WARNINGS:
1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA IN POST-MENOPAUSAL 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 equi-estrogenic 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.
Thus, patient selection must be individualized based on the balance of risk factors, and tend to show a universally salutary effect on bone. Most prospective studies of efficacy for this indication have been car-

Equilibrium of metabolic interconversions, estradiol is the principal hormone in normally cycling adult women. Although circulating estrogens exist in a dynamic equilibrium of circulating conjugated and unconjugated estrogenic forms which interact with catecholamine metabolism, especially in the central nervous system, and conjugation with glutaronic acids which are then rapidly excreted in the urine.

When given orally, naturally-occurring estrogens and their esters are extensively metabolized first-pass effects 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 nonsteroidal estrogens, are degraded very slowly in the liver and other tissues, which results in their prolonged duration of action. Also, conjugated estrogens are excreted principally via the bile, which enters the enterohepatic recycling, which might occur during menopause and they should not be used to treat these conditions.

Treatment of vulval and vaginal atrophy.

5. Treatment of hypogonadism due to hypogonadism, castration or primary ovarian failure.


Since estrogen administration is associated with risk, selection of patients should ideally be based on prospective identification of risk factors. 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 risk factors, and tend to show a universally salutary effect on bone.
risks and benefits. A more favorable risk/benefit ratio exists in a hysterectomized woman because she has no risk of endometrial cancer.

**WARNINGS**

1. Induction of malignant neoplasms.
   
   a. Endometrial cancer. The reported endometrial cancer risk among unopposed estrogen users is about 2-12-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 15-24-fold for five to ten years or more. In three studies, persistence of risk was not related to the estrogen dose used. Studies also suggest a trend toward increased risk with duration 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.

   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, some have reported a moderately increased risk relative to 1.0-2.0 in those taking higher doses or those taking longer doses for prolonged periods of time, especially in excess of 10 years. Other studies have not shown this relationship.

   c. Congenital lesions with malignant potential. Estrogen therapy during pregnancy is associated with an increased risk of fetal congenital malformations, especially those of the reproductive tract, and possibly other birth defects. Women of childbearing age who are receiving postmenopausal estrogen therapy should avoid pregnancy for at least seven or more days of a cycle of estrogen administration have a significantly increased risk relative to 1.0-2.0 in those taking higher doses or those taking longer doses for prolonged periods of time, especially in excess of 10 years. Other studies have not shown this relationship.

   d. Active thrombophlebitis or thromboembolic disorders.

**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 women).

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.

**Precautions**

1. Addition of a progestin.

2. Cardiovascular disease. Large doses of estrogen may be associated with a theoretical cardiovascular risk to women caused by high estrogen doses, the dose for estrogen replacement therapy should not exceed the lowest effective dose.

3. Hypercalcemia in patients with breast cancer and bone metastases. If hypercalcemia occurs, the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

**Precautions**

1. Atypical estrogen metabolism. Estrogen replacement therapy reduces bone resorption and retards or halts postmenopausal bone loss. Case-control studies have shown an approximately 50 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 rate of vertebral fractures. Even when started as late as 6 years after menopause, estrogen prevents further loss of bone mass for as long as the treatment is continued. The results of a double-blind, placebo-controlled two-year study have shown that treatment with one tablet of OTC of 4.25 mg conjugated estrogens is associated with a significantly greater decrease in bone 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.

2. Blood pressure should be monitored at regular intervals with estrogen use. Postmenopausal women 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.

3. Hyperprolactinemia. Hyperprolactinemia may occur in patients receiving estrogen replacement therapy. If hyperprolactinemia is severe, the drug should be stopped and appropriate measures taken to reduce the serum level.

**Precautions**

1. Atypical estrogen metabolism. Estrogen replacement therapy may lead to severe 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 higher 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.

2. Hyperprolactinemia. Hyperprolactinemia may occur in patients receiving estrogen replacement therapy. If hyperprolactinemia is severe, the drug should be stopped and appropriate measures taken to reduce the serum level.
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, but these issues remain to be clarified.

2. Physical examination. A complete medical and family history should be taken prior to the initiation of any estrogen therapy. The examination should include a 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 reevaluation of the patient.

3. Hypercoagulability. Some studies have shown that women taking estrogen replacement therapy have hypercoagulability primarily related to decreased antithrombin activity. This effect appears dose- and duration-dependent and is less pronounced than that associated with oral contraceptive use. Also, postmenopausal women tend to have increased coagulation parameters at baseline compared to premenopausal women. There is some suggestion that low dose postmenopausal estrogen may increase the risk of thromboembolism, although the majority of studies are not consistent. No consistent elevation in estrogen users report no such increase. In some studies, increases in prothrombin time, partial thromboplastin time, and antithrombin III have been observed. However, since many drugs are excreted in human milk, in addition, estrogen drug therapy should be used only when clearly necessary and should be administered with caution.

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

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

8. Information for the Patient. See text of Patient Package Insert below.

C. Laboratory Tests.

1. Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time, increased platelet count, increased factors V, VIII, X, and fibrinogen activity, and decreased levels of antithrombin III and antithrombin III.

2. Fluid retention. Conditions which might be exacerbated by this factor such as asthma, epilepsy, migraine, and cardiac or renal disease require careful observation.

3. Impaired glucose tolerance. 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.


5. Impaired plasma protein binding. Some patients may develop increased plasma protein binding, leading to increased circulating corticosteroids and sex steroids.

6. Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), 14 levels of thyroxine (T4) levels by column or by radiomimunoassay or T3 levels by radioimmunoassay. T3 resin uptake is decreased, reflecting the elevated TSH. Free T4 and Free T3 concentrations are unchanged.

7. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-l-antitrypsin, ceruloplasmin).

8. Decreased levels of anti-factor Xa and antithrombin III, decreased antithrombin III activity, increased levels of fibrinogen and fibrinogen activity, increased plasminogen activity and activity.

9. Increased plasma fibrinogen and fibrinogen-activity, increased plasminogen and activity.

10. Increased plasma fibrinogen and fibrinogen-activity, increased plasminogen and activity.

11. Increased plasma fibrinogen and fibrinogen-activity, increased plasminogen and activity.

B. ID. Drug/Laboratory Test Interactions.

1. For treatment of moderate to severe vasomotor symptoms, vulval dryness. Overdosage of estrogen may cause nausea and vomiting, and overdosage bleeding may occur in females.

DOSAGE AND ADMINISTRATION

1. For treatment of moderate to severe vasomotor symptoms, vulval dryness.
brand of estropipate tablets, USP

and vaginal atrophy associated with the menopause, the lowest dose and regimen that will control symptoms should be chosen and medi-
cation should be discontinued as promptly as possible.
• Administer to continue or taper medication should be made at 3-
month to 6-month intervals.
Usual dosage ranges:
Vasomotor symptoms—One OGEN .625 (0.75 mg estropipate) tablet to two OGEN 2.5 (3 mg estropipate) tablets per day. The lowest
dose that will control symptoms should be chosen. If the patient has
not menstruated within the last two months or more, cyclic admin-
istration is started arbitrarily. If the patient is menstruating, cyclic
administration is started on day 5 of bleeding.
Vulval and vaginal atrophy—One OGEN .625 (0.75 mg estropi-
pate) tablet to two OGEN 2.5 (3 mg estropipate) tablets daily, depend-
ing upon the tissue response of the individual patient. The lowest
dose that will control symptoms should be chosen. Administration
should be continued for as long as needed.

1. For treatment of female hypogonadism due to hypogonadism,
castration, or primary ovarian failure.
Usual dosage range:
Female hypogonadism—daily dose of one OGEN 1.25 (1.5 mg
estropipate) tablets to three OGEN 2.5 (3 mg estropipate) tablets may
be given for the first three weeks of a theoretical cycle, followed by a
rest period of eight to ten days. The lowest dose that will control
symptoms should be chosen. If bleeding does not occur by the end
of this period, the same dosage schedule is repeated. The number of
courses of estrogen therapy necessary to produce bleeding may vary
depending on the responsiveness of the endometrium. If satisfactory
withdrawal bleeding does not occur, an oral progestogen may be
given in addition to estrogen during the third week of the cycle.
Female castration or primary ovarian failure—daily dose of
estrogens is based on the height and weight of the individual.
Treated patients with an intact uterus should be monitored closely
for signs of endometrial cancer and appropriate diagnostic measures
should be taken to rule out malignancy in the event of persistent or
recurring abnormal vaginal bleeding.

• To reduce moderate or severe menopausal symptoms.

Reference", which is available in many book stores and public libraries.
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. You can also look up the
specific estrogen product in a book called the "Physicians’ Desk

PATIENT INFORMATION


cain should be discontinued as promptly as possible.
Attempts to discontinue or taper medication should be made at 3-
month to 6-month intervals.

TOXICOLOGICAL CONSIDERATIONS

A daily dose of one OGEN 1.25 (1.5 mg estropipate) tablet for 25 days of a 31-day cycle per month.

HOW SUPPLIED

OGEN (estropipate tablets, USP) is supplied as OGEN .625 (0.75 mg
estropipate) calculated as sodium estrone sulfate 0.625 mg), yellow,
peach-colored, scored tablets, imprinted U 3772, NDC 0009-3772-01; OGEN 1.25
(1.5 mg estropipate, calculated as sodium estrone sulfate 1.25 mg),
peach-colored, scored tablets, imprinted U 3775, NDC 0009-3775-01; and
OGEN 2.5 (3 mg estropipate, calculated as sodium estrone sulfate
2.5 mg, blue, scored tablets, imprinted U 3774, NDC 0009-3774-01.
Tablets of all three dosage levels are standardized to provide uniform
estrogen activity and are scored to provide dosage flexibility. All tablet sizes of OGEN are available in bottles of 100.
Recommended storage: Store below 77°F (25°C).

USAGES OF NEWTROGEN

Uses of Neotrogen (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 phar-
macist to show you the professional labeling. You can also look up the
specific estrogen product in a book called the "Physicians’ Desk Refer-
cence", which is available in many book stores and public libraries,
cain should be discontinued as promptly as possible.

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cence", which is available in many book stores and public libraries,
Ogen
brand of estropipate tablets, USP

- 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 more likely to break. Both men and women start to lose bone mass after age 40, but women lose bone mass faster after the menopause. Using estrogens after the menopause slows bone thinning and may prevent bone loss from breaking. Taking 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 have osteoporosis should use estrogens whether or not they have arthritis or other signs of osteoporosis.

- To treat certain cancers in special situations, in men and women.
- To prevent certain cancers in special situations, in men and women.

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. Women with breast or prostate cancer, estrogen use may be harmful. Women who have had breast cancer or who have relatives who have breast cancer often, because their ovaries were removed during an operation or 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:
- If you have ever had cancer.
- If you have any circulation problems.
- If you have any unusual vaginal bleeding which has not been evaluated by your doctor (see BOXED WARNINGS).
- 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 serious harm if your vaginal bleeding is caused by cancer of the uterus.

- If you have had cancer.
- 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. Women with breast or prostate cancer, estrogen use may be harmful. Women who have had breast cancer or who have relatives who have breast cancer often, because their ovaries were removed during an operation or surgical menopause, are more likely to develop osteoporosis than women whose menopause happens at the average age.

- If you have any unusual vaginal bleeding which has not been evaluated by your doctor (see BOXED WARNINGS).
- 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 that estrogens 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.

- After childbirth or when breastfeeding a baby.
- 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. 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 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 or 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.
- Regular breast examinations by a health professional and monthly self-examinations are recommended for all women.

- Gallbladder disease.
- 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.
- 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. Abnormal blood clots, by cutting off blood flow to the brain, can cut off the blood supply to vital organs, causing serious problems. These problems may include strokes by cutting off blood flow 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 breast tumors (fibroadenomas) of the uterus.
- Retention of excess fluid. This may make some conditions worse, such as asthma, epilepsy, migraine, heart disease, or kidney disease.
- A spasmy splintering of the skin, particularly on the Face.

REDUCING RISK OF ESTROGEN USE
If you use estrogens, you can reduce your risks by doing these things:
- See your doctor regularly. While you are using estrogens. It is important to visit your doctor at least once a year for a check-up. If you develop vaginal bleeding while taking estrogens, you may need further evaluation. If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram (breast x-ray), you may need to have more frequent breast examinations.
- Reassess your need for estrogens. You and your doctor should reevaluate whether or not you still need estrogens at least every six months.
- Be alert for signs of trouble. If any of these warning signals (or any other unusual symptoms) happen while you are using estrogens, call your doctor immediately.
- Abnormal bleeding from the vagina possible uterine cancer.
It is possible that you may experience the symptoms listed below.

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

Some doctors may choose to prescribe a progestin, a different hormonal drug, for you to take together with your estrogen treatment. Progestins lower your risk of developing endometrial hyperplasia (a possible pre-cancerous condition of the uterus) while using estrogens. Taking estrogens and progestins together may also protect you from the higher risk of uterine cancer, but this has not been clearly established. Combined use of progestin and estrogen treatment may have additional risks; however, the possible risks include unhealthy effects on blood fats (especially a lowering of HDL cholesterol, the “good” blood fat which protects against heart disease risk), unhealthy effects on blood sugar (which might worsen a diabetic condition), and a possible further increase in the breast cancer risk which may be associated with long-term estrogen use. The type of progestin drug used and its dosage schedule may be important in minimizing these effects.

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

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.

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

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

OGEN (estropipate tablets, USP) is supplied as: OGEN .625 (0.75 mg estropipate), yellow tablets; OGEN 1.25 (1.5 mg estropipate), peach-colored tablets; OGEN 2.5 (3 mg estropipate), blue tablets.

Manufactured for
Pharmacia & Upjohn Company
A subsidiary of Pharmacia Corporation
Kalamazoo, MI 49001, USA
By Abbott Laboratories
North Chicago, IL 60064, USA

Revised August 2001 816 035 304 632851

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brand of estropipate tablets, USP