Guidance for Industry

Labeling Guidance for Non-Contraceptive Estrogen Drug Products —Prescribing Information for Health Care Providers, and Patient Labeling

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

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should be submitted within 60 days of publication of the *Federal Register* notice announcing the availability of the draft guidance.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Copies of this draft guidance are available on the Internet at http://www.fda.gov/cder/guidance/index.htm. If you have questions on the content of the draft document contact Lana L. Pauls, M.P.H. at (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 INDUSTRY[1]
Labeling Guidance for Non-Contraceptive Estrogen Drug Products — Prescribing Information for Health Care Providers, and Patient Labeling

I. INTRODUCTION

This guidance describes recommended *prescribing information* for estrogen drug products for new drug applications (NDAs). For ANDAs, differences between the *prescribing information* 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 *prescribing information* protected by patent or accorded exclusivity under section 505(j)(5)(D) of the Federal Food, Drug, and Cosmetic Act. It also provides labeling for patients.

II. LABELING FOR HEALTH CARE PROVIDERS

The recommended text of the *prescribing information* for health care providers is as follows:

[1]This 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.

ESTROGENS INCREASE THE RISK OF ENDOMETRIAL CANCER

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 the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens at equivalent estrogen doses.

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 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:

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 prescribing information.
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.
1. Data for all the anatomical application sites that will be proposed in the prescribing information (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. Estrogens circulate in the blood largely bound to sex hormone binding globulin (SHBG) and albumin. The conjugated estrogens bind mainly to albumin; the unconjugated estrogens bind to both albumin and SHBG.

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, 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 proportion 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

The following information should be included:

The following section contains information on drug interactions with ethinyl estradiol-containing products (specifically, oral contraceptives) that have been reported in the public

literature. It is unknown whether such interactions occur with drug products containing other types of estrogens.

1. The metabolism of ethinyl estradiol is increased by rifampin and anticonvulsants such as phenobarbitol, phenytoin and carbamazepine. Coadministration of troglitazone and certain ethinyl-estradiol containing drug products (e.g., oral contraceptives containing ethinyl estradiol) reduce the plasma concentrations of ethinyl estradiol by 30 percent.

   Ascorbic acid and acetaminophen may increase AUC and/or plasma concentrations of ethinyl estradiol. Coadministration of atorvastatin and certain ethinyl-estradiol containing drug products (e.g., oral contraceptives containing ethinyl estradiol) increase AUC values for ethinyl estradiol by 20 percent.

   Clinical pharmacokinetic studies have not demonstrated any consistent effect of antibiotics (other than rifampin) on plasma concentrations of synthetic steroids.

2. Drug products containing ethinyl estradiol may inhibit the metabolism of other compounds. Increased plasma concentrations of cyclosporin, prednisolone, and theophylline have been reported with concomitant administration of certain drugs containing ethinyl estradiol (e.g., oral contraceptives containing ethinyl estradiol). In addition, these drugs containing ethinyl estradiol may induce the conjugation of other compounds.

Decreased plasma concentrations of acetaminophen and increased clearance of temazapam, salicylic acid, morphine and clofibric acid have been noted when these drugs were administered with certain ethinyl-estradiol containing drug products (e.g., oral contraceptives containing ethinyl estradiol).

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 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.

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, dosage form and clinical trials performed, the prescribing information 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.

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:

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 or a history of these conditions in association with previous estrogen use.

6. (Trademark) should not be used in patients hypersensitive to its ingredients.

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**

Five 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 risk appeared to be higher in the first year of use and decreased thereafter. The findings were similar for ERT alone or with added progestin and pertain to commonly used oral and transdermal doses, with a possible dose-dependent effect on risk. 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.

Embolic cerebrovascular events have been reported in women receiving postmenopausal estrogens.

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 (e.g., lowering HDL, raising LDL) ; and

(b) impairment of glucose tolerance.

2. **Elevated blood pressure**

In a small number of case reports, substantial increases in blood pressure during estrogen replacement therapy have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of estrogen therapy on blood pressure was not seen.

3. **Familial hyperlipoproteinemia**

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

4. **Impaired liver function**

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

5. **Hypothyroidism**

Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T4 and T3 serum concentrations in the normal range. Patients dependent on thyroid hormone replacement therapy, however, may require increased doses in order to maintain their free thyroid hormone levels in an acceptable range.

B. INFORMATION FOR THE PATIENT

See text of PATIENT LABELING, below.

C. LABORATORY TESTS

This section will be specific for the product in question.

D. DRUG/LABORATORY TEST INTERACTIONS

1. Changes seen with estrogen administration include 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) levels occur with estrogen administration. This leads to increased circulating total thyroid hormone levels as measured by protein-bound iodine (PBI), T4 levels (by column or by radioimmunoassay) or T3 levels by radioimmunoassay, while T3 resin uptake is decreased. Patients with normal thyroid function will be able to compensate for the increased TBG levels, but patients on replacement therapy may require higher doses of replacement thyroid hormone.

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

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

5. Impaired glucose tolerance.

6. Reduced response to metyrapone test.

7. Reduced serum folate concentration.

E. 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 has been used for the induction of puberty in adolescents 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.

I. GERIATRIC USE

Complete as appropriate in accordance with 21 CFR 201.57(f)(10)

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, gallbladder disease, risk of thromboembolism, 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.

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; anaphylactoid reactions.

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, dosage form the prescribing information 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 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.

3. For treatment of female hypoestrogenism due to hypogonadism, castration, or primary ovarian failure.

   Manufacturer to supply specific dosage information.

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

   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 needed. 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 check any unusual vaginal bleeding to find out the cause. Women who do not have a uterus have no risk of endometrial cancer.

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.

Estrogens are used:

- **To reduce moderate to severe menopausal symptoms**. Estrogens are hormones made by the ovaries of healthy women. Between ages 45 and 55, the ovaries normally stop making estrogens. This drop in estrogen levels in the body 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." If ovarian function is compromised following chemotherapy or radiation therapy for certain conditions, manopause may be induced prematurely. However, use of estrogen in cancer patients with chemotherapy-induced menopause should be carefully discussed with the patients health care provider.

  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. Your response to the effects of menopause and hormonal therapy will be unique. It is possible to adjust therapies and dosage levels to meet your individual needs. Be sure to work with your healthcare provider to find your ideal treatment regimen.

- **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 cancers in special situations, in men and women.**

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. Although some people believe estrogens prevent miscarriage, estrogens have not been proven to do this.

- **If you have unusual vaginal bleeding that has not been checked 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**

Estrogens may increase the risk of certain types of cancer. Therefore, you should not use estrogens unless your doctor recommends that you take them.

- **If you have any circulation problems**

Men and women with abnormal blood clotting conditions should not use estrogens (see RISKS OF ESTROGENS, below).

- **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 RISKS OF ESTROGENS, below). When breastfeeding, consider discussing any drug use with your healthcare provider.

- **If you are allergic to any ingredient in (Trademark)**

RISKS OF ESTROGENS

Talk with your healthcare provider about the risks of using estrogens, which include:

- **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 used estrogens at some time in their lifetimes. However, some studies suggest there may be a higher risk of breast cancer in women who use estrogens for a long period of time, especially 10 years or more.

All women should do monthly self-exams of their breasts and have regular breast exams by a health professional. Women ages 40 and above should have periodic mammograms to check for early signs of breast cancer. Ask your health professional how to do a breast self-exam.

- **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), pulmonary clot (by cutting off blood to the lungs), or other problems. Any of these conditions may cause death or serious long term disability.

- **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
- Hair loss

- Breast tenderness or enlargement
- Enlargement of non-cancerous (benign) tumors of the uterus (fibroids)
- Retention of excess fluid (edema)
- Spotty darkening of the skin, particularly on the face

USE IN CHILDREN

Estrogens may be given to adolescent girls whose ovaries do not work normally (see USES OF ESTROGEN, above). For other conditions, estrogen treatment has not been shown to be 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 using estrogens, it is important to visit your doctor at least once a year for a check-up. If you develop unexpected vaginal bleeding while taking estrogens, you should check with your healthcare professional right away.

- **Reassess your need for estrogens**

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

- **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). Check your breasts every month. Ask your doctor or healthcare professional to show you how to examine your breasts.
- Yellowing of the skin or eyes (possible liver problem)
- Pain, swelling, or tenderness in the abdomen (stomach area; possible gallbladder problem)

OTHER INFORMATION

Estrogens increase the risk of getting 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 getting 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. It could be dangerous for someone else.

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

HOW SUPPLIED

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

COMIS #2215

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