

TEXT OF PROPOSED LABELING: PATIENT INSTRUCTIONS

PATIENT INSTRUCTIONS

INFORMATION FOR THE PATIENT

INTRODUCTION

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

Estrogens/progestins 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 reason for use.

ESTROGENS INCREASE THE RISK OF CANCER OF THE UTERUS

THIS FINDING REFERS TO ESTROGENS GIVEN WITHOUT PROGESTIN

Progestin drugs taken with estrogen-containing drugs significantly reduce, but do not eliminate, this risk.

If you use any drug containing 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.

If you take ORTHO-PREFEST™ and later find you were pregnant when you took it, be sure to discuss this with your doctor as soon as possible.

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 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 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), are also 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 which has not been evaluated by your doctor

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

Women with abnormal blood clotting conditions should avoid estrogen use (see **RISKS OF ESTROGENS AND/OR PROGESTINS**, 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 AND/OR PROGESTINS**, below).

RISKS OF ESTROGENS AND/OR PROGESTINS

Cancer of the uterus

Your risk of developing cancer of the uterus gets higher the longer you use estrogens and the larger the 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 reduces, but does not eliminate, 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

Studies suggest a higher risk of breast cancer in women who have used estrogens for long periods of time (especially more than 10 years), or who use higher doses for shorter time periods. The effects of added progestin on the risks of breast cancer are unknown.

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 a 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.

Gallbladder disease

Women who use estrogens after menopause are more likely to develop gallbladder 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 and/or progestin use:

- Nausea and vomiting

- Breast tenderness or enlargement
- Enlargement of benign tumors of the uterus (“fibroids”)
- Retention of excess fluid
- A spotty darkening of the skin, particularly on the face
- Irregular vaginal bleeding or spotting
- Headache, migraine, dizziness, faintness or change in vision including intolerance to contact lenses
- Mental depression
- Vaginal yeast infections

USE IN CHILDREN

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

While you are using ORTHO-PREFEST™:

See your doctor regularly

Visit your doctor regularly for a check-up. If you develop vaginal bleeding, you may need further evaluation.

Reassess your need for treatment

You and your doctor should reevaluate whether or not you still need ORTHO-PREFEST™ 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 ORTHO-PREFEST™, call your doctor immediately:

- Abnormal bleeding from the vagina (possible uterine cancer).
- Pains in the calves or chest, a sudden shortness of breath or coughing blood (indicating possible clots in the legs, heart, or lungs).
- Severe headache or vomiting, dizziness, faintness, or changes in vision or speech, weakness or numbness of an arm or leg (indicating possible clots 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 and/or whites of the eyes (possible liver problems).
- 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 hormonal drug, with estrogens lowers

the risk of developing this condition. Since you still have your uterus, your doctor has prescribed ORTHO-PREFEST™ which has both an estrogen and progestin.

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

ORTHO-PREFEST™ therapy consists of the daily administration of a single tablet containing 1 mg estradiol (pink color) for three days followed by a single tablet of 1 mg estradiol combined with 0.09 mg norgestimate (white color) for three days. The three days of pink tablets followed by 3-days of white tablets are repeated continuously during treatment.

ORTHO-PREFEST™ is available as two separate, round-shaped tablets for oral administration and is supplied in a blister card with the following configuration: 4 rows of 7 tablets each and one row with 2 tablets, with space on the blister to place one of 7 weekday schedules.