

PART III: CONSUMER INFORMATION

Pr **PREMARIN**[®] (conjugated estrogens sustained release tablets)

This leaflet is part III of a three-part "Product Monograph" published when PREMARIN was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about PREMARIN. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

- To relieve menopausal and post-menopausal symptoms (vasomotor symptoms like hot flashes and night sweats).
- To prevent osteoporosis caused by low estrogen levels associated with menopause. Osteoporosis is a thinning of the bones that makes them weaker and easier to break.
- To treat certain types of abnormal uterine bleeding due to hormonal imbalance when your doctor has found no serious cause of the bleeding.
- To treat vulva and vaginal atrophy associated with menopause (itching, burning, dryness in or around the vagina, difficulty or burning on urination)

PREMARIN tablets for the prevention of osteoporosis is recommended only for women who are at risk of developing this condition. Talk to your doctor about whether a different treatment or medicine without estrogens might be better for you.

Adequate diet, calcium and vitamin D intake, cessation of smoking as well as regular weight-bearing exercise should be discussed with your doctor or pharmacist in addition to taking PREMARIN.

If you use PREMARIN tablets only to treat symptoms of vulvar and vaginal atrophy associated with menopause, talk with your healthcare provider about whether a vaginal (topical) treatment might be better for you.

PREMARIN Tablets should not be used by women with intact uteri unless it is prescribed in association with a progestin.

PREMARIN should be used only under the supervision of a doctor, with regular follow-up at least once a year to identify side effects associated with its use.

Your first follow-up visit should be within 3 to 6 months of starting treatment. Your visit may include a blood pressure check, a breast exam, a Pap smear and pelvic exam. You should have a mammogram before starting treatment and at regular intervals as recommended by your doctor. Your doctor may recommend some blood tests.

You should carefully discuss the risks and benefits of hormone

replacement therapy (HRT) with your doctor. You should regularly talk with your doctor about whether you still need treatment with HRT.

What it does:

When taking PREMARIN women are using a hormone, estrogen (i.e. conjugated equine estrogen tablets). PREMARIN replaces estrogen in your body, which naturally decreases at menopause.

Estrogens are female hormones that are produced by a woman's ovaries and are necessary for normal sexual development and the regulation of menstrual periods during the childbearing years.

When a woman is between the ages of 45 and 55, the ovaries normally stop making estrogens. This leads to a drop in body estrogen levels and marks the beginning of menopause (the end of monthly menstrual periods). A sudden drop in estrogen levels also occurs if both ovaries are removed during an operation before natural menopause takes place. This is referred to as 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"). In some women the symptoms are mild; in others they can be severe. These symptoms may last only a few months or longer. Taking PREMARIN can alleviate these symptoms. If you are not taking estrogen for other reasons, such as the prevention of osteoporosis, you should take PREMARIN only as long as you need it for relief from your menopausal symptoms.

After menopause, some women develop osteoporosis. This is a thinning of the bones that makes them weaker and allows them to break more easily, often leading to fractures of the vertebrae, hip and wrist bones.

Using PREMARIN Tablets, in addition to taking adequate calcium (1000 milligrams to 1500 milligrams per day) and vitamin D, and regular weight-bearing exercise, slows down bone thinning and may prevent bones from breaking.

When it should not be used:

Do not take PREMARIN if you:

- Have a known, suspected, or past history of breast cancer.
- Have a known or suspected hormone-dependent cancer (e.g. endometrial cancer).
- Estrogens may increase the chances of getting certain types of cancers, including cancer of the breast or uterus. If you have or had cancer, talk with your healthcare provider about whether you should take PREMARIN.
- Have unexpected or unusual vaginal bleeding
- Have (or have had) blood clot disorders, including blood clots in the legs or lungs or thrombophlebitis (inflammation of the veins).
- Have serious liver disease
- Have active or past history of heart disease, heart attacks or stroke.

- are allergic to conjugated equine estrogens or any non-medicinal ingredient in the formulation
- are pregnant or suspect you may be pregnant. If pregnancy occurs while using PREMARIN contact your doctor immediately.
- Since pregnancy may be possible early in the pre-menopause while you are still having spontaneous periods, the use of non-hormonal birth control should be discussed with your physician at this time. If you accidentally take estrogen during pregnancy, there is a small risk of your unborn child having birth defects.
- have partially or completely lost vision due to blood vessel disease of the eye.
- have overgrowth of the lining of the uterus.
- Have some types of congenital coagulation abnormalities (e.g. protein C, protein S, or antithrombin deficiency).
- experience migraines with or without aura.

What the medicinal ingredients are:

PREMARIN Tablet contains a mixture of conjugated equine estrogens, which are a mixture of sodium estrone sulphate and sodium equilin sulphate and other components include sodium sulphate conjugates, 17β-dihydroequilin, 17β-estradiol, and 17α-dihydroequilin.

What the nonmedicinal ingredients are:

Each PREMARIN Tablet contains the following nonmedicinal ingredients:
 Calcium Phosphate, Tribasic, Carnauba Wax, Hydroxypropyl Cellulose, Hypromellose, Lactose Monohydrate, Magnesium Stearate, Microcrystalline Cellulose, Polyethylene Glycol, Purified Water, Sucrose.

In addition, the following ingredients are contained in specific strengths as indicated:

- 0.3 mg (green color): hypromellose, quinoline yellow lake, macrogol, FD&C Blue No. 2, Indigo carmine aluminum lake, titanium dioxide, polysorbate 80. The white branding ink contains the following: titanium dioxide, purified water, isopropyl alcohol, propylene glycol, hypomellose.
- 0.625 mg (maroon color): hypromellose, titanium dioxide, FD&C Red #40 aluminum lake, macrogol, FD&C Blue #2 aluminum lake. The white branding ink contains the following: titanium dioxide, purified water, isopropyl alcohol, propylene glycol, hypomellose
- 1.25 mg (yellow color): hypromellose, titanium dioxide, quinoline yellow aluminum lake, macrogol, polysorbate, FD&C yellow #6 sunset yellow FCF aluminum lake. The black branding ink contains the following: purified water, iron oxide black, isopropyl alcohol, propylene glycol, hypromellose.

What dosage forms it comes in:

PREMARIN is available as tablets, as follows:
 0.3 mg (green) tablets in blister strips of 28;
 0.625 mg (maroon) tablets in blister strips of 28;
 1.25 mg (yellow) tablets in blister strips of 14.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

The Women’s Health Initiative (WHI) is a large clinical study that assessed the benefits and risks of oral combined *estrogen plus progestin* therapy and oral *estrogen-alone* therapy compared with placebo (a pill with no active ingredients) in postmenopausal women.

The WHI trial indicated an increased risk of myocardial infarction (heart attack), stroke, breast cancer, pulmonary emboli (blood clots in the lungs) and deep vein thrombosis (blood clots in the large veins) in postmenopausal women taking oral combined *estrogen plus progestin*.

The WHI trial indicated an increased risk of stroke and deep vein thrombosis in postmenopausal women with prior hysterectomy (surgical removal of the uterus) taking oral *estrogen-alone*.

Therefore, you should highly consider the following:

- There is an increased risk of developing invasive breast cancer, heart attack, stroke and blood clots in both lungs and large veins with the use of estrogen plus progestin therapy.
- There is an increased risk of stroke and blood clots in the large veins with the use of estrogen-alone therapy.
- Estrogens with or without progestins should not be used for the prevention of heart disease or stroke.
- Estrogens with or without progestins should be used at the **lowest effective dose** and for the **shortest period of time** possible. Regular medical follow-up is advised.

Breast Cancer

The results of the WHI trial indicated an increased risk of breast cancer in postmenopausal women taking combined *estrogen plus progestin* compared to women taking placebo.

The results of the WHI trial indicated no difference in the risk of breast cancer in post-menopausal women with prior hysterectomy taking *estrogen-alone* compared to women taking placebo.

Estrogens should not be taken by women who have a personal history of breast cancer.

In addition, women with a family history of breast cancer or women with a history of breast lumps, breast biopsies or abnormal mammograms (breast x-rays) should consult with their doctor before starting HRT.

Women should have a mammogram before starting HRT and at regular intervals during treatment as recommended by their doctor.

Regular breast examinations by a doctor and regular breast self-examination are recommended for all women. You should review technique for breast self-examination with your doctor.

Overgrowth of the lining of the uterus and cancer of the uterus

The use of *estrogen-alone* therapy by post-menopausal women who still have a uterus increases the risk of developing endometrial hyperplasia (overgrowth of the lining of the uterus), which increases the risk of endometrial cancer (cancer of the lining of the uterus).

If you still have your uterus, you should take a progestin medication (another hormone drug) regularly for a certain number of days of each month to reduce the risk of endometrial hyperplasia.

You should discuss progestin therapy and risk factors for endometrial hyperplasia and endometrial carcinoma with your doctor. You should also report any unexpected or unusual vaginal bleeding to your doctor.

If you have had your uterus removed, you are not at risk of developing endometrial hyperplasia or endometrial carcinoma. Progestin therapy is therefore not generally required in women who have had a hysterectomy.

Ovarian Cancer

Some studies have indicated that taking *estrogen-alone* for 5 or more years may increase the risk of ovarian cancer. It is not yet known whether other kinds of hormone therapy increase the risk in the same way.

Heart Disease and Stroke

The results of the WHI trial indicated an increased risk of stroke and coronary heart disease in post-menopausal women taking combined *estrogen plus progestin* compared to women taking placebo.

The results of the WHI trial indicated an increased risk of stroke, but no difference in the risk of coronary heart disease in post-menopausal women with prior hysterectomy taking *estrogen-alone* compared to women taking placebo.

Abnormal Blood Clotting

The results of the WHI trial indicated an increased risk of blood clots in the lungs and large veins in post-menopausal women taking combined *estrogen plus progestin* compared to women taking placebo.

The results of the WHI trial indicated an increased risk of blood clots in the large veins, but no difference in the risk of blood clots in the lungs in post-menopausal women with prior hysterectomy taking *estrogen-alone* compared to women taking placebo.

The risk of blood clots also increases with age, if you or a family member has had blood clots, if you smoke or if you are severely overweight. The risk of blood clots is also temporarily increased if you are immobilized for long periods of time and following major surgery. You should discuss risk factors for blood clots with your

doctor since blood clots can be life-threatening or cause serious disability.

Gallbladder Disease

The use of estrogens by postmenopausal women has been associated with an increased risk of gallbladder disease requiring surgery.

Dementia

The Women's Health Initiative Memory Study (WHIMS) was a substudy of the WHI trial and indicated an increased risk of dementia (loss of memory and intellectual function) in post-menopausal women age 65 and over taking oral combined *estrogen plus progestin* compared to women taking placebo.

The WHIMS indicated no difference in the risk of dementia in post-menopausal women age 65 and over with prior hysterectomy taking oral *estrogen-alone* compared to women taking placebo.

BEFORE you use PREMARIN talk to your doctor or pharmacist if you:

- have a history of allergy or intolerance to any medications or other substances
- have a personal history of breast disease (including breast lumps) and/or breast biopsies, or a family history of breast cancer
- have experienced any unusual or undiagnosed vaginal bleeding
- have a history of uterine fibroids or endometriosis
- have a history of liver disease, jaundice (yellowing of the eyes and/or skin) or itching related to estrogen use or during pregnancy
- have a history of migraine headache
- have a history of high blood pressure
- have a personal or family history of blood clots, or a personal history of heart disease or stroke
- have a history of kidney disease, asthma or epilepsy (seizures)
- have a history of bone disease (this includes certain metabolic conditions or cancers that can affect blood levels of calcium and phosphorus)
- have been diagnosed with diabetes
- have been diagnosed with porphyria (a disease of blood pigment)
- have been diagnosed with otosclerosis (hearing loss due to a problem with the bones in your ear)
- have a history of high cholesterol or high triglycerides
- are pregnant or may be pregnant. If pregnancy occurs while using PREMARIN contact your doctor immediately.
- have had a hysterectomy (surgical removal of the uterus)
- smoke
- have been told that you have a condition called hereditary angioedema or if you have had episodes of rapid swelling of the hands, feet, face, lips, eyes, tongue, throat (airway blockage), or digestive tract

- have been diagnosed with lupus
- have a history of depression
- have one of the following rare hereditary diseases:
 - Galactose intolerance
 - Lapp lactase deficiency
 - Glucose-galactose malabsorption

Because lactose is a non-medicinal ingredient in PREMARIN.

Other existing conditions you should discuss with your health professional include very low calcium levels, thyroid problems, fluid retention, gallbladder disease, depression, and breastfeeding. If you have upcoming surgery or prolonged bedrest, you should also discuss these.

Clinical studies have not been conducted in the pediatric population. PREMARIN is not indicated for use in children.

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor, nurse, or pharmacist about all the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.

The following may interact with PREMARIN:

- Acetaminophen used to treat pain and fever
- anticoagulant medications used to thin the blood
- antidiabetic medications (eg. troglitazone)
- antihypertensives (for high blood pressure)
- antiviral medications (such as, ritinovir).
- ascorbic acid (such as vitamin C)
- atorvastatin, clofibrac acid (medication to lower cholesterol)
- carbamazepine, phenytoin, or phenobarbital (medications to prevent epilepsy or seizures)
- cimetidine (medication generally used to treat stomach problems)
- cyclosporin (medication used in suppressing the immune system)
- dexamethasone, prednisolone (corticosteroids used to treat joint pain and swelling)
- erythromycin, clarithromycin (antibiotic medications to treat infections)
- grapefruit juice
- herbal products containing St. John's Wort
- ketoconazole, itraconazole (medications to treat fungal infections)
- morphine
- oral contraceptives (birth control pills) and other medicines containing estrogen
- rifampicin (medication used in the treatment of tuberculosis)
- salicylic acid
- temazepam (medication used to treat insomnia)
- theophylline (medication used to treat breathing problems such as asthma)

PREMARIN may interfere with laboratory testing.

PROPER USE OF THIS MEDICATION

Usual adult dose:

You should follow the dosage regimen prescribed by your healthcare provider. PREMARIN may be taken without regard to meals. Tablets should be taken whole; do not divide, crush, chew, or dissolve tablets in mouth.

Estrogens should be used at the lowest dose possible for your treatment only as long as needed. You and your healthcare provider should talk regularly (for example every 3 to 6 months) about the dose you are taking and whether you still need treatment with PREMARIN.

Do not give PREMARIN to other people, even if they have the same symptoms you have. It may harm them.

Overdose:

If you think you have taken too much PREMARIN contact your doctor, nurse, pharmacist, hospital emergency department or regional Poison control Centre immediately, even if there are no symptoms.

Overdosage with estrogens may cause nausea and vomiting, breast discomfort, fluid retention, bloating or vaginal bleeding may occur in women.

Overdosage may result in a period of amenorrhea (lack of menses) of a variable length and may be followed by irregular menses for several cycles.

Missed Dose:

If you miss a dose, take it as soon as possible. If it is almost time for your next dose, skip the missed dose and go back to your normal schedule. Do not take 2 doses at the same time.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:

- Breast pain, leaking of milk from the nipple
- Inflammation of the vagina, vaginal itching and/or discharge
- Breakthrough bleeding, spotting, changes in menstrual flow, painful periods
- Joint pain, leg pain
- Hair loss
- Changes in weight (increase or decrease)
- Nausea, vomiting, bloating, abdominal pain, diarrhea
- Dizziness
- Headache (including migraine)
- Changes in libido
- Mood disturbances, irritability, problems sleeping
- Rash, itching, hives, tender red nodules on the shins and legs, acne

If any of these affects you severely, tell your doctor, nurse or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Frequency	Symptom / possible side effect	Talk with your doctor or pharmacist		Stop taking drug and seek immediate medical help
		Only if severe	In all cases	
Common	Blood clot: Pain or swelling in the leg.			√
	Breast Cancer: Breast lump, unusual discharge.		√	
	Edema: Swelling of the hand and/or feet.	√		
	High Blood Pressure: headaches, dizziness, vision problems, shortness of breath		√	
	Persistent sad mood.		√	
	Unexpected vaginal bleeding.		√	
Rare	Blood clot in the lung: Sharp pain in the chest, coughing blood or sudden shortness of breath.			√
	Stroke: Sudden severe headache or worsening of headache, vomiting, dizziness, fainting, disturbance of vision or speech or weakness or numbness in an arm or leg.			√
Very rare	Blood clot in the eye: Sudden partial or complete loss of vision.			√

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Frequency	Symptom / possible side effect	Talk with your doctor or pharmacist		Stop taking drug and seek immediate medical help
		Only if severe	In all cases	
Very rare	Liver disorder: Yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite.		√	
Unknown	Angioedema and Severe Allergic Reactions: swelling of the face, eyes, or tongue, difficulty swallowing, wheezing, hives and generalized itching, rash, fever, abdominal cramps, chest discomfort or tightness, difficulty breathing, unconsciousness.			√
	Cerebrovascular insufficiency: visual disturbances, migraines, trouble speaking, paralysis or loss of consciousness.			√
	Gallbladder disorder: severe pain in the upper right abdomen, pain in the back between the shoulder blades, nausea and vomiting.		√	
	Heart Attack: Crushing chest pain, pain in the arm, back, neck or jaw, shortness of breath, cold sweat, nausea, light-headedness.			√

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Frequency	Symptom / possible side effect	Talk with your doctor or pharmacist		Stop taking drug and seek immediate medical help
		Only if severe	In all cases	
Unknown	Heart palpitations	√		
	Increased blood sugar: frequent urination, thirst, and hunger.	√		
	Worsening of asthma: wheezing, coughing, shortness of breath, difficulty breathing			√

This is not a complete list of side effects. For any unexpected effects while taking PREMARIN, contact your doctor or pharmacist.

HOW TO STORE IT

Store **PREMARIN** at 15° C to 30° C (room temperature).

Keep out of reach and sight of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - o Fax toll-free to 1-866-678-6789, or
 - o Mail to:
Canada Vigilance Program
Health Canada
Postal Locator 0701E
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor,

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toll-free, at: 1-800-463-6001

or at www.pfizer.ca

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