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Guidance for Industry

Labeling Guidance for Non- Contraceptive Estrogen Drug Products — Physician and Patient Labeling

DRAFT GUIDANCE

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Comments and suggestions regarding this draft document should be submitted within 60 days of publication of the *Federal Register* notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

Copies of this draft guidance are available on the Internet at <http://www.fda.gov/cder/guidance/index.htm>. For questions on the content of the draft document contact John C. Markow (301) 827-4260.

U.S. Department of Health and Human Services
Food and Drug Administration
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Labeling #

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GUIDANCE FOR INDUSTRY¹
Labeling Guidance for Non-Contraceptive Estrogen Drug Products —
Physician and Patient Labeling

I. INTRODUCTION

This guidance describes recommended labeling for estrogen drug products for new drug applications (NDAs). For ANDAs, differences between the labeling for the reference listed drug and the product covered by the ANDA may exist, including differences in expiration date, formulation, bioavailability, pharmacokinetics, or omission of an indication or other aspects of labeling protected by patent or accorded exclusivity under section 505(j)(5)(D) of the Federal Food, Drug, and Cosmetic Act.

II. PHYSICIAN LABELING

The recommended text of the physician labeling is as follows:

ESTROGENS INCREASE THE RISK OF ENDOMETRIAL CARCINOMA.

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 equivalent estrogen doses.

¹This guidance has been prepared by the Division of Reproductive and Urologic Drug Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance document represents the Agency's current thinking on estrogen class labeling. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

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DESCRIPTION

Supplied by manufacturer.

CLINICAL PHARMACOLOGY

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

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

Pharmacokinetics

Absorption

This section will be specific for the product in question.

If the product in question is an oral dosage form the following information should be included:

1. The rate and extent of absorption (e.g., C_{max} , T_{max} , C_{avg} , AUC, Fluctuation index, and parent/metabolite ratio) generated during the pivotal clinical pharmacology and biopharmaceutic studies.
2. Dose proportionality data for the proposed dosing range.
3. The effect of food on the bioavailability of the product in question.
4. Tables and Figures should include baseline unadjusted levels of estradiol and metabolites. In the event that baseline adjusted levels are more appropriate, this fact should be clearly indicated.

If the product in question is a transdermal delivery system the following information should be included:

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1. The rate and extent of absorption (e.g., C_{max} , T_{max} , C_{avg} , AUC, Fluctuation index, and parent/metabolite ratio) generated during the pivotal clinical pharmacology and biopharmaceutic studies.
2. Data for all the anatomical application sites that will be proposed in the labeling
3. Dose proportionality data for the proposed dosing range.
4. Tables and Figures should include baseline unadjusted levels of estradiol and metabolites. In the event that baseline adjusted levels are more appropriate, this fact should be clearly indicated.
5. The nominal mean in vivo delivery rate.

If the product in question is a topical dosage form or a dosage form to be administered vaginally and the estrogen is systemically available the following information should be included:

1. The rate and extent of absorption (e.g., C_{max} , T_{max} , C_{avg} , AUC, Fluctuation index, and parent/metabolite ratio) generated during the pivotal clinical pharmacology and biopharmaceutic studies.
2. Data for all the anatomical application sites that will be proposed in the labeling (except for vaginally administered products)
3. Dose proportionality data for the proposed dosing range.
4. Tables and Figures should include baseline unadjusted levels of estradiol and metabolites. In the event that baseline adjusted levels are more appropriate, this fact should be clearly indicated.

If the product in question is a topical dosage form or a dosage form to be administered vaginally and the estrogen is not systemically available this should be clearly stated.

Distribution

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

Additional protein binding and pharmacokinetic information should be specific for the product in question.

Metabolism

Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to estrone,

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and both can be converted to estriol, which is the major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the gut followed by reabsorption. In postmenopausal women a significant portion of the circulating estrogens exist as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens.

Additional metabolic and pharmacokinetic information should be specific for the product in question.

Excretion

Estradiol, estrone, and estriol are excreted in the urine along with glucuronide and sulfate conjugates.

Additional pharmacokinetic information (e.g., apparent half-life(s), and clearance) should be specific for the product in question.

Special Populations

This section will be specific for the product in question.

Drug Interactions

This section will be specific for the product in question.

If the product in question is a transdermal delivery system the following section on Adhesion should be added:

Adhesion

Since the adhesion or lack of adhesion of transdermal systems to the skin is a critical factor directly related to drug delivery, therapeutic effect, and possibly to its compliance, in vivo adhesion information on the percentage of systems that lifted and/or were detached and replaced during the pharmacokinetic and clinical studies should be included. Adhesion information will be specific for the transdermal product in question.

Clinical Studies

This section will be specific for the product in question and should include information concerning the appropriate endpoints to assess the efficacy for the indication sought.

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A concise and objective description of the pivotal efficacy studies should include brief summaries of the following:

- a. study designs;*
 - b. demographics of the intent-to-treat study populations;*
 - c. study results*
- *For the indication of treatment of vasomotor symptoms, a table of results should be included that provides the sample size and the mean number (SD) of hot flashes per week at baseline and at weeks 4, 8, and 12 for each treatment group.*
 - *Results from individual studies should be reported separately.*

INDICATIONS AND USAGE

Depending on the specific drug and dosage form, the labeling can include appropriate indications from those listed here.

1. Treatment of moderate to severe vasomotor symptoms associated with the menopause.
2. Treatment of vulvar and vaginal atrophy.
3. Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure.

The following indications and text may only be included if specifically studied and approved by CDER..

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 and management of postmenopausal osteoporosis

CONTRAINDICATIONS

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

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1. Known or suspected pregnancy (see PRECAUTIONS).
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

a. 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, and this risk has been shown to persist for at least 8-15 years after estrogen therapy is discontinued.

b. 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, there are conflicting data whether there is an increased risk in women using estrogens for prolonged periods of time, especially in excess of 10 years.

2. Venous thromboembolism

Three epidemiologic studies have found an increased risk of venous thromboembolism (VTE) in users of estrogen replacement therapy (ERT) who did not have predisposing conditions for VTE, such as past history of cardiovascular disease or a recent history of pregnancy, surgery, trauma, or serious illness. The increased risk was found only in current ERT users; it did not persist in former users. The findings were similar for ERT alone or with added progestin and pertain to commonly used ERT types and doses, including 0.625 mg or more per day orally of conjugated estrogens, 1 mg or more per day orally of estradiol, and 50 µg or more

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per day of transdermal estradiol. The studies found the VTE risk to be about one case per 10,000 women per year among women not using ERT and without predisposing conditions. The risk in current ERT users was increased to 2-3 cases per 10,000 women per year.

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.

4. 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.

5. Gallbladder disease

A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in women receiving postmenopausal estrogens has been reported.

PRECAUTIONS

A. GENERAL

1. Addition of a progestin when a woman has not had a hysterectomy.

Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone.

There are, however, possible risks that may be associated with the use of progestins in estrogen replacement regimens. These include:

- (a) adverse effects on lipoprotein metabolism (lowering HDL and raising LDL)
- (b) impairment of glucose tolerance; and

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- (c) possible enhancement of mitotic activity in breast epithelial tissue, although few epidemiological data are available to address this point.

The choice of progestin, its dose, and its regimen may be important in minimizing these adverse effects.

2. Elevated blood pressure

Substantial increases in blood pressure during estrogen replacement therapy have been attributed to idiosyncratic reactions to estrogens in a small number of case reports. A generalized effect of estrogen therapy on blood pressure was not found in the one randomized, placebo-controlled study that has been reported.

3. Familial hyperlipoproteinemia

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

4. Impaired liver function

Estrogens may be poorly metabolized in patients with impaired liver function.

B. INFORMATION FOR THE PATIENT

See text of PATIENT LABELING, below.

For those products with the indication of prevention and management of postmenopausal osteoporosis, the following text should be included:

Osteoporosis management

Most prospective studies of efficacy for this indication have been carried out in white post-menopausal women, without stratification by other risk factors, and tend to show a universally beneficial effect on bone. Since estrogen administration is associated with risk, patient selection must be individualized based on the balance of risks and benefits.

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 after menopause. Studies also suggest that estrogen reduces the rate of vertebral fractures. When estrogen therapy is discontinued, bone mass declines at a rate

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comparable to the immediate postmenopausal period.

White and Asian women are at higher risk for osteoporosis than black women, and thin women are at higher risk than heavier women, who generally have higher endogenous estrogen levels. Early menopause is one of the strongest predictors for the development of osteoporosis. Other factors associated with osteoporosis include genetic factors (small build, family history), lifestyle (cigarette smoking, alcohol abuse, sedentary exercise habits) and nutrition (below average body weight and dietary calcium intake).

The mainstays of prevention and management of osteoporosis are weight-bearing exercise, adequate calcium intake, and, when indicated, estrogen. 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. The average calcium intake in the USA is 400-600 mg/day. Therefore, when not contraindicated, calcium supplementation may be helpful for women with suboptimal dietary intake.

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. *Delete the next sentence except when approved by CDER.* For prevention and treatment of osteoporosis, however, see DOSAGE AND ADMINISTRATION section.

D. DRUG AND 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

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(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. CARCINOGENESES, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

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. See CONTRAINDICATIONS and WARNINGS.

F. PREGNANCY

Estrogens are not indicated for use during pregnancy or the immediate postpartum period. Estrogens are ineffective for the prevention or treatment of threatened or habitual abortion. Treatment with diethylstilbestrol (DES) during pregnancy has been associated with an increased risk of congenital defects and cancer in the reproductive organs of the fetus, and possibly other birth defects. The use of DES during pregnancy has also been associated with a subsequent increased risk of breast cancer in the mothers.

G. NURSING MOTHERS

As a general principle, 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. Estrogens are not indicated for the prevention of postpartum breast engorgement.

H. PEDIATRIC USE

Estrogen replacement therapy is indicated for the induction of puberty in adolescents

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with some forms of pubertal delay (See INDICATIONS and DOSAGE AND ADMINISTRATION sections). Safety and effectiveness in pediatric patients have not otherwise been established.

Large and repeated doses of estrogen over an extended time period have been shown to accelerate epiphyseal closure, which could result in short adult stature if treatment is initiated before the completion of physiologic puberty in normally developing children. If estrogen is administered to patients whose bone growth is not complete, periodic monitoring of bone maturation and effects on epiphyseal centers is recommended during estrogen administration.

Estrogen treatment of prepubertal girls also induces premature breast development and vaginal cornification, and may induce vaginal bleeding. In boys, estrogen treatment may modify the normal pubertal process and induce gynecomastia.

ADVERSE REACTIONS

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

1. **Genito-urinary 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**

Cholestatic jaundice; pancreatitis; nausea; vomiting; abdominal cramps; bloating.

4. **Skin**

Chloasma or melasma; which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism.

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5. **Central nervous system**

Mental depression; chorea; headache; migraine; dizziness.

6. **Miscellaneous**

Increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; changes in libido; edema; intolerance to contact lenses.

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

Depending on the specific drug and dosage form, the labeling can include appropriate dosage and administration from those listed here.

1. For treatment of moderate to severe vasomotor symptoms, vulvar 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.

Manufacturer to supply specific dosage information.

2. For treatment of female hypoenestrogenism due to hypogonadism, castration, or primary ovarian failure.

Manufacturer to supply specific dosage information.

3. For 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.

Manufacturer to supply specific dosage information.

4. For treatment of breast cancer (for palliation only) in appropriately selected women and men with metastatic disease.

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Manufacturer to supply specific dosage information.

5. For treatment of advanced androgen-dependent carcinoma of the prostate, for palliation only.

Manufacturer to supply specific dosage information.

6. For prevention and management of osteoporosis.

Manufacturer to supply specific dosage information.

HOW SUPPLIED

Manufacturer to supply information on available dosage forms, potency, color, and packaging.

Manufacturer to include statement such as "Keep out of reach of children" to both the instructions and dispenser.

III. PATIENT LABELING

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 are acceptable in comparison to the benefits. If you use estrogens, make 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 reasons for use.

ESTROGENS INCREASE THE RISK OF CANCER OF THE UTERUS

If you use any drug that contains estrogen, 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.

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USES OF ESTROGEN

Not every estrogen drug is approved for every use listed in this section. If you want to know which of these uses are approved for the medicine prescribed for you, ask your doctor or pharmacist to show you the professional labeling.

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 vulvar 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). 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

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1000 milligrams per day before menopause or 1500 milligrams per day after menopause), may help to prevent osteoporosis. Regular weight-bearing exercise 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, women who are likely to develop osteoporosis should use estrogens for prevention. Women who are likely to develop osteoporosis often have one or more of 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), also 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

If you think you may be pregnant, do not use any form of estrogen-containing drug. Using some types of 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 that 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.

If you have had cancer

Since estrogens may increase the risk of certain types of breast and uterine cancer, you should not use estrogens unless your doctor recommends that you take it. (For certain patients with breast or prostate cancer, estrogens may help.)

If you have any circulation problems

Men and women with abnormal blood clotting conditions should avoid estrogen use (see DANGERS OF ESTROGENS, below).

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After childbirth or when breast feeding 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).

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 dose you use. 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 (see also 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. Yearly mammography is recommended for women beginning at age 50.

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 stroke (by cutting off blood to the brain), heart attack (by cutting off blood to the heart), a pulmonary clot (by cutting off blood to the lungs), or other problems. Any of these conditions may cause death or serious long term disability.

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Gall bladder disease

Women who use estrogens after menopause are more likely to develop gall bladder disease needing surgery than women who do not use estrogens.

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 of the uterus (fibroids)

Retention of excess fluid

Spotty darkening of the skin, particularly on the face

USE IN CHILDREN

Estrogens may be prescribed for certain adolescent girls whose ovaries do not work normally (see USES OF ESTROGEN, above). Otherwise, estrogen treatment has not been shown either effective or safe for use by infants, children, or adolescent boys or girls.

REDUCING THE RISKS 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.

Reassess your need for estrogens

You and your doctor should reevaluate whether or not you still need estrogens every

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six to 12 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

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.

Your doctor has prescribed this drug for you and you alone. Do not give the drug to anyone else.

Keep this and all drugs out of the reach of children. In case of overdose, call your doctor, hospital or poison control center immediately.

HOW SUPPLIED

A description of the particular product, to be supplied by the manufacturer.

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