CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 040138

Trade Name : ESTRADIOL TABLETS USP

Generic Name: Estradiol Tablets USP 0.5mg, 1mg and 2mg

Sponsor : Endeavor Pharmaceuticals, Inc.

Approval Date: January 30, 1998

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 040138

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	Included	Pending Completion	Not Prepared	Not Required
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Medical Review(s)				
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Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
Administrative Document(s)				
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 040138

APPROVAL LETTER

ANDA 40-138

JAN 30 1998

Endeavor Pharmaceuticals, Inc.
Attention: Christopher Smith
5051 New Centre Drive
Wilmington, NC 28403

Dear Sir:

This is in reference to your abbreviated new drug application dated March 10, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Estradiol Tablets USP, 0.5 mg, 1 mg and 2 mg.

Reference is also made to your amendments dated November 3, 4, 17 and 18, 1997, December 18, 1997, and January 8, 14, and 15, 1998.

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 Tablets USP, 0.5 mg, 1 mg and 2 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Estrace® Tablets 0.5 mg, 1 mg and 2 mg, respectively of Bristol-Myers Squibb Co.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, 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. 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 which 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-240). 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-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

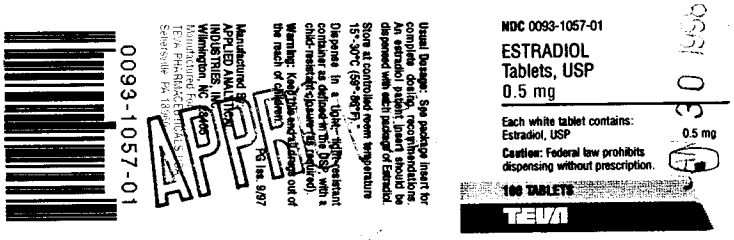
1-30-98

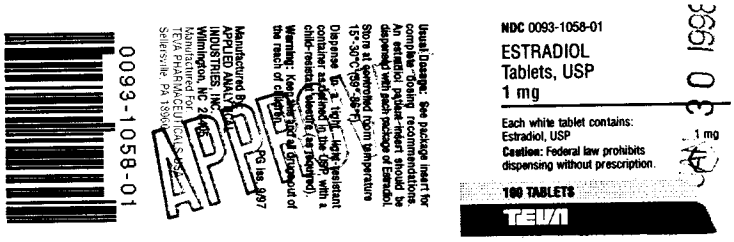
CENTER FOR DRUG EVALUATION AND RESEARCH

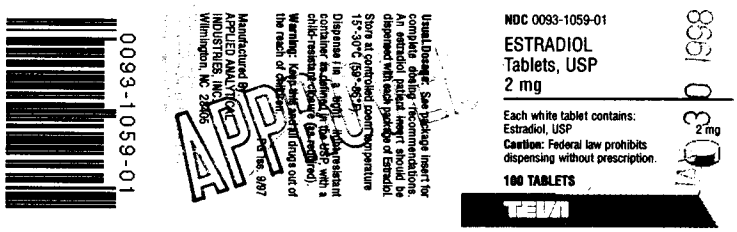
APPLICATION NUMBER 040138

FINAL PRINTED LABELING

ANDA 40-138
Estradiol Tablets, USP
0.5, 1 and 2 mg
Bottle Labels







ESTRADIOL
(INFORMATION FOR THE PATIENT)

135600

Rev. 10/97

INFORMATION FOR THE PATIENT

INTRODUCTION

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.

WARNINGS

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 child birth. 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.

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 to 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 Warnings).**
  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 Warnings).**
  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**).
- **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**).
  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-examinations 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 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 the estrogen.

You should know, however, that taking estrogens with progestins may have additional risks. These include:

- unhealthy effects on blood fats (especially the 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 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 treatment 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.

HOW SUPPLIED

Estradiol Tablets, USP, 0.5 mg; oval white scored tablets debossed with "0.5" on one side and "G" on the other side.

NDC 0093-1057-01 Bottles of 100

Estradiol Tablets, USP, 1 mg; hexagon-shaped white scored tablets debossed with "1" on one side and "G" on the other side.

NDC 0093-1058-01 Bottles of 100

Estradiol Tablets, USP, 2 mg; round white scored tablets debossed with "2" on one side and "G" on the other side.

NDC 0093-1059-01 Bottles of 100

Store at controlled room temperature 15°-30°C (59°-86°F).

[redacted]

Manufactured by:
Applied Analytical Industries, Inc.
Wilmington, North Carolina 28405

Manufactured for:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Rev. 10/97

WARNINGS

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 no evidence that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.

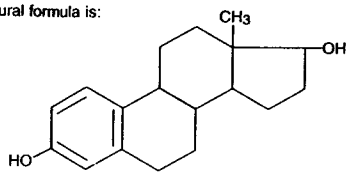
There is no indication for estrogen therapy during pregnancy or during the immediate postpartum period. Estrogens are ineffective for the prevention or treatment of threatened or habitual abortion. Estrogens are not indicated for the prevention of postpartum breast engorgement.

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.

DESCRIPTION

Estradiol Tablets, US, for oral administration contain 0.5, 1 or 2 mg of micronized estradiol per tablet. Estradiol (17β-estradiol) is a white, crystalline solid, 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:



Estradiol Tablets, USP, 0.5 mg, 1 mg and 2 mg contain the following inactive ingredients: mannitol granular, magnesium stearate, microcrystalline cellulose, and croscarmellose sodium.

CLINICAL PHARMACOLOGY

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 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 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.

Estrogens used in therapy are well absorbed through the skin, mucous membranes, and gastrointestinal tract. When applied for a local action, absorption is usually sufficient to cause systemic effects. When conjugated with aryl and alkyl groups for parenteral administration, the rate of absorption of oily preparations is slowed with a prolonged duration of action, such that a single intramuscular injection of estradiol valerate or estradiol cypionate is absorbed over several weeks.

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 estrogen prevents further loss of bone mass for as long as the treatment is continued. The results of a two-year, randomized, placebo-controlled, double-blind, dose-ranging study have shown that treatment with 0.5 mg estradiol daily for 23 days (of a 28 day cycle) prevents vertebral bone mass loss in postmenopausal women. When estrogen therapy is discontinued, bone mass declines at a rate comparable to the immediate postmenopausal period. There is no evidence that estrogen replacement therapy restores bone mass to premenopausal levels.

At skeletal maturity there are sex and race differences in both the total amount of bone present and its density, in favor of men and blacks. Thus, women are at higher risk than men because they start with less bone mass and, for several years following natural or induced menopause, the rate of bone mass decline is accelerated. White and Asian women are at higher risk than black women.

Early menopause is one of the strongest predictors for the development of osteoporosis. In addition, other factors affecting the skeleton which are associated with osteoporosis include genetic factors (small build, family history), endocrine factors (nulliparity, thyrotoxicosis, hyperparathyroidism, Cushing's syndrome, hyperprolactinemia, Type I diabetes), lifestyle (cigarette smoking, alcohol abuse, sedentary exercise habits) and nutrition (below average body weight, dietary calcium intake).

The mainstays of prevention and management of osteoporosis are estrogen, an adequate lifetime calcium intake, and exercise. Postmenopausal women absorb dietary calcium less efficiently than premenopausal women and require an average of 1500 mg/day of elemental calcium to remain in neutral calcium balance. By comparison, premenopausal women require about 1000 mg/day and the average calcium intake in the USA is 400-600 mg/day. Therefore, when not contraindicated, calcium supplementation may be helpful.

Weight-bearing exercise and nutrition may be important adjuncts to the prevention and management of osteoporosis. Immobilization and prolonged bed rest produce rapid bone loss, while weight-bearing exercise has been shown both to reduce bone loss and to increase bone mass. The optimal type and amount of physical activity that would prevent osteoporosis have not been established, however in two studies an hour of walking and running exercises twice or three times weekly significantly increased lumbar spine bone mass.

CONTRAINDICATIONS

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

1. Known or suspected pregnancy (see **BOXED WARNINGS**). 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 nonusers, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than one year. The greatest risk appears associated with prolonged use -- with increased risks of 15- to 24-fold for five to ten years or more. In three studies, persistence of risk was demonstrated for 8 to over 15 years after cessation of estrogen treatment. In one study a significant decrease in the incidence of endometrial cancer occurred six months after estrogen withdrawal. Concurrent progestin therapy may offset this risk but the overall health impact in postmenopausal women is not known (see **PRECAUTIONS**).
   Breast Cancer. While the majority of studies have not shown an increased risk of breast cancer in women who have ever used estrogen replacement therapy, some have reported a moderately increased risk (relative risks of 1.3-2.0) in those taking higher doses or those taking lower doses for prolonged periods of time, especially in excess of 10 years. 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 prostate and breast, have been shown in a large prospective clinical trial in men to increase the risks of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis. These risks cannot necessarily be extrapolated from men to women. However, to avoid the theoretical cardiovascular risk to women caused by high estrogen doses, the dose for estrogen replacement therapy should not exceed the lowest effective dose.
4. Elevated blood pressure. Occasional blood pressure increases during estrogen replacement therapy have been attributed to idiosyncratic reactions to estrogens. More often, blood pressure has remained the same or has dropped. One study showed that postmenopausal estrogen users have higher blood pressure than nonusers. Two other studies showed slightly lower blood pressure among estrogen users compared to nonusers. Postmenopausal estrogen use does not increase the risk of stroke. Nonetheless, blood pressure should be monitored at regular intervals with estrogen use.
5. Hypercalcemia.
   Administration of estrogens may lead to severe hypercalcemia in

ESTRADIOL TABLETS

135600

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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.

Estrogens used in therapy are well absorbed through the skin, mucous membranes, and gastrointestinal tract. When applied for a local action, absorption is usually sufficient to cause systemic effects. When conjugated with aryl and alkyl groups for parenteral administration, the rate of absorption of oily preparations is slowed with a prolonged duration of action, such that a single intramuscular injection of estradiol valerate or estradiol cypionate is absorbed over several weeks.

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 non-esterified 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 non-estrogenic substances (catecholestrogens, which interact with catecholamine metabolism, especially in the central nervous system), and conjugation with glucuronic acid (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. By contrast, synthetic estrogens, such as ethinyl estradiol and the non-steroidal estrogens, are degraded very slowly in the liver and other tissues, which results in their high intrinsic potency. Estrogen drug products administered by non-oral routes are not subject to first-pass metabolism, but also undergo significant hepatic uptake, metabolism, and enterohepatic recycling.

INDICATIONS AND USAGE

Estradiol Tablets, USP are 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 breast cancer (for palliation only) in appropriately selected women and men with metastatic disease.
5. Treatment of advanced androgen-dependent carcinoma of the prostate (for palliation only).
6. Prevention of osteoporosis.

Since estrogen administration is associated with risk, selection of patients should ideally be based on prospective identification of risk factors for developing osteoporosis. Unfortunately, there is no certain way to identify those women who will develop osteoporotic fractures. Most prospective studies of efficacy for this indication have been carried out in white menopausal women, without stratification by other risk factors, and tend to show a universally salutary effect on bone. Thus, patient selection must be individualized based on the balance of risks and benefits. A more favorable risk/benefit ratio exists in a hysterectomized woman because she has no risk of endometrial cancer (see **BOXED WARNINGS**).

Estrogen replacement therapy reduces bone resorption and retards or halts post-menopausal bone loss. Case-control studies have shown an approximately 60 percent reduction in hip and wrist fractures in women whose estrogen replacement was begun within a few years of menopause. Studies also suggest that estrogen reduces the risk of vertebral fractures. Even when started as late as 6 years after menopause,

mous cell dysplasia of the uterine cervix, and clear cell vaginal cancer later in life; male offspring have an increased risk of urogenital abnormalities and possibly testicular cancer later in life. Although some of these changes are benign, others are precursors of malignancy.

2. Gallbladder disease.
   Two studies have reported a 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in women receiving postmenopausal estrogens.
3. Cardiovascular disease.
   Large doses of estrogen (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men to increase the risks of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis. These risks cannot necessarily be extrapolated from men to women. However, to avoid the theoretical cardiovascular risk to women caused by high estrogen doses, the dose for estrogen replacement therapy should not exceed the lowest effective dose.
4. Elevated blood pressure. Occasional blood pressure increases during estrogen replacement therapy have been attributed to idiosyncratic reactions to estrogens. More often, blood pressure has remained the same or has dropped. One study showed that postmenopausal estrogen users have higher blood pressure than nonusers. Two other studies showed slightly lower blood pressure among estrogen users compared to nonusers. Postmenopausal estrogen use does not increase the risk of stroke. Nonetheless, blood pressure should be monitored at regular intervals with estrogen use.
5. Hypercalcemia.
   Administration of estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If this occurs, the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

PRECAUTIONS

A. General

1. **Addition of a progestin.** Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration have reported a lowered incidence of endometrial hyperplasia than would be induced by treatment alone. Morphological and biochemical studies of endometria suggest that 10 to 14 days of progestin are needed to provide maximal maturation of the endometrium and to reduce the likelihood of hyperplastic changes.
   There are, however, possible risks 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 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 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 assessed this statistical association have reported a 20% to 50% reduction in coronary heart disease risk and associated mortality in estrogen takers, the following should be considered when interpreting these reports: (1) Because only one of these studies was randomized and it was too small to yield statistically significant results, all relevant studies were subject to selection bias. Thus, the apparently reduced risk of coronary artery disease cannot be attributed with certainty to estrogen replacement therapy. It may instead have been caused by life-style and medical characteristics of the women studied with the result that healthier women were selected for estrogen therapy. In general, treated women were of higher socio-economic 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 in women with intact uteri (see **PRECAUTIONS** and **WARNINGS**). While the effects of added progestins [illegible] 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 hypercoagulabilty, primarily related to decreased antithrombin activity. This effect appears dose- and duration-dependent and is less pronounced than that associated with oral contraceptive use. Also, postmenopausal women tend to have increased coagulation parameters at baseline compared to premenopausal women. There is some suggestion that low dose postmenopausal mestranol may increase the risk of thromboembolism, although the majority of studies (of primarily conjugated estrogens users) report no such increase. There is insufficient information on hypercoagulability in women who have had previous, thromboembolic disease.
5. **Familial hyperlipoproteinemia.** Estrogen therapy may be associated with massive elevation 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** below.)

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. (For prevention and treatment of osteoporosis, however, see **DOSAGE AND ADMINISTRATION** section.)

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 coagulan 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 corticosteriods and sex steriods, 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. Longterm 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. (See **CONTRAINDICTIONS** and **WARNINGS**.)

F. Pregnancy Category X. Estrogens should not be used during pregnancy. (See **CONTRAINDICATIONS** and **BOXED WARNINGS**.)

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,

H. Pediatric Use. Safety and effectiveness in pediatric patients have not been established. Large and repeated doses of estrogen over an extended period of time have been shown to accelerate epiphyseal closure, resulting in short adult stature if treatment is initiated before the completion of physiologic puberty in normally developing children. In patients in whom bone growth is not complete, periodic monitoring of bone maturation and effects on epiphyseal centers is rec-

I. Estrogen treatment of prepubertal children also induces

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H. Pediatric Use. Safety and effectiveness in pediatric patients have not been established. Large and repeated doses of estrogen over an extended period of time have been shown to accelerate epiphyseal closure, resulting in short adult stature if treatment is initiated before the completion of physiologic puberty in normally developing children. In patients in whom bone growth is not complete, periodic monitoring of bone maturation and effects on epiphyseal centers is recommended. Estrogen treatment of prepubertal children also induces premature breast development and vaginal cornification, and may potentially induce vaginal bleeding in girls. In boys, estrogen treatment may modify the normal pubertal process. All other physiological and adverse reactions shown to be associated with estrogen treatment of adults could potentially occur in the pediatric population, including thromboembolic disorders and growth stimulation of certain tumors. Therefore, estrogens should only be administered to pediatric patients when clearly indicated and the lowest effective dose should always be utilized.

ADVERSE REACTIONS

The following additional adverse reactions have been reported with estrogen therapy (see **WARNINGS** regarding induction of neoplasia, adverse effects on the fetus, increased incidence of gallbladder disease, cardiovascular disease, elevated blood pressure, and hypercalcemia).

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 which 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.
   Reduces 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

1. **For treatment of moderate to severe vasomotor symptoms, vulval and vaginal atrophy associated with the menopause, the lowest dose and regimen that will control symptoms should be chosen and medication should be discontinued as promptly as possible.**
   Attempts to discontinue or taper medication should be made at 3-month to 6-month intervals.
   The usual initial dosage range is 1 to 2 mg daily of estradiol adjusted as necessary to control presenting symptoms. The minimal effective dose for maintenance therapy should be determined by titration. Administration should be cyclic (e.g. 3 weeks on and 1 week off.)
2. **For treatment of female hypoestrogenism due to hypogonadism, castration, or primary ovarian failure.**
   Treatment is usually initiated with a dose of 1 to 2 mg daily of estradiol, adjusted as necessary to control presenting symptoms; the minimal effective dose for maintenance therapy should be determined by titration.
3. **For treatment of breast cancer, for palliation only, in appropriately selected women and men with metastatic disease.**
   Suggested dosage is 10 mg three times daily for a period of at least three months.
4. **For treatment of advanced androgen-dependent carcinoma of the prostrate, for palliation only.**
   Suggested dosage is 1 to 2 mg three times daily. The effectiveness of therapy can be judged by phosphatase determinations as well as by symptomatic improvement of the patient.
5. **For prevention of osteoporosis,**
   Therapy with Estradiol Tablets, USP, to prevent postmenopausal bone loss should be initiated as soon as possible after menopause. A daily dosage of 0.5 mg should be administered cyclically (i.e., 23 days on and 5 days off). The dosage may be adjusted if necessary to control concurrent menopausal symptoms.
   Discontinuation of estrogen replacement therapy may re-establish the natural rate of bone loss.

HOW SUPPLIED

Estradiol Tablets, USP, 0.5 mg; oval white scored tablets debossed with "0.5" on one side and "G"on the other side.

NDC 0093-1057-01 Bottles of 100

Estradiol Tablets, USP, 1 mg; hexagon-shaped white scored tablets debossed with "1" on one side and "G"on the other side.

NDC 0093-1058-01 Bottles of 100

Estradiol Tablets, USP, 2 mg; round white scored tablets debossed with "2" on one side and "G"on the other side.

NDC 0093-1059-01 Bottles of 100

Store at controlled room temperature 15° -30°C (59° -86°F)

INFORMATION FOR THE PATIENT

INTRODUCTION

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.

WARNINGS

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 child birth. 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.

USES OF ESTROGEN

(Not every estrogen drug is approved for every

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 Warnings).**
  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 Warnings).**
  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**).
- **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**).
  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-examinations 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.**

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.

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 to 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.

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-examinations 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 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 the estrogen.

   You should know, however, that taking estrogens with progestins may have additional risks. These include:

   - unhealthy effects on blood fats (especially the 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 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 treatment 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.

HOW SUPPLIED

Estradiol Tablets, USP, 0.5 mg; oval white scored tablets debossed with "0.5" on one side and "G" on the other side.

NDC 0093-1057-01 Bottles of 100

Estradiol Tablets, USP, 1 mg; hexagon-shaped white scored tablets debossed with "1" on one side and "G" on the other side.

NDC 0093-1058-01 Bottles of 100

Estradiol Tablets, USP, 2 mg; round white scored tablets debossed with "2" on one side and "G" on the other side.

NDC 0093-1059-01 Bottles of 100

Store at controlled room temperature 15°-30°C (59°-86°F).

Manufactured by:
Applied Analytical Industries, Inc.
Wilmington, North Carolina 28405

Manufactured for:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Rev. 12/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040138

CHEMISTRY REVIEW(S)

Chemistry Closed

1. CHEMISTRY REVIEW NO. 5

2. ANDA 40-138

3. NAME AND ADDRESS OF APPLICANT

Endeavor Pharmaceuticals, Inc.
5051 New Centre Drive
Wilmington, NC 28403

Agent: AAI, Inc.

4. LEGAL BASIS FOR SUBMISSION

21 CFR 505(j)

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Estradiol

8. SUPPLEMENT(s) PROVIDE(s) FOR

N/A

9. AMENDMENTS AND OTHER DATES

Original Filing	3/10/95	Refuse to File Letter 4/5/95
Amendment	4/14/95	Acknowledgment letter 5/5/95
Amendment	6/30/95	NA letter 11/8/95
Amendment	12/8/95	BIO NA letter 1/18/96
NC	2/7/96	Telecon 12/21/95
BIO Amendment	2/16/96	Na letter 5/14/96
Telecon	5/23/96	BIO NA letter 5/20/96
FAX	4/11/96	BIO NA letter 1/27/97
BIO NC	8/30/96	FAX (chem) 2/7/97
Amendment	9/13/96	Hard copy of FAX 2/20/97
BIO NC	10/25/96	
NC	2/13/97	
NC	2/27/97	
Amendment	4/30/97	
BIO NC	5/20/97	
FAX	9/18/97	Chemistry Deficiency
*Amendment	11/3/97	Bio
*Amendment	11/4/97	Response to 9/18/97 FAX
*Amendment	11/17/97	Bio
*Amendment	11/18/97	Labeling

*Denotes submissions since last review.

10. PHARMACOLOGICAL CATEGORY

Estrogen

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM

Tablets

14. POTENCY

0.5 mg, 1 mg, 2 mg

15. CHEMICAL NAME AND STRUCTURE

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

See *USP 23* for structure.

16. RECORDS AND REPORTS

N/A

17. COMMENTS

Applicant was asked to note and acknowledge the following in the September 18, 1997 FAX:

1. **A satisfactory compliance evaluation of firms referenced in the ANDA is required prior to approval. Please note that the Office of Compliance currently**

Response: Inspection has been completed. A letter from the FDA Atlanta District to the applicant stated that there were no significant deficiencies and approval of the manufacturing site had been recommended.

2. **Bioequivalence of the drug products has not been established. Your bioequivalence information is under review.**

Response: The applicant has responded to a request from the Division of Bioequivalence requesting additional information. No bioequivalence issues are pending.

3. **Your response must also address the labeling deficiencies.**

Response: Requested changes have been made. Final printer's proofs of the labels and photocopies of printer's proofs of the physician and patient inserts

are submitted with this amendment. Teva will distribute the product. At this time, only the 100s will be marketed.

18. CONCLUSIONS AND RECOMMENDATIONS

The application is not approvable.

A. Chemistry issues are closed.

B. Labeling is not satisfactory.

See November 21, 1997 review.

C. Bio is pending.

19. REVIEWER

Shirley S. Brown

DATE COMPLETED

12/8/97
December 8, 1997

12/8/97

EER acceptable per
Bio acceptable per review dated 12/9/97
Labeling acceptable per review dated
1/29/98 after submission of
new amendment on 12/18/97 and
1/8, 1/14 and 1/15/98.

1/23/98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040138

BIOEQUIVALENCE REVIEW(S)

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-138 APPLICANT: GenerEst

DRUG PRODUCT: Estradiol Tablets, U.S.P. 0.5 mg, 1 mg and 2 mg

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

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in U.S.P. 23.

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,

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

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

Estradiol Tablets, USP	GenerEst
0.5 mg, 1 mg and 2 mg Tablets	Wilmington, NC
ANDA #40-138	Submission Date: 6/27/97
Reviewer: Moo Park	

REF PRODUCT	Bristol-Myers Squibb's 2 mg potency Estrace[R] Tablets
BE STUDY DESIGN	GenerEst's single dose, two-way crossover bioequivalence study under fasting conditions comparing GenerEst's 2 mg potency Estradiol Tablets to Bristol-Myers Squibb's 2 mg potency Estrace[R] Tablets.
STUDY RESULTS	Acceptable.
WAIVER	Waivers for 0.5 mg and 1 mg tablets granted.

INITIAL: _____ DATE: 12/10/97
REVIEWER: Moo Park, Ph.D.
BRANCH: III

INITIAL: _____ DATE: 12/15/97
TEAM LEADER: Ramakant M. Mhatre, Ph.D.
BRANCH: III

INITIAL: _____ DATE: 12/30/97
DIRECTOR: Dale P. Conner, Pharm.D.
DIVISION OF BIOEQUIVALENCE

INITIAL: _____ DATE: _____
DIRECTOR
OFFICE OF GENERIC DRUGS

Estradiol Tablets, USP	GenerEst
0.5 mg, 1 mg and 2 mg Tablets	Wilmington, NC
ANDA #40-138	Submission Date: 11/3/97; 11/17/97
Reviewer: Moo Park	
Filename: 40138a.n97	

Review of Amendments

I. Objective

Review of GenerEst's amendments dated 11/3/97 and 11/17/97 responding to Agency's deficiency letter dated 10/7/97.

II. Review of the Amendments

The following three questions raised by the Division of Bioequivalence in the deficiency letter dated 10/7/97. The firm collected the necessary data during the 10/13/97-10/15/97 period for short-term room temperature stability and freeze-thaw cycle stability. Long-term stability data were historical data borrowed from an estradiol study #89574 conducted at L.A.B. in the 1992-1993 period for a third party. Answers to each question were reviewed as follows:

Q1. Submit pre-study validation data for the free estradiol assay including data for recovery, long-term stability (a minimum of 12 months), short-term stability and freeze-thaw cycle stability.

A1. **Pre-study validation data for free estradiol by RIA**

1. Recovery data

Table 1 shows the summary of recovery data for quality control samples at three concentration levels for free estradiol in plasma. The recovery data are acceptable.

Table 1. Recovery of Free Estradiol in Plasma

QC Sample pg/mL	N	Found pg/mL	%Recovery	%CV
5	15	4.77	95.4	10.4
20	15	20.06	100.3	5.57
250	15	257.3	102.9	13.2

2. Short-term room temperature stability

Plasma samples containing estradiol were assessed for room temperature stability up to 8 hours and the data were summarized in Table 2. Nine different concentrations ranging between 15.6 pg/mL and 53.4 pg/mL were used in the study and the data were pooled to calculate the stability in percentage. The short-term stability of estradiol is acceptable.

Table 2. Room Temperature Stability of Free Estradiol in Plasma

Sample	Storage	N	%Found	%CV
Free Estradiol in Plasma	8 hours at room termperature	9	97.5	4.97

3. Freeze-thaw cycles

Plasma samples containing estradiol were assessed for three freeze-thaw cycle stability and the data were summarized in Table 3. Three different concentrations, 16.3 pg/mL, 45.4 pg/mL and 53.4 pg/mL, were used in the study and the data were pooled to calculate the stability in percentage. The freeze-thaw stability of estradiol is acceptable.

Table 3. Freeze-Thaw Stability of
Free Estradiol in Plasma

Sample	Storage	N	%Found	%CV
Free Estradiol in Plasma	1st freeze-thaw cycle	3	95.5	5.87
Free Estradiol in Plasma	2nd freeze-thaw cycle	3	86.9	7.53
Free Estradiol in Plasma	3rd freeze-thaw cycle	3	78.9	7.88

4. Long-term stability of free estradiol in plasma

The firm submitted the long-term stability data obtained for study #89574 conducted for a third party during 1992-1993 period. The plasma samples were stored at -11°C for 20 months and there was no sign of degradation for free estradiol during the long-term storage. Submitted data are acceptable.

Q2. Submit pre-study validation data for free estrone assay including data for recovery, long-term stability (a minimum of 12 months), short-term stability and freeze-thaw cycle stability.

A1. **Pre-study validation data for free estrone by RIA**

1. Recovery data

Table 4 shows the summary of recovery data for quality control samples at three concentration levels for free estrone in plasma. The recovery data are acceptable.

Table 4. Recovery of Free Estrone in Plasma

QC Sample pg/mL	N	Found pg/mL	%Recovery	%CV
15	20	15.74	104.9	8.34
35	18	32.86	93.89	6.89
350	20	357.1	102.0	4.18

2. Short-term room temperature stability

Plasma samples containing free estrone were assessed for room temperature stability up to 8 hours and the data were summarized in Table 5. Nine different concentrations ranging between 12.78 pg/mL and 67.89 pg/mL were used in the study and the data were pooled to calculate the stability in percentage. The short-term stability of estrone is acceptable.

Table 5. Room Temperature Stability of Free Estrone in Plasma

Sample	Storage	N	%Found	%CV
Free Estrone in Plasma	8 hours at room termperature	9	95.21	9.58

3. Freeze-thaw cycles

Plasma samples containing estrone were assessed for three freeze-thaw cycle stability and the data were summarized in Table 6. Three different concentrations, 12.78 pg/mL, 23.12 pg/mL and 63.26, were used in the study and the data were pooled to calculate the stability in percentage. The freeze-thaw stability of estrone is acceptable.

Table 3. Freeze-Thaw Stability of
Free Estrone in Plasma

Sample	Storage	N	%Found	%CV
Free Estrone in Plasma	1st freeze-thaw cycle	3	92.96	5.18
Free Estrone in Plasma	2nd freeze-thaw cycle	3	95.62	12.16
Free Estrone in Plasma	3rd freeze-thaw cycle	3	113.2	5.43

4. Long-term stability of free estrone in plasma

The firm submitted the long-term stability data obtained for study #89574 conducted for a third party during 1992-1993 period. The plasma samples were stored at -11°C for 20 months and there was no sign of degradation for free estrone during the long-term storage. Submitted data are acceptable.

Q3. Submit reasons for selecting two analytical facilities.

The firm explained how they selected for the assay of estrone sulfate in plasma in 1996 and L.A.B. for the assay of free estradiol and free estrone in plasma in 1997. The firm explained that it was a business decision. AAI, the parent company of GenerEst, acquired L.A.B. in 1997.

III. Comments

The firm responded satisfactorily to the three questions raised in the deficiency letter dated 10/7/97. The second *in vivo* bioequivalence study (submission date: 10/25/96; 6/27/97) by RIA method is acceptable. The original *in vivo* bioequivalence study (submission date: 3/10/95) by GC/MS method was not acceptable.

IV. Deficiency

None.

V. Recommendations

1. The *in vivo* bioequivalence study conducted under fasting conditions by GeneRest on its Estradiol Tablets, 2 mg strength, lot #94171, comparing it to Bristol-Myers Squibb's Estrace[R] Tablets, 2 mg strength, lot #MFJ26, has been found acceptable. The studies demonstrate that GenerEst's Estradiol Tablets, 2 mg strength, is bioequivalent to the reference product, Bristol-Myers Squibb's Estrace[R] Tablets, 2 mg strength.

2. The USP dissolution testing conducted by GenerEst on its Estradiol Tablets, 2 mg strength, lot #94171, 1 mg strength, lot #94165, and 0.5 mg strength, lot #94164, is acceptable. The formulations for the 0.5 mg and 1 mg strengths are proportionally similar to the 2 mg strenghth of the test product which underwent acceptable bioequivalency testing. The waivers of *in vivo* bioequivalence study requirements for the 0.5 mg and 1 mg strengths tablets of the test product are granted. The 0.5 mg and 1 mg tablets of the test product are therefore deemed bioequivalent to the corresponding strengths of Bristol-Myers Squibb's Estrace[R] Tablets.

3. The USP dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 500 mL of water with 0.3% sodium lauryl sulfate at 37°C using USP 23 Apparatus 2 (paddle) at 100 rpm. The test product should meet the following specifications:

   Not less than (Q) of the labeled amount of the drug in the dosage form is dissolved in 60 minutes.

CC: ANDA 40-138
ANDA DUPLICATE
DIVISION FILE
HFD-650/ Nerurkar for BioSign Off
HFD-658/ M. Park
BIO DRUG FILE

Endorsements: (Draft and Final with Dates)
HFD-658/M. Park
HFD-658/R. Mhatre
HFD-617/N. Chamberlin
HFD-650/D. Conner 12-9-97

Printed in Draft on 12-3-97 mp
Printed in Final on 12-5-97 mp
X:NEW\FIRMSAM\generest\ltrs&rev\40138a.n97

BIOEQUIVALENCY - ACCEPTABLE
sub date:11/3/97; 11/17/97

1. **STUDY AMENDMENT** (STA) — **Strengths: 2 mg** **Outcome: (AC)**

2. **WAIVER** (WAI) — **Strengths: 0.5 mg and 1 mg** **Outcome: (AC)**

OUTCOME DECISIONS: ACCEPTABLE
AC - Acceptable
NC - No Action
UN - Unacceptable (fatal flaw)
IC - Incomplete

WINBIO COMMENTS:
Study acceptable. Waivers granted for 0.5 mg and 1 mg tablets.