

**INFORMATION FOR THE PATIENT\***  
**WHAT YOU SHOULD KNOW ABOUT ESTROGENS**  
**Covaryx and Covaryx H.S. Esterified Estrogens and Methyltestosterone**

Estrogens are female hormones produced by the ovaries. The ovaries make several different kinds of estrogens. In addition, scientists have been able to make a variety of synthetic estrogens. As far as we know, all these estrogens have similar properties and therefore much the same usefulness, side effects, and risks. This leaflet is intended to help you understand what estrogens are used for, the risks involved in their use, and how to use them as safely as possible. This leaflet includes the most important information about estrogens, but not all the information. If you want to know more, you can ask your doctor or pharmacist to let you read the package insert prepared for the doctor.

**USES OF ESTROGEN**

Estrogens are prescribed by doctors for a number of purposes, including:

1. To provide estrogen during a period of adjustment when a woman's ovaries no longer produce it, in order to prevent certain uncomfortable symptoms of estrogen deficiency. (All women normally stop producing estrogens, generally between the ages of 45 and 55; this is called the menopause).
2. To prevent symptoms of estrogen deficiency when a woman's ovaries have been removed surgically before the natural menopause.
3. To prevent pregnancy: (Estrogens are given along with a progestogen, another female hormone; these combinations are called oral contraceptives or birth control pills. Patient labeling is available to women taking oral contraceptives and they will not be discussed in this leaflet).
4. To treat certain cancers in women and men.

THERE IS NO PROPER USE OF ESTROGENS IN A PREGNANT WOMAN.

**ESTROGENS IN THE MENOPAUSE**

In the natural course of their lives, all women eventually experience a decrease in estrogen production. This usually occurs between ages 45 and 55 but may occur earlier or later. Sometimes the ovaries may need to be removed before natural menopause by an operation, producing a "surgical menopause." When the amount of estrogen in the blood begins to decrease, many women may develop typical symptoms: Feelings of warmth in the face, neck, and chest or sudden intense episodes of heat and sweating throughout the body (called "hot flashes" or "hot flushes"). These symptoms are sometimes very uncomfortable. A few women eventually develop changes in the vagina (called "atrophic vaginitis") which cause discomfort, especially during and after intercourse. Estrogens can be prescribed to treat these symptoms of the menopause. It is estimated that considerably more than half of all women undergoing the menopause have only mild symptoms or no symptoms at all and therefore do not need estrogens. Other women may need estrogens for a few months, while their bodies adjust to lower estrogen levels. Sometimes the need will be for periods longer than six months. In an attempt to avoid over stimulation of the uterus (womb), estrogens are usually given cyclically during each month of use, that is three weeks of pills followed by one week without pills. Sometimes women experience nervous symptoms or depression during menopause. There is no evidence that estrogens are effective for such symptoms and they should not be used to treat them, although other treatment may be needed. You may have heard that taking estrogens for long periods (years) after the menopause will keep your skin soft and supple and keep you feeling young. There is no evidence that this is so, however, and such long-term treatment carries important risks.

**THE DANGERS OF ESTROGENS**

1. **Cancer of the uterus.** If estrogens are used in the postmenopausal period for more than a year, there is an increased risk of endometrial cancer (cancer of the uterus). Women taking estrogens have roughly 5 to 10 times as great a chance of getting this cancer as women who take no estrogens. To put this another way, while a postmenopausal woman not taking estrogens has 1 chance in 1,000 each year of getting cancer of the uterus, a woman taking estrogens has 5 to 10 chances in 1,000 each year. For this reason it is important to take estrogens only when you really need them. The risk of this cancer is greater the longer estrogens are used and also seems to be greater when larger doses are taken. For this reason, it is important to take the lowest dose of estrogen that will control symptoms and to take it only as long as it is needed. If estrogens are needed for longer periods of time, your doctor will want to reevaluate your need for estrogens at least every six months. Women using estrogens should report any irregular vaginal bleeding to their doctors; such bleeding may be of no importance, but it can be an early warning of cancer of the uterus. If you have undiagnosed vaginal bleeding, you should not use estrogens until a diagnosis is made and you are certain there is no cancer of the uterus.
2. **Other possible cancers.** Estrogens can cause development of other tumors in animals, such as tumors of the breast, cervix, vagina, or liver, when given for a long time. At present there is no good evidence that women using estrogen in the menopause have an increased risk of such tumors, but there is no way yet to be sure they do not; and one study raises the possibility that use of estrogens in the menopause may increase the risk of breast cancer many years later. This is a further reason to use estrogens only when clearly needed. While you are taking estrogens, it is important that you go to your doctor at least once a year for a physical examination. Also, if members of your family have had breast cancer or if you have breast nodules or abnormal mammograms (breast x-rays), your doctor may wish to carry out more frequent examinations of your breasts.
3. **Gallbladder disease.** Women who use estrogens after menopause are more likely to develop gallbladder disease needing surgery as women who do not use estrogens. Birth control pills have a similar effect.
4. **Abnormal blood clotting.** Oral contraceptives increase the risk of blood clotting in various parts of the body. This can result in a stroke (if the clot is in the brain), a heart attack (clot in a blood vessel of the heart), or pulmonary embolus (a clot which forms in the

legs or pelvis, then breaks off and travels to the lungs). Any of these can be fatal. At this time use of estrogens in the menopause is not known to cause such blood clotting, but this has not been fully studied and there could still prove to be such a risk. It is recommended that if you have had clotting in the legs or lungs or a heart attack or stroke while you were using estrogens or birth control pills, you should not use estrogens (unless they are being used to treat cancer of the breast or prostate). If you have had a stroke or heart attack or if you have angina pectoris, estrogens should be used with great caution and only if clearly needed (for example, if you have severe symptoms of the menopause). The larger doses of estrogen used to prevent swelling of the breasts after pregnancy have been reported to cause clotting in the legs and lungs.

5. **Other Potential Risks.** Using estrogens and progestins may increase your chances of getting heart attacks, strokes, breast cancer, or blood clots.

**SPECIAL WARNING ABOUT PREGNANCY**

You should not receive estrogen if you are pregnant. If this should occur, there is a greater than usual chance that the developing child will be born with a birth defect, although the possibility remains fairly small. A female child may have an increased risk of developing cancer of the vagina or cervix later in life (in the teens or twenties). Every possible effort should be made to avoid exposure to estrogens during pregnancy. If exposure occurs, see your doctor.

**OTHER EFFECTS OF ESTROGENS**

In addition to the serious known risks of estrogens described above, estrogens have the following side effects and potential risks:

1. **Nausea and vomiting.** The most common side effect of estrogen therapy is nausea. Vomiting is less common.
2. **Effects on breasts.** Estrogens may cause breast tenderness or enlargement and may cause the breasts to secrete a liquid. These effects are not dangerous.
3. **Effects on the uterus.** Estrogens may cause benign fibroid tumors of the uterus to get larger. Some women will have menstrual bleeding when estrogens are stopped. But if the bleeding occurs on days you are still taking estrogens you should report this to your doctor.
4. **Effects on liver.** Women taking oral contraceptives develop on rare occasions a benign tumor of the liver which can rupture and bleed into the abdomen. So far, these tumors have not been reported in women using estrogens in the menopause, but you should report any swelling or unusual pain or tenderness in the abdomen to your doctor immediately. Women with a past history of jaundice (yellowing of the skin and white parts of the eyes) may get jaundice again during estrogen use. If this occurs, stop taking estrogens and see your doctor.
5. **Other effects.** Estrogens may cause excess fluid to be retained in the body. This may make some conditions worse, such as epilepsy, migraine, heart disease, or kidney disease.

**SUMMARY**

Estrogens have important uses, but they have serious risks as well. You must decide, with your doctor, whether the risks are acceptable to you in view of the benefits of the treatment. Except where your doctor has prescribed estrogens for use in special cases of cancer of the breast or prostate, you should not use estrogens if you have cancer of the breast or uterus, are pregnant, have undiagnosed abnormal vaginal bleeding, or have had a stroke, heart attack or angina, or clotting in the legs or lungs in the past while you were taking estrogens. You can use estrogens as safely as possible by understanding that your doctor will require regular physical examinations while you are taking them and will try to discontinue the drug as soon as possible and use the smallest dose possible. Be alert for signs of trouble including:

1. Abnormal bleeding from the vagina.
2. Pains in the calves or chest or sudden shortness of breath, or coughing blood (indicating possible clots in the legs, heart, or lungs).
3. Severe headache, dizziness, faintness, or changes in vision (indicating possible developing clots in the brain or eye).
4. Breast lumps (you should ask your doctor how to examine your own breasts).
5. Jaundice (yellowing of the skin).
6. Mental depression.

Based on his or her assessment of your medical needs, your doctor has prescribed this drug for you. Do not give the drug to anyone else.

**HOW SUPPLIED**

**COVARYX™** is a combination of Esterified Estrogens and Methyltestosterone.

**COVARYX™** is supplied in bottles of 100 Tablets. Each light yellow, capsule-shaped, film coated tablet debossed "C010" on obverse and plain on the reverse contains 1.25 mg of Esterified Estrogens, USP and 2.5 mg of Methyltestosterone, USP.

**COVARYX™ H.S. (Half-Strength)** is a combination of Esterified Estrogens and Methyltestosterone.

**COVARYX™ H.S.** is supplied in bottles of 100 Tablets. Each light pink, capsule-shaped, film coated tablet debossed "C020" on obverse and plain on the reverse contains 0.625 mg of Esterified Estrogens, USP and 1.25 mg of Methyltestosterone, USP.

\*This product has not obtained FDA-market approval applicable for new drugs.

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