11.91	0.92-1.07
LNAUCI	12.05	11.99	0.91-1.23	12.03	11.96	0.93-1.22	12.03	11.96	0.94-1.21
LNCMAX	7.15	7.21	0.84-1.04	7.16	7.19	0.88-1.08	7.16	7.19	0.89-1.06

Reviewer's Comments:

a. The firm's calculation of PK parameters has been confirmed by the reviewer.

b. Statistical analysis with carryover effect have been reviewed by the QMR staff (see attached review of 4/20/99). It was concluded that, using SAS PROC MIXED model and without carryover effects, the 90% confidence intervals for all pivotal parameters fall within 80-125% for total estrone. However, if the statistical model (PROC MIXED) including carryover effects is used, the 90% confidence intervals of all pivotal parameters fail to fall within 80-125% by a wide margin for total estrone.

#2. *Using the estrone sulfate data you submitted , the 90% confidence intervals of LNAUCT and LNCmax of estrone sulfate (108-146% and 100-144%, respectively), calculated by the statistician of the Agency using SAS mixed model with carryover due to treatment-by-residual effect in the model, are outside the acceptable limits of 80-125%.*

Two types of carryover were estimated, first-order residual effects and treatment-by-residual effects. It was concluded that data you submitted supported the bioequivalence of the test and reference treatments for the components estradiol and estrone, but the bioequivalence of estrone sulfate was not supported. This was due to the significant treatment-by-residual carryover on the LNAUCT and LNCmax of estrone sulfate (p = 0.0047 and 0.0281 respectively) and resulted in above mentioned out-of-limit 90% confidence intervals.

Firm's Response:

a. The data was re-analyzed by the firm using SAS mixed model with carryover effect in the model. The firm, however, was unable to replicate the results obtained by the Agency statistician.

b. In addition, the study samples were re-analyzed for estrone sulfate using specific An

[illegible] with the organic solvent.

the mass of the unlabelled standards.

The results of pre- and during-study validation are presented below in Table 4:

Table 4: RIA Validation for Estrone Sulfate		
Parameter	**Pre-Study**	**During-Study**
Sensitivity/LOQ (pg/mL)	40 (1.25/RIA tube)	40 (1.25/RIA tube)
Quality Control Conc. (pg/mL) (Lo, Med, Hi)	100, 700, 4200	128, 1359, 3383
Linear Range (pg/mL)	40-4900 (spiked plasma samples)	1.25-80 per RIA tube
Linearity	$R^2 \geq 0.99706$ (based on curves of 1.25-80 per RIA tube)	$R^2 \geq 0.99720$

Intra-run Precision (%CV)	2.0 - 7.3	N/A
Intra-run Accuracy (%Actual)	96.5 - 108	N/A
Inter-run Precision (%CV)	2.5 - 14.4	3.53-12.41
Inter-run Accuracy (%CV)	92.0 - 104.2	95.5 - 105.4
Selectivity	cross-reaction <3%	N/A
Stability (%) a) Plasma Sample @ Room Temp. for 48 hours b) Plasma Sample after 5 freeze-thaw cycles c) Plasma Sample at -15°C for 24 months	Hi Lo 101.0 82.6 Hi Lo 101.8 103.9 Hi Lo 91.4 86.9	N/A
Percent Recovery of internal standard in the QCs & LOQ	Hi Med Lo LOQ 59.2 64.5 58.5 58.3	N/A

c. Estrone sulfate data obtained from the above analysis are presented below in Tables 5-6 and Figure 2.

TABLE 5: MEAN PLASMA CONCENTRATIONS OF ESTRONE SULFATE

	TEST MEAN	SD	REF. MEAN	SD	TEST/REF.
TIME HR					
-48	15.54	47.23	12.01	28.46	1.29
-24	16.22	33.60	14.59	25.85	1.11
0	25.62	40.62	25.46	46.39	1.01
6	311.57	235.33	267.71	211.14	1.16
12	671.80	440.28	623.23	316.66	1.08
18	806.76	499.15	841.79	441.50	0.96
24	1167.00	640.19	1267.57	727.54	0.92
48	1478.16	804.79	1561.53	957.10	0.95
72	1439.76	927.52	1447.11	845.97	0.99
96	1269.20	905.50	1196.23	841.14	1.06
120	1123.41	825.83	1090.91	785.84	1.03
144	958.82	605.96	885.70	620.60	1.08
168	800.76	565.22	794.57	514.47	1.01
169	810.65	672.76	777.68	505.82	1.04
170	725.88	513.82	738.94	468.31	0.98
176	639.94	508.53	713.74	554.00	0.90
182	350.99	345.74	382.47	316.01	0.92

TABLE 6: ARITHMETIC MEANS OF PK PARAMETERS OF ESTRONE SULFATE

	TEST MEAN	SD	REF. MEAN	SD	TEST/REF.
PARAMETER					
AUCI	216186.33	132267.85	220744.01	113849.59	0.98
AUCT	201019.62	114199.93	201621.44	116517.63	1.00
CMAX	1805.71	985.49	1818.40	937.42	0.99
KE	0.07	0.04	0.08	0.06	0.88
LAUCI	12.078305	0.69	12.161532	0.58	0.92a
LAUCT	12.047281	0.60	12.060282	0.58	0.99a
LCMAX	7.352030	0.56	7.385454	0.51	0.97a
THALF	12.59	5.68	13.84	8.64	0.91
TMAX	73.12	44.82	61.28	34.60	1.19

a = RATIOS OF GEOMETRIC MEANS

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releasable.

figure 2- data

d. ANOVA of the above data was conducted by the firm using PROC GLM with carryover effect ("residual 1" and "treatment*residual 1" were both included in the model). The p value of the factor "treatment*residual 1" was 0.0089 for LNAUCL and 0.0825 for LNCMAX. Results obtained by the firm with carryover effect in its SAS model indicate 90% intervals of all 3 pivotal PK parameters are within the acceptable range of 80-125%.

TABLE 7: STATISTICAL ANALYSIS OF ESTRONE SULFATE USING PROC GLM WITH CARRYOVER EFFECT

PARAMETER	TEST LSM	REF. LSM	90% CI
AUCT	193689.37	204480.30	0.854 - 1.040
AUCI	190642.97	203853.60	0.822 - 1.048
CMAX	1745.04	1877.06	0.822 - 1.037
LNAUCT	12.03	12.08	0.878 - 1.043
LNAUCI	12.00	12.03	0.852 - 1.123
LNCMAX	7.34	7.42	0.827 - 1.036

Reviewer's Comments:

a. The analytical method conducted by the firm using specific sulfatase and co measure plasma concentration of estrone sulfate is acceptable.

b. The firm's calculation of PK parameters was confirmed by the reviewer.

c. Statistical analysis with carryover effect have been reviewed by the QMF staff in comments 1-3 of the attached review of 4/20/99. The Agency's conclusion is different from the firm's results in Table 7. It was concluded by the agency that, using SAS PROC MIXED and without carryover effects, the 90% confidence intervals of all pivotal parameters fall within 80-125% for estrone sulfate. However, if the statistical model (PROC MIXED) including carryover effects is used, the 90% confidence intervals of all pivotal parameters fail to fall within 80-125% by a wide margin for estrone sulfate.

#3. *For the assay of total estrone, please address the issue of glucuronide conjugate, and if it was included in the total estrone or estrone sulfate you reported.*

Firm's Response:

The firm indicates that the total estrone reported in the original submission did include the glucuronide and sulfate conjugates; and the estrone sulfate reported in the original

submission was a combination of estrone sulfate and estrone beta-glucuronide.

In addition, the study samples were re-analyzed for estrone sulfate using specific
Results of this re-analysis were reviewed and commented in deficiency #2 (see reviewer's comments a-c of #2).

Reviewer's Comment:
The firm's response is adequate.

#4. *For the assay of estrone sulfate, please clarify if standards and QC samples were prepared by spiking plasma samples with free estrone or with estrone sulfate.*

The preferred method to prepare standards and QC samples for the analysis of estrone sulfate would be to spike plasma with

Firm's Response:
Free estrone was used in the original assay to prepare both standards and QC samples. This practice was supported by the fact that the assay was validated to show complete hydrolysis of the estrone conjugates to free estrone.

However, the new assay method conducted for the re-analysis of estrone sulfate did use estrone sulfate to prepare the standard curve and QC samples; and tritiated estrone sulfate (2,4,6,7,-3H estrone sulfated was used as internal standard.

Reviewer's Comment:
The firm's explanation is acceptable.

#5.

Firm's Response:

[illegible] had mostly sulfatase activity (20-40 units/mg) and very little glucuronidase activity (<3 units/mg).

Reviewer's Comment:
The firm's explanation is acceptable.

#6. *Please report whether estrone or estrone sulfate was used in the recovery and stability studies during analytical method validation for total estrone.*

Firm's Response:
Estrone sulfate was used in both the recovery and stability studies. It was also used in the new ethod conducted for report submitted in this amendment.

Reviewer's Comment:
The firm's explanation is acceptable.

#7. *Please submit adequate stability data for total estrone since the maximum number of days for samples storage during the analysis of total estrone was reported to be 153 days, yet the stability of frozen samples was documented for only 106 days.*

Firm's Responses:
a. Frozen stability (109.1%) of estrone sulfated in human plasma was extended to 174 days (ending 7/29/97, about 6 months after the study).

b. In addition, frozen stability (86.9-91.4%) of 24 months (ending 2/3/98, about 25 months after the study) was documented, which is longer than maximal possible time period of 604 days for analysis by which was conducted during 7/29-8/21/98.

Reviewer's Comment:
The stability data submitted by the firm is acceptable.

Overall Comments:

1. The firm has satisfactorily addressed all the deficiencies except when the statistical model (PROC MIXED) including carryover effects is used, the 90% confidence intervals of all pivotal parameters fail to fall within 80-125% by a wide margin for estrone sulfate and total estrone.

2. However, as commented in earlier review of 6/10/98, at this point in time, the Division is not enforcing testing for carryover in the statistical model.

3. Using the correct statistical model and without carryover effects, the 90% confidence interval falls within the acceptable range of 80-125% for LNAUCT, LNAUCI and LNCMAX of all 4 analytes: non-conjugated estradiol, non-conjugated estrone, estrone sulfate, and total estrone.

4. In addition, the firm has conducted "A 21-day Evaluation of Cumulative Skin Irritation Potential In Humans for a 0.05 mg/day Estradiol Transdermal Patch". It was reviewed by the medical officer (see Attachment 2), and concluded the test and reference products are similar in their skin irritation potential.

5. The comparative formulations show proportionality between the 0.1 mg/day strength and 0.05 mg/day strength for the active and inactive ingredients in both test and reference drugs.

Recommendations:

1. The single-dose, fasted bioequivalence study conducted by Bertek. Inc. on its estradiol transdermal system, 0.1 mg/day, lot #26C001L, comparing it to Climara^{R} transdermal system, lot #P50169, has been found acceptable by the Division of Bioequivalence. The firm's estradiol transdermal system, 0.1 mg/day is deemed bioequivalent to Climara^{R} transdermal system, 0.1 mg/day, when administered under fasting conditions.

2. The dissolution testing conducted by Bertek, Inc. on its Estradiol transdermal system, 0.05 mg/day and 0.1 mg/day, lot #26C001L & #26D011D, respectively, comparing them to Climara^{R} transdermal system, 0.1 mg/day and 0.05 mg/day, respectively, has been found acceptable by the Division of Bioequivalence. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program and conducted in 500 mL of 0.3% sodium lauryl sulfate in 0.005 N NaH_2PO_4, pH 5.5, at 32° C using USP 23 apparatus 5 (paddle over disk) at 100 rpm. The test products should meet the following specifications:

3. Waiver of the *in vivo* bioequivalence testing requirements for Bertek's estradiol transdermal system, 0.05 mg/day, is granted per 21 CFR 320.24(b)(6). The firm's estradiol transdermal system, 0.05 mg/day is deemed bioequivalent to Climara[R] transdermal system, 0.05 mg/day.

/S/ 6/7/99

Lin-Whei Chuang
Division of Bioequivalence /S/
Review Branch I

RD INITIALLED YHUANG 6/7/99
FT INITIALLED YHUANG

Concur /S/ Date: 6/15/99
Director, Division of Bioequivalence
Dale Conner, Pharm. D.

ATTACHMENT 1

Statistical Review: ANDA 75-182, Estradiol Transdermal System, 0.1 mg/day, Bertek, Inc.

Material reviewed: 1. One red-colored volume of ANDA 75-182, volume 5.1.
6. Original statistical review of ANDA 75-182, dated June 17, 1998, by Stella G. Machado, Ph.D., QMR staff, HFD-705.

Data for my analyses were provided on diskette in data files included with volume 5.1.

Stella G. Machado, Ph.D. carried out the original statistical review, dated June 17, 1998, of this bioequivalence study. Lin Whei Chuang, Ph.D. is the Division of Bioequivalence reviewer for this submission.

The issues in this review involve the sponsor's response to points made by the agency in correspondence dated July 15, 1998. Of the seven deficiencies listed in that correspondence, the first three will be the subject of this statistical review. These deficiencies, plus the sponsor's responses are as follows:

FDA DEFICIENCY 1: Please conduct statistical analysis (with and without carryover effects) on the total estrone data; because the method of calculation from which the concentration of estrone sulfate was derived, i.e. subtracting free estrone concentration from total estrone concentration, involved two sets (total estrone and of free estrone) of intra-subject variabilities.

BERTEK RESPONSE 1: The presentation of data and pharmacokinetic analysis for baseline subtracted total estrone (with a non-specific sulfatase incubation) can be found in Attachment 1A. The mean concentration versus time profiles are illustrated graphically in Attachment 1A, Section C. Mean plasma profiles are similar between Bertek estradiol transdermal system and Climara® (Berlex) estradiol transdermal system.

Attachment 1B provides statistical analysis and 90% confidence intervals using the model with and without carryover effects in the model on the baseline subtracted total estrone. For the model with residual 1 and treatment*residual 1 in the model, the 90% confidence intervals are 88% to 104%, 91% to 124%, and 84% to 104% for LNAUCL, LNAUCI, and LNCPEAK, respectively. For the model without residual 1 and treatment*residual 1 in the model, the 90% confidence intervals are 92% to 107%, 96% to 121%, and 89% to 106% for LNAUCL, LNAUCI, and LNCPEAK, respectively.

The 90% confidence intervals calculated for all of the above-mentioned LN transformed pharmacokinetic parameters for baseline subtracted total estrone are within the bioequivalence limits of 80% to 125%.

FDA DEFICIENCY 2: Using the estrone sulfate data you submitted, the 90% confidence intervals of LNAUCT and LNCmax of estrone sulfate (108%-146% and 100%-144%, respectively), calculated by the statistician of the Agency using SAS mixed model with carryover due to treatment-by-residual effect in the model, are outside the acceptable limits of 80-125%.

BERTEK RESPONSE 2: Attachment 2A presents Bertek's statistical re-analysis, using SAS mixed model with carryover due to treatment-by-residual effect in the model as requested by the FDA reviewer, on the original baseline subtracted estrone sulfate data submitted in the original ANDA 75-182. The results indicate the treatment-by-residual carryover are not significant (p=0.0704 and 0.2510 for LNAUCL, and LNCPEAK, respectively). The 90% confidence intervals for LNAUCL, LNAUCI and LNCPEAK are 88% to 104%, 90% to 108%, and 84% to 105%, respectively. The confidence intervals are within bioequivalence limits of 80% to 125%. Bertek was unable to replicate the results obtained by the Agency statistician. Bertek is available to discuss the differences in the results with the Agency.

For the above-mentioned data, the samples were assayed from March 24, 1997 to May 30, 1997 at the Pharmakinetics Laboratory of Mylan Pharmaceuticals, Inc. The method developed for the analysis of plasma estradiol, estrone, and total estrone was performed using a

For the analysis of total estrone, plasma samples were incubated with a non-specific sulfatase enzyme

(Sigma Cat# S 9751) before being measured for estrone concentration. Thus, the total estrone may contain some estrone ß-glucuronide in addition to free estrone and estrone sulfate. Likewise, the estrone sulfate defined in the original submission contained estrone ß-glucuronide and estrone sulfate.

In this Amendment, we also include the most recent data using a method for estrone sulfate assayed at The samples were assayed from July 29, 1998 to August 21, 1998. For the analysis of estrone sulfate, a specific sulfatase (Sigma Cat# S 9754) was used. Attachment 3A contains the analytical report for the estrone sulfate using the chment 3B contains the validation report for the

The presentation of data and pharmacokinetic analysis for baseline subtracted estrone sulfate can be found in Attachment 2B. The mean concentration versus time profiles are illustrated graphically in Attachment 2B, Section C. Mean plasma profiles are similar between Bertek estradiol transdermal system and Climara® (Berlex) estradiol transdermal system.

Attachment 2C provides statistical analysis and 90% confidence intervals using the model with carryover due to treatment-by-residual effect in the model. The 90% confidence intervals for LNAUCL, LNAUCI, and LNCPEAK are 88% to 104%, 86% to 112%, and 83% to 104%, respectively.

Overall, no matter if we use the estrone sulfate data submitted in the original ANDA or the estrone sulfate currently assayed, the results indicate the 90% confidence intervals are similar for the above-mentioned LN transformed pharmacokinetic parameters and the 90% confidence intervals are within bioequivalence limits of 80% to 125%.

FDA DEFICIENCY 3: For the assay of total estrone, please address the issue of glucuronide conjugate, and if it was included in the total estrone or estrone sulfate you reported.

BERTEK RESPONSE 3: The assay for the original submission conducted was validated for Total Estrone, which includes the glucuronide conjugates. As it pertains to the Assay Method used for the original submission, Total Estrone is defined as a combination of free estrone, estrone sulfate and estrone ß-glucuronide. The Estrone Sulfate reported in the original submission was a combination of estrone sulfate and estrone ß-glucuronide.

However, in the analysis by the assay was specific for estrone sulfate only. Please reference Attachment 3B, the validation report from for results from cross reactivity experiments demonstrating the specific analysis for estrone sulfate.

The other four deficiencies relate to technical aspects of the assay method, and are not addressed here.

Study Design

The experimental design for this bioequivalence (BE) study was a two-treatment, four-sequence, three-period replicated-crossover design. 32 subjects (out of 34 subjects enrolled) completed the BE study.

The two treatments studied were:

Test Product (treatment B) - Mylan Estradiol Transdermal System – 31 cm2

Reference Product (treatment A) - Climara® Estradiol Transdermal System – 25 cm2 (Berlex)

The study was conducted in three groups of subjects. The experimental design and subject numbers for those subjects who completed the study are as follows:

week

		1	2	3	4	5	6	7	8	9		
group 1	sequence 1		A			B			A			
	sequence 2		B			A			B			
	sequence 3		B			A			A			
	sequence 4		A			B			B			
group 2	sequence 1			A			B			A		
	sequence 2			B			A			B		
	sequence 3			B			A			A		
	sequence 4			A			B			B		
group 3	sequence 1				A			B			A	
	sequence 2				B			A			B	
	sequence 3				B			A			A	
	sequence 4				A			B			B	

subject numbers:

group 1, sequence 1:	1 5
group 1, sequence 2:	2 6 11
group 1, sequence 3:	3 8 9
group 1, sequence 4:	4 7 10
group 2, sequence 1:	12
group 2, sequence 2:	14 17
group 2, sequence 3:	16
group 2, sequence 4:	13
group 3, sequence 1:	20 22 29 33
group 3, sequence 2:	21 26 30
group 3, sequence 3:	19 23 27 32
group 3, sequence 4:	18 24 28 31 34

Since the participation in the study by three groups of subjects overlaps in time, the possibility of Group-by-Treatment interaction (i.e. that the difference between the treatments depends in a systematic way on which group is considered) does not seem to be a reasonable concern.

Three PK parameters (AUCl, AUCinf, and Cpeak) were analyzed. All PK parameters were statistically analyzed after log-transformation. These log-transformed parameters are designated as LAUCL=ln(AUCl), LAUCINF=ln(AUCinf), and LCPEAK=ln(Cpeak).

Statistical Models

The statistical model assumed initially for the analyses was:

[The subscripts "T" and "R" in these cases refer to the Test product and Reference product, respectively.]

Statistical analyses using this model were carried out using SAS PROC MIXED (SAS version 6.12). For analyses without carryover effects, the SAS statements used for LAUCL and LCPEAK were:

where <y> is the particular response (LAUCL, LCPEAK) being analyzed. These SAS statements allow for possible subject-by-treatment interaction and also allow the within-subject variances of T and R to differ.

In the case of LAUCINF, the dramatic number of missing observations (42 out of 96 observations were missing for estrone sulfate, 37 out of 96 observations were missing for total estrone) made it essentially impossible to estimate all of the parameters of this statistical model. For this reason, the following SAS statements were used to analyze LAUCINF

For analyses including carryover effects, additional terms were added to the CLASS and MODEL statements in the PROC MIXED runs to model the carryover effects. Only first-order carryover effects were considered. However, the possibility of Direct-by-Carryover interaction(i.e. the possibility that carryover effects depended both on the preceding treatment and on the treatment being preceded) was considered in modeling the carryover effects.

Summary of Findings from Dr. Machado's Original Review

Dr. Machado found no evidence of bias in the treatment difference estimate due to carryover effects in her analysis of Estrone (i.e. Free Estrone) and of Estradiol. The 90% confidence intervals she obtained in those cases all fell within the limits of 80% to 125% for all three PK parameters (LAUCL, LAUCINF, and LCPEAK).

In the case of Estrone Sulfate, Dr. Machado found statistical evidence ($p < 0.10$) of possible bias due to carryover effects for LAUCL and LCPEAK. The 90% confidence intervals she obtained for LAUCL and LCPEAK using a model that included carryover effects fell outside of the limits of 80% to 125%. These confidence intervals for

Estrone Sulfate were 108.16% to 146.43% for LAUCL and 99.62% to 143.88% for LCPEAK. The 90% confidence interval for LAUCINF using a model that did not include carryover effects fell within the limits of 80% to 125%.

These results for Estrone Sulfate have been rendered moot by the reassay of the plasma samples for estrone sulfate in response to FDA DEFICIENCY 3.

Dr. Machado was not asked to carry out an analysis of Total Estrone.

Comments on the Sponsor's Statistical Model and Analyses

There were a number of deficiencies in the statistical model used by the sponsor for their PROC MIXED analyses of the original Estrone Sulfate data and their PROC GLM analyses of the reassayed Estrone Sulfate and Total Estrone data:

7. The sponsor failed to include any factors in their model to allow for subject-by-treatment interaction. The variation due to the subject-by-treatment interaction random effect forms the basis for the estimated standard error of the estimated treatment difference in a replicated-treatment crossover study.

8. The sponsor's model does not allow the possibility that the period effects might be different in the three different groups of subjects. The three periods of the study fell in different weeks for the three groups.

9. For analyses with carryover effects, the sponsor has attempted to model the carryover effects by including a CLASS variable called "RESID1" which captures the simple first-order carryover effects, and by also including TREAT*RESID1 in their model. This is a valid way of doing the analysis with carryover if it is done correctly. However, the sponsor has not done it correctly.

The variable RESID1 appears to have the following definition:

RESID1	=	1	if the preceding treatment was A
	=	-1	if the preceding treatment was B
	=	0	if the observation is in the first period

It is necessary to define this third level, level "0", for RESID1 when using SAS, since each observation must have a level of the RESID1 variable. Since by definition there is no carryover effect in period 1, this "0" level of RESID1 is an indicator of period 1. The situation becomes more complicated when we include an interaction with the RESID1 variable. Including TREAT*RESID1 in the model causes SAS to define the following levels of TREAT*RESID1:

TREAT	RESID1	TREAT*RESID1
A	0	A 0
A	1	A 1
A	-1	A -1
B	0	B 0
B	1	B 1
B	-1	B -1

Since there is no carryover effect in period 1, the "A 0" level of TREAT*RESID1 is just an indicator for treatment A in period 1, and the "B 0" level of TREAT*RESID1 is just an indicator for treatment B in period 1. On the other hand, the levels "A 1", "A -1", "B 1", and "B -1" are true indicators of treatment-specific carryover effects.

The goal of the analysis is to obtain an unbiased estimate of the difference between the treatment means. In particular, the estimate should be unbiased by carryover effects. Thus, the coefficients for levels of the carryover effect variables that represent true carryover effects should all be zero. The sponsor appears to have used an ESTIMATE statement of the form:

ESTIMATE 'B VS A' TREAT –1 1/cl alpha=0.1;

in their SAS PROC MIXED code, and a similar statement in their PROC GLM code, in order to obtain their estimate and confidence interval for the difference between the treatment means (the sponsor did not actually report their SAS code in this submission, but I was able to reproduce their analysis using the above ESTIMATE statement). Unfortunately, they did not specify coefficients for the levels of TREAT*RESID1, which is an interaction factor that "contains" TREAT (in the jargon of SAS). The SAS algorithm thus chose default coefficients for the levels of TREAT*RESID1 in order to obtain an estimable comparison, and unfortunately these default coefficients are not the appropriate ones for the objective of the analysis. The default coefficients for TREAT*RESID1 chosen by the SAS algorithm may be obtained by specifying the E option in the ESTIMATE statement. In the following table, I give the coefficients on thelevels of TREAT, RESID1, and TREAT*RESID1 that produce the sponsor's estimates, as well as the correct coefficients for obtaining an unbiased estimate of the treatment mean difference:

Effect	level	coefficients used by the sponsor	correct coefficients
TREAT	A	-1	-1
	B	1	1
RESID1	0	0	0
	1	0	0
	-1	0	0
TREAT*RESID1	A 0	-1/3	-1
	A 1	-1/3	0
	A –1	-1/3	0
	B 0	1/3	1
	B 1	1/3	0
	B –1	1/3	0

The non-zero coefficients on the "A 0" and "B 0" levels of TREAT*RESID1 in the "correct coefficients" column are necessary to make the comparison estimable. Because these levels of TREAT*RESID1 do not reflect carryover effects (because by definition there are no carryover effects in the first period of the study), they do not bias the treatment comparison.

An estimate using the correct coefficients could have been obtained by using an ESTIMATE statement of the form:

ESTIMATE 'B VS A' TREAT –1 1 TREAT*RESID1 –1 0 0 1 0 0/cl alpha=0.1;

This assumes that the sort order of the levels of TREAT*RESID1 is A 0, A 1, A –1, B 0, B 1, and B –1, which in turn depends on the order in which the CLASS variables are listed in the CLASS statement.

The fact that the sponsor's approach resulted in inappropriate coefficients for the levels of TREAT*RESID1 is the most important reason why the sponsor "was unable to replicate the results obtained by the Agency statistician".

10. In the sponsor's "BERTEK RESPONSE 2", referring to their PROC MIXED analysis of the original estrone sulfate data, they state "The results indicate the treatment-by-residual carryover are not significant (p = 0.0704 and 0.2510 for LNAUCL, and LNCPEAK, respectively)." It is our standard practice when testing for carryover to use a level of significance of _ = 0.10, rather then the more usual _ = 0.05, for purposes of deciding whether the carryover effects do or do not need to be included in the statistical model to be used for the final inference.

Under this criterion, the sponsor's result of p = 0.0704 is statistically significant. Also, due to the deficiencies in the sponsor's statistical model, as described in 1. and 2. above, the p-value for TREAT*RESID1 they obtained is questionable, and in fact would have been lower if a more appropriate statistical model had been used.

Our Analyses without Carryover Effects

We have carried out analyses of the reassayed estrone sulfate and total estrone data using the statistical models described above without carryover effects. The resulting 90% confidence intervals (in percentages) for the ratio of test product geometric mean response over reference product geometric mean response are:

	Estrone Sulfate	Total Estrone
LAUCL	94.24% , 110.02%	90.92% , 107.52%
LCPEAK	90.65% , 110.37%	87.49% , 107.52%
LAUCINF	84.62% , 111.83%	89.11% , 123.90%

In all cases, these 90% confidence intervals fall within the usual limits of 80% to 125%.

Our Analyses with Carryover Effects

We have carried out analyses of the reassayed estrone sulfate and total estrone data using the statistical models described above with the addition of carryover effects. The possibility of carryover effects in this study is a legitimate concern given the fact that it involves an endogenous substance.

If a treatment administered in a crossover study has an effect on the response to a treatment administered at a later period of the study, this is called a carryover effect. In bioequivalence studies, we have generally assumed that we only need to worry about first-order carryover effects – i.e. effects that a treatment has on the response to a treatment administered in the next period. However, we do need to consider the possibility that the carryover effect depends not only on the preceding treatment but also on the treatment being preceded. This is called Direct-by-Carryover interaction.

If these carryover effects are not all equal, then the estimate of the difference between the average response to T and the average response to R that we would obtain with no carryover effects in themodel may be biased. It is possible to estimate this bias and test the hypothesis that the bias is zero. The p-values for the test of this bias are as follows:

	p-values for bias	
	Estrone Sulfate	Total Estrone
LAUCL	0.0007	0.0032
LCPEAK	0.0233	0.0170
LAUCINF	0.0044	0.1596

For technical reasons, I have also carried out the test for bias with an additional factor, SEQ*TREAT interaction, included in the model. The p-values for the test of bias with this model are as follows:

	p-values for bias	
	Estrone Sulfate	Total Estrone
LAUCL	0.0011	0.0071
LCPEAK	0.0170	0.0289
LAUCINF	0.0116	0.0445

In the analysis of bioequivalence studies where the possibility of unequal carryover needs to be considered, it has been the practice to test for bias due to carryover effects and to drop carryover effects from the statistical model if the p-value for such bias is greater than 0.10. If the p-value for bias is less than or equal to 0.10, carryover effects are retained in the statistical model used to make the final inference. In the above tables, the p-value for bias is less than 0.10 (indeed, it is less than 0.05) in all cases but one: LAUCINF for Total Estrone in the model without SEQ*TREAT. Thus, from a statistical point of view, we cannot justify dropping carryover effects from the model, with the possible exception of Total Estrone LAUCINF.

I have calculated the 90% confidence intervals resulting from analyses using a statistical model that includes carryover effects. These 90% confidence intervals are:

	Estrone Sulfate	Total Estrone
LAUCL	119.47% , 163.69%	108.38% , 144.95%
LCPEAK	105.64% , 160.38%	99.91% , 142.11%
LAUCINF	116.86% , 203.79%	96.46% , 184.17%

As may be seen, none of these 90% confidence intervals fall within the limits of 80% to 125%. I have also tried a number of alternate carryover models, and the conclusion is always the same: with carryover effects in the model, the 90% confidence intervals fail to fall within the limits of 80% to 125% by a wide margin, in all cases.

Summary

11. If a statistical model without carryover effects is used, the 90% confidence intervals for the ratio of the average response for treatment B (the Test product) over the average response for treatment A (the Reference product) fall within the usual bioequivalence limits of 80% to 125% for all three PK parameters (AUCl, Cpeak, and AUCinf), for both Estrone Sulfate and Total Estrone, as submitted by the sponsor after reassay of the plasma samples.

12. If a statistical model including carryover effects is used, the 90% confidence intervals fail to fall within the usual bioequivalence limits of 80% to 125% by a wide margin, for all three PK parameters (AUCl, Cpeak, and AUCinf) for both Estrone Sulfate and Total Estrone.

13. Potential bias due to carryover effects was statistically significant (p considerably less than 0.10) for all three PK parameters in the case of Estrone Sulfate and for LAUCL and LCPEAK in the case of Total Estrone. The test was ambiguous in the case of Total Estrone LAUCINF.

14. Because Estrone is an endogenous substance, Estrone Sulfate and Total Estrone do not meet the usual criteria that would lead us to discount the possibility of carryover effects. It is clear that this study does not meet the usual bioequivalence criteria for Estrone Sulfate or Total Estrone unless the possibility of carryover effects may be discounted.

15. Results for Estrone (i.e. Free Estrone) and Estradiol were reported in Dr. Machado's original Statistical Review.

Donald J. Schuirmann
Expert Mathematical Statistician
Quantitative Methods & Research staff

Concur: Stella Green Machado, Ph.D.
Director, Quantitative Methods & Research staff

k

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:75-182 (0.1 mg/day) APPLICANT: Bertek, Inc.
75-233 (0.05 mg/day)

DRUG PRODUCT: Estradiol Transdermal System

The Division of Bioequivalence has completed its review and has no further questions at this time.

The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 500 mL of 0.3% sodium lauryl sulfate in 0.005 N NaH_2PO_4, pH 5.5, at 32° C using USP 23 apparatus 5 (paddle over disk) at 100 rpm. The test products should meet the following specifications:

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

2.1

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-182 APPLICANT: Bertek, Inc.

DRUG PRODUCT: Estradiol Transdermal System, 0.1 mg/day

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. Your product contains a greater amount of propylene glycol compared to any other transdermal product. The pharmacology/toxicology reviewer in the Division of Dermatologic and Dental Products noted that this could lead to greater irritation and a three week skin irritation study has been recommended.

2. The recommended study design for skin irritation studies measures cumulative irritation over a 3 week period of repeated application. The cumulative irritation design allows for maximal irritation to occur during the study in order to detect differences and determine the maximum potential for irritation.

3. This product is worn for a full week during regular use. A repeated application would therefore be a total of three patches applied consecutively for 1 week each. Conversely, daily application over a three week period with daily observations would also be an acceptable design.

Sincerely yours,

/S/

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-182 APPLICANT: Bertek, Inc.

DRUG PRODUCT: Estradiol Transdermal System, 0.1 mg/day

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. Your product contains a greater amount of propylene glycol compared to any other transdermal product. The pharmacology/toxicology reviewer in the Division of Dermatologic and Dental Products noted that this could lead to greater irritation and a three week skin irritation study has been recommended.

2. The recommended study design for skin irritation studies measures cumulative irritation over a 3 week period of repeated application. The cumulative irritation design allows for maximal irritation to occur during the study in order to detect differences and determine the maximum potential for irritation.

3. This product is worn for a full week during regular use. A repeated application would therefore be a total of three patches applied consecutively for 1 week each. Conversely, daily application over a three week period with daily observations would also be an acceptable design.

Sincerely yours,

/S/

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCE DEFICIENCIES

ANDA: 75-182 APPLICANT: Bertek, Inc.

DRUG PRODUCT: Estradiol Transdermal System

The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet. The following deficiencies have been identified:

1. Please conduct statistical analysis (with and without carryover effects) on the total estrone data; because the method of calculation from which the concentration of estrone sulfate was derived, i.e. subtracting free estrone concentration from total estrone concentration, involved two sets (total estrone and of free estrone) of intra-subject variabilities.

2. Using the estrone sulfate data you submitted , the 90% confidence intervals of LNAUCT and LNCmax of estrone sulfate (108-146% and 100-144%, respectively), calculated by the statistician of the Agency using SAS mixed model with carryover due to treatment-by-residual effect in the model, are outside the acceptable limits of 80-125%.

   Two types of carryover were estimated, first-order residual effects and treatment-by-residual effects. It was concluded that data you submitted supported the bioequivalence of the test and reference treatments for the components estradiol and estrone, but the bioequivalence of estrone sulfate was not supported. This was due to the significant treatment-by-residual carryover on the LNAUCT and LNCmax of estrone sulfate ($p = 0.0047$ and 0.0281 respectively) and resulted in above mentioned out-of-limit 90% confidence intervals.

3. For the assay of total estrone, please address the issue of glucuronide conjugate, and if it was included in the total estrone or estrone sulfate you reported.

4. For the assay of estrone sulfate, please clarify if standards and QC samples were prepared by spiking plasma samples with free estrone or with estrone sulfate.

   The preferred method to prepare standards and QC samples for the analysis of estrone sulfate would be to spike plasma with sulfate ester.

5. Please define the enzymatic activities of aryl sulfatase, which was used to hydrolyze the plasma sample with internal standard to indicated if they include the

activity of glucuronidase.

6. Please report whether estrone or estrone sulfate was used in the recovery and stability studies during analytical method validation for total estrone.

7. Please submit adequate stability data for total estrone since the maximum number of days for samples storage during the analysis of total estrone was reported to be 153 days, yet the stability of frozen samples was documented for only 106 days.

In addition, the multiple-dose study stated as 'required' in the Agency's letter of 5/27/98 is no longer required.

Sincerely yours,

/S/

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Estradiol
Transdermal System,
ANDA #75-182 (0.1 mg/day)
ANDA #75-233 (0.05 mg/day)
Reviewer : Lin-Whei Chuang

Bertek, Inc.
St. Albans, VT

Submission Date:
August 6, 1997 (#75-182)
October 21, 1997 (#75-233)

REVIEW OF a BIOEQUIVALENCE STUDY

BACKGROUND

Estradiol, a naturally occurring hormone, is prescribed as replacement therapy for the women with estrogen-deficiency condition. Menopause (surgical or natural) is a major reason of this condition causing hot flushes, sleep disturbance and excessive sweating. Since orally administered estradiol is rapidly metabolized by the liver, estradiol transdermal delivery system was devised to circumvent the problem. Therapy is generally started with the application of low strength patch on the lower abdomen. A patch is in place for 84 hours (2 patches/week) and the cyclic regimen consist of the application of patches for 3 weeks followed by 1 week without patches. Estrogens have been reported to increase the risk of endometrial carcinoma. In prolonged treatment, the patients should be monitored periodically. Cyclical treatment with low level of estradiol appears to be less risky.

The estradiol patch is found to be more effective than the oral dosage forms. To obtain identical mean plasma estradiol levels, oral dose will have to be 20 times that of a dose in a patch. A single-application study with 14 post-menopausal women using Estraderm^{R}, 0.05 mg/day and 0.1 mg/day, showed an increase in plasma estradiol levels within four hour of the application and maintained the increased estradiol levels of 32 and 67 pg/mL over the baseline, respectively, for the duration of the application. At the same time, estrone serum concentration averaged only 9 and 27 pg/mL above baseline, respectively. It took about 24 hours to return to the baseline serum estradiol level after the removal of the patch. Estimated daily urinary output of estradiol conjugates also increased 5-10 times during dosing, and returned to normal in 2 days.

In a 3-week-multiple applications study with 14 post menopausal women, in which 0.05 mg estradiol patch was applied twice/week, the mean steady-state plasma estradiol and estrone levels increased by 30 pg/mL and 12 pg/mL, respectively. Urinary estradiol conjugate levels returned to the baseline within 3 days after the removal of the last (6th) patch in that study.

There are three reference listed TDS products on the market in this strength (0.1 mg/24 hr), Berlex's Climara® (NDA #20375), Ciba's Estraderm® patch (NDA # 19081), and Ciba Geigy's Vivelle® (NDA #20323). The firm is using Climara® (7-Day patch) in its study as the RLD.

In Vivo Bioequivalence Study

The protocol of this study was dated 10/30/96 and was approved by Clinical and Pharmacologic Research IRB on 12/5/96. The objective of the study was primarily to compare the relative bioavailability and secondly to compare the wearability (adhesion) and acute irritation of the test product to Climara® of Berlex Laboratories following a single application, under fasting conditions, in healthy , non-smoking, post-menopausal female subjects.

The clinical study was conducted at Clinical and Pharmacologic

during 12/26/96-2/16/97 (group A, subjects #1-11), 1/5-2/26/97 (group B, subjects #12-17), and 1/9-3/2/97 (group C, subjects #18-34). The analytical study was conducted at the

during 4/1-5/30/97.

The design of the study was a single-dose, 2-treatment, 3-period, 4-sequence crossover under fasting conditions in 33 female subjects. They were 30-64 years old, weighed within 15% of their ideal weight, and were judged healthy based on pre-study medical evaluation (physical examination, laboratory evaluation and ECG) performed within 14 days of the initial dose of study medication. They did not have history of significant chronic diseases, hepatitis or drug/alcohol abuse. Subjects were excluded from the study if they had excessive blood donation within 28 days, used of any medication within 14 days, consumed vitamins, alcohol,

caffeine- or xanthine-containing products within 2 days, participated in other drug study within 30 days, prior to the initial dose of study medication, or failed to meet baseline level for FSH and/or 17-β-estradiol.

All volunteers read and signed the informed consent form and were randomly assigned to 1 of the following 4 sequences:

Sequence	Subjects
ABB	4,7,10,13,18,24,28,31,34
ABA	1,5,12,20,22,25,29,33
BAA	3,8,9,16,19,23,27,32
BAB	2,6,11,14,17,21,26,30

After an overnight fast, in the morning of 12/28/96, 1/7/97, and 1/11/97 for group A, B, and C respectively, each subject received one of the following treatments according to her assigned sequence:

Treatment A - Reference Drug: Climara® Transdermal Systems - single application of 0.1 mg/day, on the lower abdomen for 7-day wear, under fasting conditions, Berlex lot #P50169 (7.8 mg/25 cm^2), expired in 8/97, potency 99.8%.

Treatment B - Test Drug: Estradiol Transdermal Systems - single application of 0.1 mg/day, on the lower abdomen for 7-day wear, under fasting conditions, Mylan lot #26C001L (manufactured by Bertek, 3.88 mg in 31 cm^2/42 cm^2 double disk). Biostudy lot - 384 m^2 (equivalent to nits of 31 cm^2), manufactured in 9/96, potency 102.2%.

Subjects were confined at the clinical site from 11 hours before until 24 hours after the system application. Standard meals began to be provided 5 hours after system application. The patches were removed at 168 hours post-application.

Blood samples were collected at -48, -24, 0, 6, 12, 18, 24, 48, 72, 96, 120, 144, 168 hours (7 days) and after patch removal at 169, 170, 176, 182, 190 and 200 hours. Plasma samples were stored at -70°C at the clinical site until shipped for analysis.

After a 2-week washout period from the time of patch-removal, again after an overnight fast, in the morning of 1/18/97, 1/28/97, and 2/1/97, for group A, B, and C respectively, subjects received treatment for period 2. Similarly, in the morning of 2/8/97, 2/18/97, and 2/22/97, for group A, B, and C respectively, subjects received treatment for period 3.

Skin irritation was evaluated at 0.5 and 1 hour after patch removal; and again at 3 hours and continued at 12 hours intervals if necessary.

Patch adhesion was evaluated at 6, 12, 24, 48, 72, 96, 120 and 144 hours.

Plasma samples were assayed for free estradiol, free estrone and estrone sulfate.

ANOVA was performed on AUCL, AUCI, Cmax of baseline-adjusted estradiol, estrone and estrone sulfate using PROC GLM. Group and sequence interactions were tested before combining all 3 groups. The full ANOVA model contained terms for sequences, subjects within sequences, treatments, periods and carry-over. When carry-over was not significant, the reduced ANOVA model did not contain the terms of carry-over.

The apparent dose for each subject was computed from the following equations:

Apparent Dose = Initial Patch Potency - Residual Amount
Residual amount = Residual Patch Potency + Skin Wipe

Analytical Method -- **Not for Release through FOI:**

total estrone.

The pre-study validation data for estradiol and free estrone are presented below in Table 1:

Table 1: Pre-Study Validation -- Estradiol and Free Estrone

Parameter	Estradiol	Free Estrone
Sensitivity/LOQ (pg/mL)	5	5
Quality Control Conc.(pg/mL) (Lo, Med, Hi)	10, 50, 250	15, 100, 150
Linear Range (pg/mL)	5-750	5-750
Intra-run Precision (%CV)	6.6-10.4	4.1-6.9
Intra-run Accuracy (%Actual)	96.0-100.9	96.7-103.3
Inter-run Precision (%CV)	5.3-7.4	6.1-9.7
Inter-run Accuracy (%CV)	96.8-99.2	98.0-101.3
Selectivity	no interferences	no interferences
Stability (%) a) Plasma Sample @ Room Temp. for 4 Hr* b) Processed samples @ Room Temp. for 96 Hr* c) Plasma Sample after 2 Freeze-Thaw Cycles d) Plasma Sample frozen for 179 days	101.7 100.0 Hi Lo 94.4 92.3 107.4 113.0	107.7 101.7 Hi Lo 98.4 95.0 110.4 104.0

Percent Recovery***	Hi 97.8 Lo 98.7	Hi 94.7 Lo 103.2

* concentrations were not specified

During the analysis of the study samples, 35 standard curves each for estradiol and free estrone were conducted, each with duplicates of the 3 levels of QC samples. The during-study validation for estradiol and free estrone are presented below in Table 2:

Table 2: During-Study Validation -- Estradiol and Free Estrone

Parameter	Estradiol	Free Estrone
Sensitivity/LOQ (pg/mL)	5	5
Quality Control Conc.(pg/mL) (Lo, Med, Hi)	10, 50, 250	10, 100, 250
Correlation Coefficient	≥0.9808	≥0.9793
Linear Range (pg/mL)	5-750	5-750
Precision (%CV) for Standards	3.5-7.7	3.6-7.0
Precision (%CV) for QC Samples	7.2-9.8	7.8-9.3
Accuracy (%Actual) for standards	98.7-100.9	97.0-101.9
Accuracy (%Actual) for QC Samples	96.2-99.7	96.4-97.8

For the assay of total estrone (free estrone + estrone sulfate), 2 standard curve ranges were used. The first 5 analytical batches used high range curves, and the rest of the analytical batches used low range curves (g/mL). The pre-study validation data for total estrone is presented below in Table 3:

Table 3: Pre-Study Validation -- Total Estrone (Free Estrone + Estrone Sulfate)

Parameter	High Range	Low Range
Sensitivity/LOQ (pg/mL)	200	50
Quality Control Conc.(ng/mL) (Lo, Med, Hi)	750, 5000, 25000	100, 750, 5000
Linear Range (pg/mL)	200-40000	50-8000
Intra-run Precision (%CV)	6.7-8.5	2.7-5.5
Intra-run Accuracy (%Actual)	98.3-98.9	94.4-99.1

Inter-run Precision (%CV)	4.2-8.4	4.9-6.6
Inter-run Accuracy (%CV)	97.4-104.8	95.3-98.8
Selectivity	no interferences	no interferences
Stability (%) a) Plasma Sample @ Room Temp. for 4 Hr b) Processed samples @ Room Temp. for 96 Hr c) Plasma Sample after 3 Freeze-Thaw Cycles d) Plasma Sample frozen for 106 days	97.3* 95.8* 92.1 (at 5000 pg/mL of estrone sulfate) 101.1 (at 4679.8 pg/mL)	
Percent Recovery***	4000 pg/mL 94.0	100 pg/mL 88.2

* = concentrations were not specified

During the analysis of the study samples, 33 standard curves (5 of high range and 28 of low range) were conducted for the assay of total estrone, each with duplicates of the 3 levels of QC samples. The during-study validation for estradiol and free estrone are presented below in Table 4:

Table 4: During-Study Validation -- Total Estrone (Free Estrone + Estrone Sulfate)

Parameter	High Range	Low Range
Sensitivity/LOQ (pg/mL)	200	50
Quality Control Conc.(ng/mL) (Lo, Med, Hi)	750, 5000, 25000	100, 750, 5000
Correlation Coefficient	≥0.9961	≥0.9784
Linear Range (ng/mL)	200-40000	50-8000
Precision (%CV) for Standards	2.0-4.3	3.3-8.8
Precision (%CV) for QC Samples	9.5-11.1	8.2-8.8
Accuracy (%Actual) for standards	96.2-104.7	95.7-104.2
Accuracy (%Actual) for QC Samples	98.4-98.8	97.0-99.8

Comments on the Analytical Method:

1. The analysis for free estradiol and free estrone are acceptable.

2. For the analysis of total estrone, the firm did not address the issue of glucuronide conjugate, and if it was included in the estrone sulfate reported by the firm.

3. The firm should clarify if the enzymatic activities of aryl sulfatase, which was used to hydrolyze the plasma sample with internal standard include the activity of glucuronidase.

4. For the analysis of estrone sulfate, the firm did not report if standards and QC samples were prepared by spiking plasma samples with free estrone or with estrone sulfate.

   The preferred method to prepare standards and QC samples for the analysis of estrone sulfate would be to spike plasma with sulfate ester.

5. The firm also did not report whether estrone or estrone sulfate was used in the recovery and stability studies during analytical method validation for total estrone.

6. The maximum number of days for samples storage during the analysis of total estrone was reported to be 153 days, yet the stability of frozen samples was documented for only 106 days.

Results:

All of 32 subjects (#1-32 and #34 with #25 disqualified before period 1) completed the study, subject #15 delayed her treatments from group A to group C due to personal reasons and was re-assigned as #33. Ten (10) adverse events were reported, including itching under patch, lower abdominal cramping, nausea, vomiting, and headache. The distribution of these events between the 2 treatments are summarized below in Table 5:

Table 5: Distribution of Adverse Events

	Treatment A	Treatment B
# of events Reported	5	5
# of subject made the report	4	4
# of event probably related to study drug	3	3

The apparent doses were 0.91-2.49 mg/patch (approximately 12-32% of the control patch) for treatment A; and 0.48-1.98 mg/patch (approximately 12-50% of the control patch) for treatment B.

Patch adhesion scores (0-7 with 7 being 100% attached) indicated that the reference product was rated 7 at all 8 evaluation time points for all subjects; while the test product was rated 7 at 6, 12 and 24 hours for all subjects, but 1 subject each was rated 6 at 48, 72 and 96, 120 and 144 hours, and 1 subject each was rated 3 at 120 and 144 hours.

Skin irritation data summarized below in Table 6 showed greater irritation for test product than for the reference product, however, the firm had submitted (under the same ANDA#) a separate comparative skin irritation study and was reviewed by the medical officer, M. Fanning, M.D..

Table 6: Skin Irritation after Different Time Points after Patch-Removal

	Treatment A (Reference)			Treatment B (Test)		
	0 hour	0.5 hour	1 hour	0 hour	0.5 hour	1 hour
# of Subjects with slight redness	12	10	5	19	15	8
# of Subject with Erythema	4	1	1	5	1	3
# of Subject with Erythema/Elevation	0	0	0	2	2	0

Additional toxicology data were submitted. They included a dermal sensitization study in guinea pigs and a primary dermal irritation study in rabbits, both conducted on test lot #26B005N and placebo lot #26B004N. Both lots were not considered to be dermal sensitizer in guinea pigs, and there was no meaningful difference in the level of irritation observed in rabbits administered with the test and placebo lots.

Out of the 1824 study plasma samples collected, 2 each for estradiol and estrone were not reportable due to procedure failure, 1 was re-assayed for estradiol, 4 for estrone, and 1 for total estrone due to pharmacokinetic anomaly.

Since all three components are endogenous steroids, an average baseline correction was obtained by averaging the 3 pre-application sampling times (-48, -24 and 0 hours) for each period. The mean plasma concentrations (baseline-adjusted) of estradiol, estrone and estrone sulfate at each sampling point after each treatments and the mean pharmacokinetic parameters are presented in Figures 1-3 and Tables 7-9. The AUCI of some subjects were not estimated due to irregular elimination profiles.

Table 7:
ARITHMETIC MEANS OF PLASMA ESTRADIOL LEVELS (PG/ML, BASELINE-ADJUSTED) AND RATIOS OF MEANS
--- 0.1 MG/DAY PATCH FOR 7 DAYS UNDER FASTING CONDITION (N=32 SUBJECTS)---

	MEAN-TEST	SD	MEAN-REF.	SD	RATIO T/R
TIME HR					
0	0.40	1.23	0.71	3.36	0.56
6	89.45	54.33	83.42	63.65	1.07
12	140.43	70.18	134.38	73.71	1.04
18	165.50	76.31	173.46	92.27	0.95
24	151.00	67.97	156.50	88.00	0.96
48	133.21	64.79	118.27	63.38	1.13
72	121.04	52.30	99.20	52.74	1.22
96	111.52	55.65	85.14	39.52	1.31
120	92.88	35.26	77.01	37.14	1.21
144	71.54	25.97	68.33	37.11	1.05
168	64.33	22.74	62.84	30.72	1.02
169	52.80	17.83	58.87	23.61	0.90
170	37.23	15.72	40.12	18.41	0.93
176	13.87	9.17	14.32	10.72	0.97
182	6.78	6.97	8.55	9.11	0.79
190	2.91	4.31	4.12	9.80	0.71
200	2.01	3.48	3.12	6.75	0.64

Table 8:
ARITHMETIC MEANS OF PLASMA ESTRONE LEVELS (PG/ML, BASELINE-ADJUSTED) AND RATIOS OF MEANS
--- 0.1 MG/DAY PATCH FOR 7 DAYS UNDER FASTING CONDITION (N=32 SUBJECTS)---

	MEAN-TEST	SD	MEAN-REF.	SD	RATIO T/R
TIME HR					
0	2.45	2.79	2.48	2.23	0.99
6	14.22	10.50	13.20	11.09	1.08
12	29.82	16.89	32.81	20.02	0.91
18	40.44	20.77	48.02	25.67	0.84
24	52.40	25.61	62.31	30.06	0.84
48	61.00	29.44	64.92	29.10	0.94
72	59.41	26.46	57.98	25.89	1.02
96	54.44	28.73	49.27	22.78	1.10
120	46.38	24.54	44.01	19.68	1.05
144	38.61	21.26	38.18	17.02	1.01
168	32.19	17.67	33.88	17.86	0.95
169	30.19	16.12	33.06	16.09	0.91
170	29.39	17.55	31.25	15.72	0.94

176	22.55	16.94	23.85	15.52	0.95
182	14.12	12.71	15.26	11.52	0.92
190	12.34	11.98	12.96	9.58	0.95
200	6.10	7.26	7.40	7.71	0.82

Table 9:
ARITHMETIC MEANS OF PLASMA ESTRONE SULFATE LEVELS (PG/ML, BASELINE-ADJUSTED) AND RATIOS OF MEANS
--- 0.1 MG/DAY PATCH FOR 7 DAYS UNDER FASTING CONDITION (N=32 SUBJECTS) ---

TIME HR	MEAN-TEST	SD	MEAN-REF.	SD	RATIO T/R
0	16.16	37.97	14.60	31.12	1.11
6	239.23	176.55	263.57	267.30	0.91
12	504.12	255.30	516.73	258.34	0.98
18	630.50	379.27	681.03	364.00	0.93
24	924.73	557.39	1056.45	677.95	0.88
48	1198.15	751.86	1280.25	889.61	0.94
72	1198.63	860.82	1196.38	808.18	1.00
96	1099.30	893.93	1037.73	748.71	1.06
120	927.35	703.25	957.59	761.10	0.97
144	766.48	527.70	770.09	641.74	1.00
168	644.21	485.67	660.05	484.13	0.98
169	606.80	466.30	626.77	469.70	0.97
170	578.85	438.56	607.15	401.55	0.95
176	484.52	388.50	528.70	427.36	0.92
182	278.08	269.87	342.04	303.11	0.81
190	174.41	178.16	226.97	252.62	0.77
200	130.54	140.38	208.35	271.98	0.63

The pharmacokinetic parameters for estradiol, estrone and estrone sulfate, as calculated by the reviewer, are presented below in Tables 10-12 (Cmax is the maximum concentration since patch application, and AUCs are the sum of linear trapezoidal estimation of the area from the time of dosing):

TABLE 10:
ARITHMETIC MEANS OF ESTRADIOL PHARMACOKINETIC PARAMETERS AND RATIOS OF MEANS
--- 0.1 MG/DAY PATCH FOR 7 DAYS UNDER FASTING CONDITION (N=32 SUBJECTS) ---

PARAMETER	MEAN-TEST	SD	MEAN-REF.	SD	RATIO T/R
AUCI	18362.74	6947.68	16701.50	8342.60	1.10
AUCT	18490.60	6909.80	16610.36	8010.22	1.11
CMAX	177.66	76.21	180.76	93.98	0.98
KE	0.18	0.15	0.16	0.12	1.12
LAUCI	17073.11	--	15093.75	--	1.13
LAUCT	17242.62	--	14994.03	--	1.15
LCMAX	161.13	--	159.98	--	1.01
THALF	7.13	6.11	8.58	10.87	0.83
TMAX	30.49	23.46	21.96	14.50	1.39

TABLE 11:
ARITHMETIC MEANS OF ESTRONE PHARMACOKINETIC PARAMETERS AND RATIOS OF MEANS --- 0.1 MG/DAY PATCH FOR 7 DAYS UNDER FASTING CONDITION (N=32 SUBJECTS)---

PARAMETER	MEAN-TEST	SD	MEAN-REF.	SD	RATIO T/R
AUCI	9370.58	3613.32	10054.96	3311.95	0.93
AUCT	8442.48	3622.62	8575.77	3539.53	0.98
CMAX	71.60	31.49	73.18	31.47	0.98
KE	0.09	0.07	0.07	0.06	1.28
LAUCI	8660.42	---	9495.16	---	0.91
LAUCT	7590.62	---	7772.01	---	0.98
LCMAX	64.31	---	66.60	---	0.97
THALF	13.20	12.59	15.34	10.30	0.86
TMAX	63.06	31.30	49.15	23.12	1.28

TABLE 12:
ARITHMETIC MEANS OF ESTRONE SULFATE PHARMACOKINETIC PARAMETERS AND RATIOS OF MEANS --- 0.1 MG/DAY PATCH FOR 7 DAYS UNDER FASTING CONDITION (N=32 SUBJECTS)---

PARAMETER	MEAN-TEST	SD	MEAN-REF.	SD	RATIO T/R
AUCI	184084.54	111694.46	177689.50	83667.63	1.04
AUCT	164403.98	106418.88	170050.77	114929.26	0.97
CMAX	1425.30	937.25	1469.55	875.68	0.97
KE	0.08	0.08	0.06	0.03	1.37
LAUCI	157287.83	---	158578.81	---	0.99
LAUCT	136231.99	---	142256.88	---	0.96
LCMAX	1201.82	---	1278.40	---	0.94
THALF	13.23	7.45	15.06	7.85	0.88
TMAX	74.57	42.94	62.30	29.46	1.20

Due to the replicate design of the study, statistical analysis were conducted by S. Machado, Ph.D. of QMR/OEB/CDER/FDA. A copy of her review is attached.

Two types of carryover were estimated, first-order residual effects and treatment-by-residual effects. It was concluded that data submitted by the firm supported the bioequivalence of the test and reference treatments for the components estradiol and estrone, but the bioequivalence of estrone sulfate was not supported. This was due to the significant treatment-by-residual carryover (defined as 'carry' in the model) on the LNAUCT and LNCmax of estrone sulfate ($p = 0.0047$ and 0.0281 respectively). The Least Square means, ratios of means, and 90% confidence intervals estimated by the statistician are presented below in Table 13. Basic SAS mixed model was used except for LNAUCT and LNCmax of estrone sulfate when the 'basic' and 'carry' were used.

Table 13: LS MEANS (LSMs), RATIOS of LSMs, AND 90% CONFIDENCE INTERVALS -- Conducted by the Agency using SAS Mixed Model --					
		Test LSM	Ref. LSM	Ratio (T/R)	90% C.I.
Estradiol	LNAUCT	17015.6	15750.5	1.08	1.0135-1.1517
	LNAUCI	16795.8	15202.0	1.10	1.0290-1.1863
	LNCmax	162.8	172.2	0.94	0.8784-1.0168
Estrone	LNAUCT	7968.2	8336.3	0.96	0.8859-1.0312
	LNAUCI	9380.1	8979.9	1.05	0.9345-1.1675
	LNCmax	68.2	72.5	0.94	0.8637-1.0248
Estrone Sulfate	LNAUCT	175964.0	139823.0	1.26	1.0816-1.4643
	LNAUCI	170310.1	173121.3	0.98	0.8428-1.1482
	LNCmax	1281.4	1534.1	1.20	0.9962-1.4388

Statistical analysis conducted by the firm (GLM procedures) did not indicate any carryover effect for any of the 3 analytes. Following results (Table 14) were obtained by the firm without residual covariate:

Table 14: LS MEANS (LSMs), RATIOS of LSMs, AND 90% CONFIDENCE INTERVALS -- Conducted by the Firm SAS GLM Model --					
		Test LSM	Ref. LSM	Ratio (T/R)	90% C.I.
Estradiol	LNAUCT	16481.6	15367.3	1.08	1.0131-1.1438
	LNAUCI	16647.2	14913.2	1.10	1.0390-1.1840
	LNCmax	154.5	164.0	0.94	0.8758-1.0046
Estrone	LNAUCT	7480.1	7863.6	0.96	0.8858-1.0249
	LNAUCI	8778.0	8604.1	1.05	0.9302-1.1269
	LNCmax	63.4	67.4	0.94	0.8712-1.0124
Estrone Sulfate	LNAUCT	140084.3	141492.2	1.26	0.9218-1.0710
	LNAUCI	154817.2	153276.7	0.98	0.8976-1.1381
	LNCmax	1236.4	1274.1	1.20	0.8847-1.0660

Comments on Results:

1. The method of calculation from which the concentration of estrone sulfate was derived, i.e. subtracting free estrone concentration from total estrone concentration, involved two sets (total estrone and free estrone) of intra-subject variabilities. Therefore it is preferred that the data of total estrone be statistically analyzed.

2. Due to differences in statistical methods conducted by the firm and by the Agency, the resulting pivotal data, i.e. the 90% confidence intervals, are also different. Particularly, the 90% confidence intervals of LNAUCT and LNCmax of estrone sulfate, as calculated by the statistician of the Agency, are outside the acceptable limits of 80-125%. However, this might become inconsequential because:

   a. The Division is currently formulating a policy on the testing of carryover effect. At this point in time, the Division is not enforcing testing for carryover at in the models.

   b. As mentioned in comment #1, the significance of estrone sulfate data as calculated by the firm is not clear since it involved 2 sets of intra-subject variabilities.

3. The test patch caused relatively more irritation than the reference patch (Table 6). However, the firm had submitted a separate comparative skin irritation study that was reviewed by the medical officer.

4. Tmax was substantially longer for the test patch than for the reference patch (Tables 10-12).

Comparative Formulations:

see package insert

Dissolution Testing:

The following dissolution testings were conducted by the firm:

Table 15 - In Vitro Dissolution Testing

Drug (Generic Name): Estradiol
Dosage Form: Transdermal System
Dose Strength: 0.1 mg/Day & 0.05 mg/day
ANDA No.: 75-182 & 75-233
Firm: Bertek, Inc.
Submission Date: 8/6/97 & 10/21/87

I. Conditions for Dissolution Testing:

USP XXIII Apparatus 5: Paddle over disk
RPM: 100 No. Units Tested: 12
Medium: 500 mL of 0.3% SDS, 0.005 N NaH_2PO_4, pH 5.5 @ 32° C
Proposed Tolerance: Time (hour) % Label Claim Released

Reference Drug: Climara[R] Transdermal system (Berlex)
Assay Methodology: Not Given

II. Results of In Vitro Dissolution Testing:

Sampling Times (hour)	Test Product Lot # 26C001L Strength : 0.1 mg/day (3.88 mg; 31 cm^2/42 cm^2 double disk)	Reference Product Lot # P50169 Strength : 0.1 mg/day (7.8 mg/25 cm^2)

	Mean %	Range	%CV	Mean %	Range	%CV
1	29		2.6	48		1.8
4	58		0.9	84		0.7
8	78		1.0	92		0.6
24	97		1.3	95		0.5
Sampling Times (hour)	Test Product Lot # 26D011D Strength : 0.05 mg/day (1.94 mg; 15.5 cm^2/24 cm^2 double disk)			Reference Product Lot # P50063 Strength : 0.05 mg/day (3.9 mg/12.5 cm^2)		
	Mean %	Range	%CV	Mean %	Range	%CV
1	29		1.5	50		1.3
4	60		0.6	86		0.2
8	79		2.0	93		1.5
24	96		1.3	97		0.7

Comments:

1. The dissolution specification at the 8-hour time point exceeds the maximal range of 25% normally recommended by the Agency. A revised specification of for the 8-hour time point is recommended.

2. The dissolution data of the test product comply with the recommended specification.

Waiver Request:

The firm requests waiver of the *in vivo* bioequivalence testing requirements for its estradiol transdermal system, 0.05 mg/day, per 21 CFR 320.22(d)(2).

Comments:

1. Comparative formulations demonstrate proportionality between the 0.1 mg/day patch and 0.05 mg/day patch for all ingredients in the inner disk. Ingredients in the outer disk, which is used only to provide additional adhesion of

the product to the patient, are slightly non-proportional. This difference has no effect on the delivery of the active ingredient.

2. Dissolution data on the 0.05 mg/day patch comply with the recommended specifications.

3. However, the bioequivalence study on the 0.1 mg/day is found to be incomplete at present.

Additional Comment:

In the previous Agency's letter of 5/27/98, the firm was advised that a multiple-dose study was required. However, the Office has since decided that a multiple-dose study is not required.

Overall Deficiencies:

1. The firm should conduct statistical analysis (with and without carryover effects) on the total estrone data. This is because the method of calculation from which the concentration of estrone sulfate was derived, i.e. subtracting free estrone concentration from total estrone concentration, involved two sets of intra-subject variabilities, i.e., those of total estrone and of free estrone.

2. Using the estrone sulfate data submitted by the firm, the 90% confidence intervals of LNAUCT and LNCmax of estrone sulfate (108-146% and 100-144%, respectively), calculated by the statistician of the Agency using SAS mixed model with carryover due to treatment-by-residual effect in the model, are outside the acceptable limits of 80-125%.

   Two types of carryover were estimated, first-order residual effects and treatment-by-residual effects. It was concluded that data submitted by the firm supported the bioequivalence of the test and reference treatments for the components estradiol and estrone, but the bioequivalence of estrone sulfate was not supported. This was due to the significant treatment-by-residual carryover on the LNAUCT and LNCmax of estrone sulfate ($p = 0.0047$ and 0.0281 respectively) and resulted in above mentioned out-of-limit 90% confidence

intervals.

3. For the assay of total estrone, the firm did not address the issue of glucuronide conjugate, and if it was included in the total estrone or estrone sulfate reported by the firm.

4. For the analysis of estrone sulfate, the firm did not report if standards and QC samples were prepared by spiking plasma samples with free estrone or with estrone sulfate.

   The preferred method to prepare standards and QC samples for the analysis of estrone sulfate would be to spike plasma with sulfate ester.

5. The firm should clarify if the enzymatic activities of aryl sulfatase, which was used to hydrolyze the plasma sample with internal standard (1-methylestrone), include the activity of glucuronidase.

6. The firm also did not report whether estrone or estrone sulfate was used in the recovery and stability studies during analytical method validation for total estrone.

7. The maximum number of days for samples storage during the analysis of total estrone was reported to be 153 days, yet the stability of frozen samples was documented for only 106 days.

Recommendations:

1. The single-dose, fasted bioequivalence study conducted by Bertek. Inc. on its estradiol transdermal system, 0.1 mg/day, lot #26C001L, comparing it to Climara[R] transdermal system, lot #P50169, has been found incomplete by the Division of Bioequivalence due to 7 deficiencies.

2. Waiver of the *in vivo* bioequivalence testing requirements for Bertek's estradiol transdermal system, 0.05 mg/day, can not be granted per 21 CFR 320.22(d)(2), pending approval of an acceptable bioequivalence study for Bertek's estradiol transdermal system, 0.1 mg/day.

/S/ 7/9/98

Lin-Whei Chuang
Division of Bioequivalence
Review Branch I

RD INITIALLED YHUANG 9/98
FT INITIALLED YHUANG

Concur /S/ /S/ Date: 7/10/98
Dale Conner, Pharm. D.
Director, Division of Bioequivalence

BIOEQUIVALENCE DEFICIENCIES

ANDA: 75-182 APPLICANT: Bertek, Inc.

DRUG PRODUCT: Estradiol Transdermal System

The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet. The following deficiencies have been identified:

1. Please conduct statistical analysis (with and without carryover effects) on the total estrone data; because the method of calculation from which the concentration of estrone sulfate was derived, i.e. subtracting free estrone concentration from total estrone concentration, involved two sets (total estrone and of free estrone) of intra-subject variabilities.

2. Using the estrone sulfate data you submitted , the 90% confidence intervals of LNAUCT and LNCmax of estrone sulfate (108-146% and 100-144%, respectively), calculated by the statistician of the Agency using SAS mixed model with carryover due to treatment-by-residual effect in the model, are outside the acceptable limits of 80-125%.

   Two types of carryover were estimated, first-order residual effects and treatment-by-residual effects. It was concluded that data you submitted supported the bioequivalence of the test and reference treatments for the components estradiol and estrone, but the bioequivalence of estrone sulfate was not supported. This was due to the significant treatment-by-residual carryover on the LNAUCT and LNCmax of estrone sulfate ($p = 0.0047$ and 0.0281 respectively) and resulted in above mentioned out-of-limit 90% confidence intervals.

3. For the assay of total estrone, please address the issue of glucuronide conjugate, and if it was included in the total estrone or estrone sulfate you reported.

4. For the assay of estrone sulfate, please clarify if standards and QC samples were prepared by spiking plasma samples with free estrone or with estrone sulfate.

   The preferred method to prepare standards and QC samples for the analysis of estrone sulfate would be to spike plasma with sulfate ester.

5. Please define the enzymatic activities of
   which was used to hydrolyze the plasma sample with internal standard to indicated if they include the

activity of glucuronidase.

6. Please report whether estrone or estrone sulfate was used in the recovery and stability studies during analytical method validation for total estrone.

7. Please submit adequate stability data for total estrone since the maximum number of days for samples storage during the analysis of total estrone was reported to be 153 days, yet the stability of frozen samples was documented for only 106 days.

In addition, the multiple-dose study stated as 'required' in the Agency's letter of 5/27/98 is no longer required.

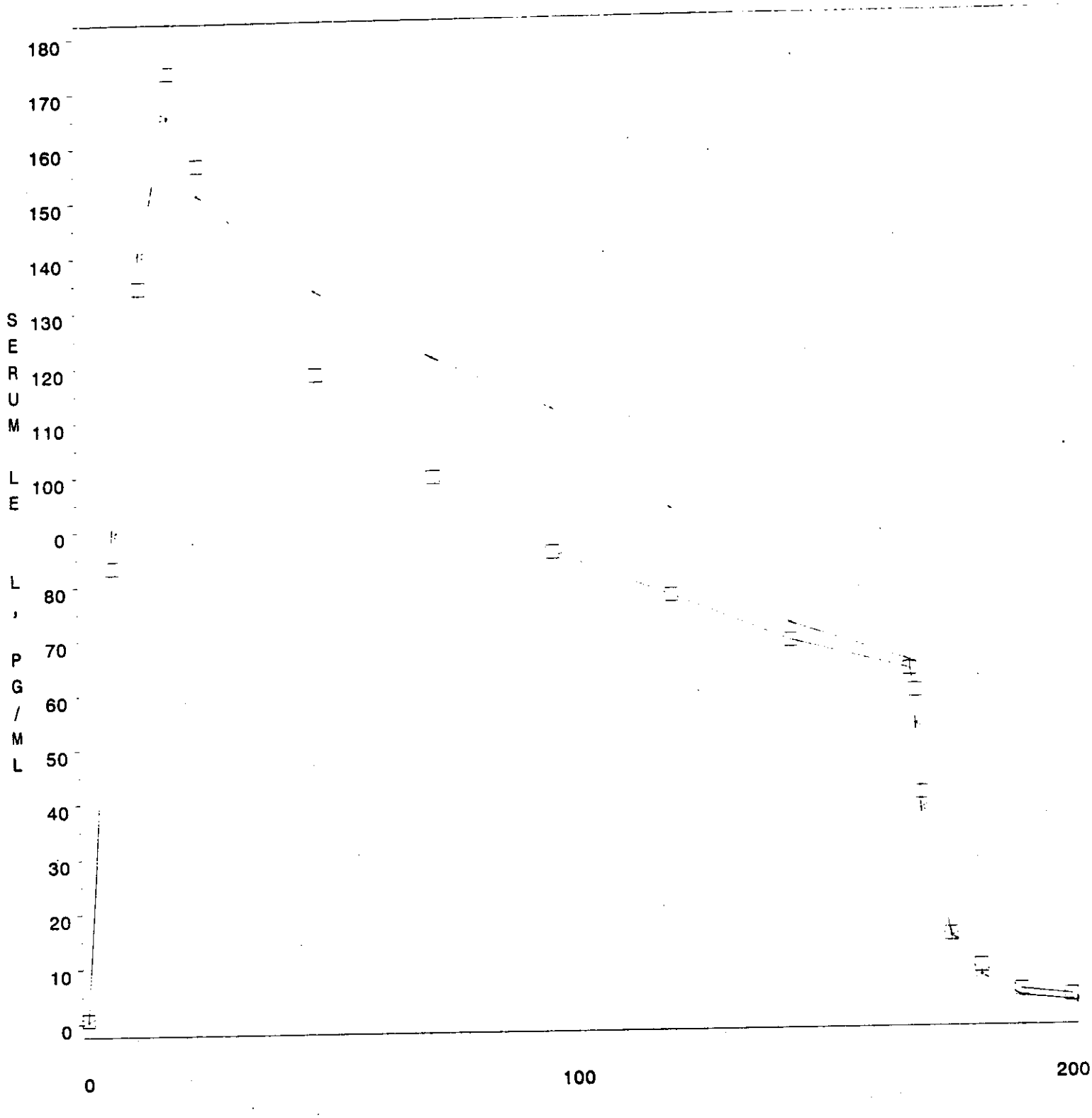
Sincerely yours,

/S/

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

FIG 1 PLASMA ESTRADIOL LEVELS

ESTRADIOL PATCH 0.1 MG/DAY FOR 7 DAYS, ANDA #75-182
UNDER FASTING
DOSE=0.1 MG/DAY FOR 7 DAYS



1=TEST(BERTEK) 2=REF(BERLEX)

FIG 2 PLASMA ESTRONE LEVELS

ESTRADIOL PATCHES, 0.1 MG/DAY, ANDA #75-182
UNDER FASTING CONDITIONS
DOSE= 0.1 MG/DAY FOR 7 DAYS

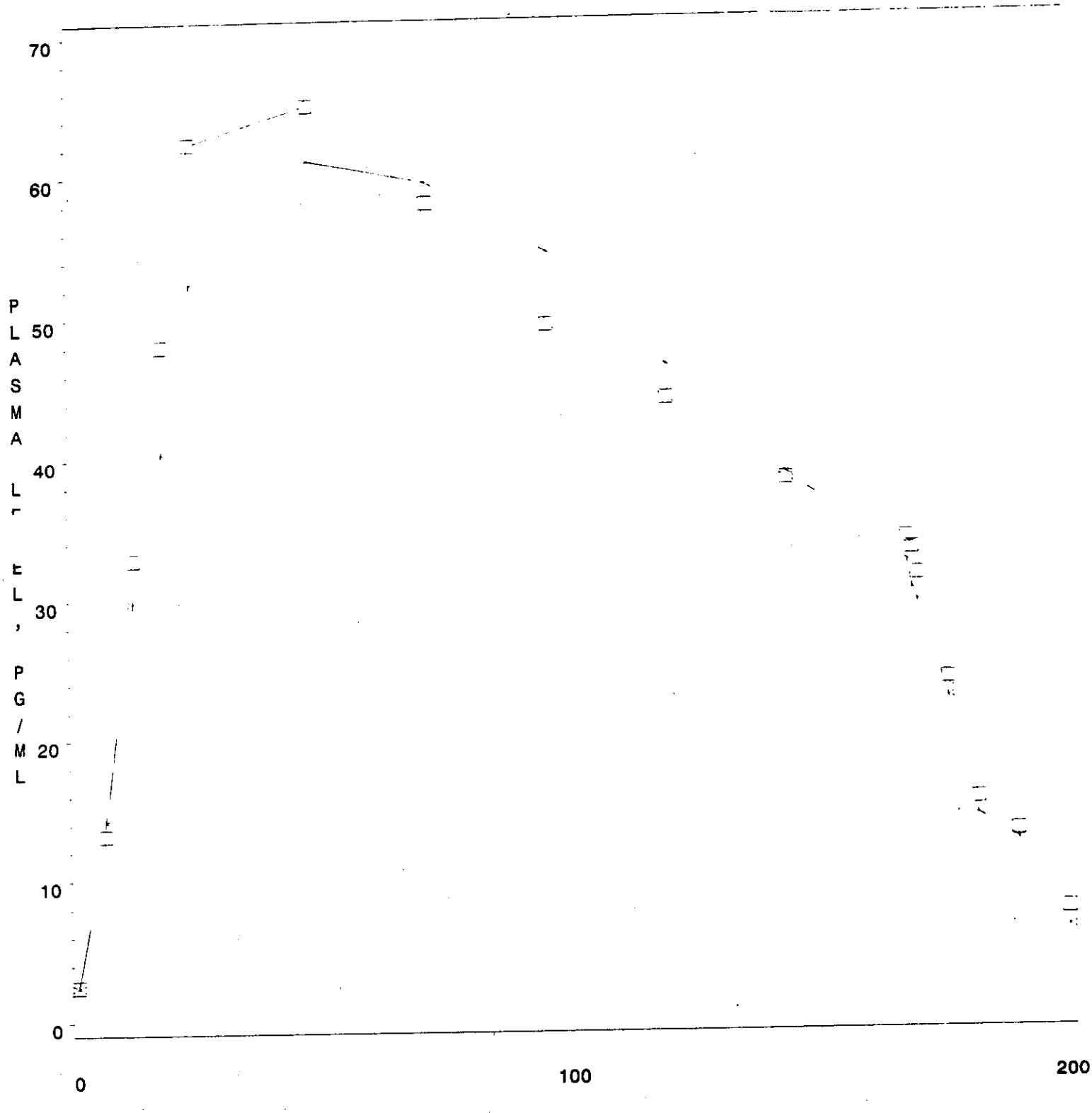
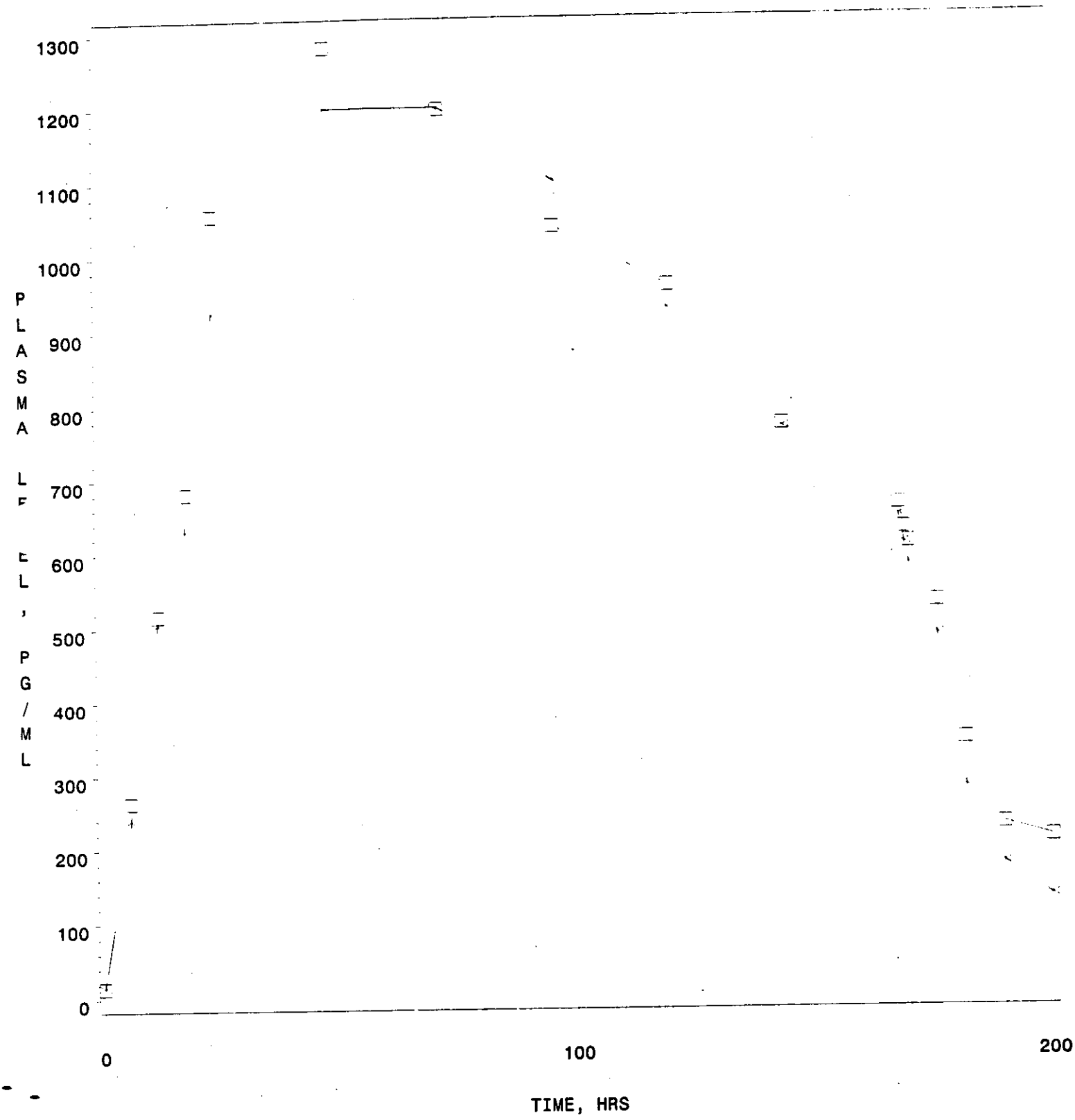


FIG 3 PLASMA ESTRONE SULFATE LEVELS

ESTRADIOL PATCHES, 0.1 MG/DAY, ANDA #75-182
UNDER FASTING CONDITIONS
DOSE= 0.1 MG/DAY FOR 7 DAYS



1=TEST(BERTEK) 2=REF(BERLEX)

505(j)(1)(2) 9/9/97

BERTEK

Office of Generic Drugs, CDER, FDA
Douglas L. Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ELECTRONIC DATA ENCLOSED
BIOEQUIVALENCE DATA ENCLOSED

August 6, 1997

RE: Estradiol Transdermal System, 0.1 mg/day

Dear Mr. Sporn,

Pursuant to section 505(j) of the Federal Food, Drug and Cosmetic Act and 21 CFR § 314.92 and 314.94 we submit the enclosed abbreviated new drug application for:

Proprietary name: None
Established name: Estradiol Transdermal System, 0.1 mg/day

This application consists of a total of 22 volumes:

Archival Copy - 9 volumes.
Review Copy - 11 volumes.
Technical Section For Chemistry - 3 volumes.
Technical Section For Pharmacokinetics - 8 volumes.
Analytical Methods - 2 extra copies, 1 volume each.

NOTE: The technical sections for Pharmacokinetics of the review copy and the archival copy each contain a set of data diskettes for the bioequivalence studies.

This application provides for the manufacture of patches (31 cm^2/42 cm^2) containing estradiol with a release rate of 0.1 mg per day. The product will be manufactured by Bertek, Inc., 110 Lake Street, St. Albans, VT 05478. Bertek is a wholly owned subsidiary of Mylan Laboratories Inc.

As required by 21 CFR § 314.94(d)(5) we certify that a true copy of the technical sections of this application, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Boston District Office.

For more detailed information regarding the organization of this ANDA, please refer to the Introduction, Reader's Guide and Master Table of Contents following this letter.

I:\andas\estradio\jacket.1\intro.1

All correspondence regarding this application should be directed to the attention of the undersigned at Bertek, Inc., 110 Lake Street, St. Albans, VT 05478 [FAX No. (802) 527-0486, Phone No. (802) 527-7792].

Sincerely,

Elizabeth Ash
for Lamont Fulton

Lamont Fulton
Manager of Regulatory Affairs

BERTEK INC., 110 LAKE STREET, ST. ALBANS, VT 05478, 802-527-7792, FAX 802-527-0486, TELEX 11 710-991-8483

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-182

ADMINISTRATIVE DOCUMENTS

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-182** Date of Submission: **June 2, 1999**

Applicant's Name: **Bertek Inc.**

Established Name: **Estradiol Transdermal System 0.1 mg/day**

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):Do you have 12 Final Printed Labels and Labeling? Yes
Patch Labels: Satisfactory as of June 2, 1999 submission. Photocopy OK per pg 5

Pouch Labeling: (1 patch per pouch) Satisfactory as of April 30, 1999 submission.

Carton Labeling: (4's) Satisfactory as of April 30, 1999 submission.

Professional Package Insert Labeling: Satisfactory as of June 2, 1999 submission.

Patient Package Insert Labeling: Satisfactory as of June 2, 1999 submission.

Revisions needed post-approval:
BASIS OF APPROVAL:
Was this approval based upon a petition? No

What is the RLD on the 356(h) form:Climara® (Estradiol Transdermal System)

NDA Number: 20-375/S-013
NDA Drug Name: Climara® (Estradiol Transdermal System)
NDA Firm: Berlex Pharmaceuticals

Date of Approval of NDA Insert and supplement #: May 20, 1999.
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: Side-by-side comparison labels submitted in jacket.
Basis of Approval for the Carton Labeling: Side-by-side comparison labeling submitted in jacket.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book? Estradiol Film, extended-release Transdermal.	X		
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).	X		
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	

Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			X
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.	X		
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

1. Review based on the labeling of the listed drug(Climara®; NDA#20-375/S-013; Approved May 20, 1999).

2. Patent/ Exclusivities:

   There one patent that exists for this product. 5223261 - Expires June 29, 2010. This patent is for the adhesive material of the patch. The generic has filed a paragraph IV certification.

   There two exclusivities that pertains to this drug product.

   D-26 - One weekly application. This expired on December 22, 1997.

   I-254 - Expires March 5, 2002 - Prevention of Postmenopausal osteoporosis (Loss of Bone Mass). The applicant has not included this information in its insert.

3. Storage/Dispensing Conditions:

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

   ANDA: Store at 15° - 30°C (59° - 86°F). Do not store unpouched. Apply immediately upon removal from the protective pouch. Requested firm revise to read "Store at controlled room temperature..."

   USP: Not a monograph in the USP nor purposed the PF.

4. Product Line:

   The innovator markets their product in 0.05 mg/day (12.5 sq cm) patch and a 0.1 mg/day (25 sq cm) patch. The patches are contained in pouches then placed in cartons of 4 and 6. The innovator also has a physician sample size of 1.

   The applicant proposes to market their product in a 0.1 mg/day (31 sq cm) patch. The patch is contained in a pouch then placed in a cartons of 4s.

Note: Prevention of osteoporosis is covered by exclusivity, however, the reference to use in osteoporosis appeared in the Patient Package insert prior to the granting of exclusivity. It was decided to that it should remain in the patient insert only per John Grace

5. Inactive Ingredients:

   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on pages 3972 and 3973, Vol. 1.8.

6. All manufacturing will be performed by Burtek. Burtek is a wholly owned subsidiary of Mylan Pharmaceuticals. All outside firms are utilized for testing. See pages 4156 and 4126, Vol. 1.8.

7. Container/Closure:

   The patch is heat sealed between 2 layers of pouching material. Laminate of white paper on one side and dull silver on the other. See page 4343 and 4340, Vol. 1.8.

8. There are several differences which exist between the RLD and this generic product.

   a. The NDA is a 3 layer system that consists of a film backing, Drug/Adhesive Layer/Protective Layer. The ANDA has a 4 layer system that consists of foam backing with adhesive layer, polyester film, acrylate adhesive matrix and a protective liner.

   b. The NDA patch size is 25 sq cm and the ANDAs patch size is 31 sq cm.

   c. The CLINICAL PHARMACOLOGY, Pharmacokinetics subsection was revised to reflect the delivery rate rather than the surface area. See FTR in file folder regarding this entire section.

Date of Review: June 7, 1999
Date of Submission: June 2, 1999

Reviewer: J. Watts **Date:** 6/7/99

Team Leader: [signature] **Date:** 6/8/1999

cc:

Concur: [signature] 6/9/99

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-182

CORRESPONDENCE

MYLAN TECHNOLOGIES INC.

CRIG AMENDMENT
AM

Office of Generic Drugs, CDER, FDA
Douglas L. Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

September 3, 1999

TELEPHONE AMENDMENT
(CMC INFORMATION ENCLOSED)

Re: ESTRADIOL TRANSDERMAL SYSTEM, 0.1 mg/day ANDA 75-182
ESTRADIOL TRANSDERMAL SYSTEM, 0.05 mg/day ANDA 75-233
Response to Agency Telephone Request for Information on September 2, 1999

Dear Mr. Sporn:

Reference is made to the pending Abbreviated New Drug Applications identified above and to the Agency's comments received via telephone on September 2, 1999. A copy of MYLAN TECHNOLOGIES, INC.'s telephone log is provided in Attachment A for the reviewer's convenience.

MYLAN TECHNOLOGIES, INC. wishes to amend this application with the following:

MYLAN TECHNOLGIES, INC. hereby commits to revising its Estradiol, USP raw material specifications based upon our interpretation of the "Other Impurities" General Notice in USP 24 (page 7) as follows:

PREVIOUS SPECIFICATIONS (EFFECTIVE DATE JULY 26, 1999)

Related Compounds d

RECD
SEP 07 1999
CBD
EVALUATION AND RESEARCH

PROPOSED SPECIFICATIONS

A. Chromatographic Purity

B. Other Impurities Proceed as directed in STM 0404

C. Total Impurities

As required by 21 CFR 314.96(b) we certify that a true copy of the technical sections of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Boston District Office.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (802) 527-7792 or via facsimile at (802) 527-0486.

Sincerely,

Elizabeth Ash

Elizabeth Ash, M.S., RAC
Regulatory Manager, CMC
MYLAN TECHNOLOGIES, INC.
110 Lake Street
St. Albans, VT 05478

FDA TELEPHONE REPORT

CALL DATE: September 2, 1999

TIME: 5:30 pm

FROM: Alan Rudman, Deputy Director Division I Chemistry Review, OGD, FDA
Robert Trimmer, Chemistry Review, OGD, FDA

TO: Elizabeth Ash, Regulatory Manager, CMC

PRODUCT:

Estradiol Transdermal System, 0.1 mg/hr	ANDA 75-182
Estradiol Transdermal System, 0.05 mg/hr	ANDA 75-233

DESCRIPTION: Dr. Rudman and Dr. Trimmer telephoned to request clarification on issues surrounding MTI's Estradiol, USP raw material specifications. Per our amendment dated, September 29, 1998, MTI committed to testing for "Other Impurities" for Estradiol, USP raw material. Upon review of our July 29, 1999 amended raw material specifications, Dr. Rudman said that the Agency saw no evidence of the requested testing in our revised specifications and asked if there had been an oversight to explain this fact. He stated that a letter of commitment to do the requested testing would be sufficient and could be sent via facsimile to him directly as well as submitted in hard copy.

At 6:00 pm, Michael Sturm, Director of Quality, and I called Dr. Rudman back to request further clarification of his concerns. MTI had reviewed its specifications and believed the specifications to be in compliance with Supplement 10 to the USP, currently in effect. Dr. Rudman said that the Agency did not consider the specifications to be in compliance with the current USP and requested revisions based upon the USP 24 General Notice entitled, "Other Impurities," as found on page 7 of the referenced USP. Mr. Sturm and I assured Dr. Rudman that MTI would revise its specifications accordingly.

ACTION: The Estradiol, USP raw material specifications were reworded using the appropriate compendial terminology in order to incorporate the Agency's request. A letter of commitment is to be sent to Dr. Rugman's attention today, September 3, 1999 as well as via a hard copy telephone amendment.

ORIGINATOR: Elizabeth Ash **DATE:** 9/3/99

Elizabeth Ash, M.S., RAC
Regulatory Manager, CMC

cc: **M. Costigan, L. DeBone, J. Fauteux, M. Friedly, S. Govil, J. O'Donnell, F. Sisto, M. Sturm, F. Tackett**

MYLAN TECHNOLOGIES INC.

Office of Generic Drugs, CDER, FDA
Douglas L. Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP
N 3

July 29, 1999

CORRESPONDENCE

Re: ESTRADIOL TRANSDERMAL SYSTEM, 0.1 mg/day ANDA 75-182 ✓
ESTRADIOL TRANSDERMAL SYSTEM, 0.05 mg/day ANDA 75-233

Dear Mr. Sporn:

Reference is made to the pending Abbreviated New Drug Application identified above. MYLAN TECHNOLOGIES, INC. wishes to amend this application with the following:

- A copy of correspondence regarding the referenced applications from Dr. John O'Donnell of Mylan Pharmaceuticals, Inc. to Mr. Douglas Sporn, Director, Office of Generic Drugs, CDER, FDA

As required by 21 CFR 314.96(b) we certify that a true copy of the technical sections of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Boston District Office.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (802) 527-7792 or via facsimile at (802) 527-0486.

Sincerely,

Elizabeth Ash

Elizabeth Ash, M.S., RAC
Regulatory Associate
MYLAN TECHNOLOGIES, INC.
110 Lake Street
St. Albans, VT 05478

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUL 30 1999
OGD

MYLAN TECHNOLOGIES INC.

ORIG AMENDMENT
N\ Amy

Office of Generic Drugs, CDER, FDA
Douglas L. Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MINOR AMENDMENT
(CMC INFORMATION ENCLOSED)

Re: ESTRADIOL TRANSDERMAL SYSTEM, 0.1 mg/day ANDA 75-182 ✓
ESTRADIOL TRANSDERMAL SYSTEM, 0.05 mg/day ANDA 75-233
Response to Agency Correspondence Dated July 14, 1999

Dear Mr. Sporn:

Reference is made to the pending Abbreviated New Drug Applications identified above and to the Agency's comments submitted via facsimile on July 14, 1999. A copy of the Agency correspondence is provided in Attachment A for the reviewer's convenience.

Effective April 5, 1999, Bertek Inc. changed its name to MYLAN TECHNOLOGIES, INC. The change is in name only and a copy of MYLAN TECHNOLOGIES, INC.'s name change notification is provided in Attachment B for the reviewer's convenience.

MYLAN TECHNOLOGIES, INC. wishes to amend this application with the following:

Chemistry Deficiencies:

MYLAN TECHNOLOGIES, INC. RESPONSE:

MYLAN TECHNOLOGIES, INC. has incorporated the indicated dissolution testing and specifications into our stability and control programs. Revised drug product specifications, stability protocols and stability data tables can be found in Attachment D.

MYLAN TECHNOLOGIES, INC. confirms that the dissolution data for release and stability for the bioequivalence / test batches does conform to these specifications.

As required by 21 CFR 314.96(b) we certify that a true copy of the technical sections of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Boston District Office.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (802) 527-7792 or via facsimile at (802) 527-0486.

Sincerely,

Elizabeth Ash

Elizabeth Ash, M.S., RAC
Regulatory Associate
MYLAN TECHNOLOGIES, INC.
110 Lake Street
St. Albans, VT 05478