PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]PREMARIN®

conjugated estrogens sustained release tablets

Read this carefully before you start taking **PREMARIN** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **PREMARIN**.

Serious Warnings and Precautions

The Women's Health Initiative (WHI) trial 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.

What is PREMARIN used for?

- To relieve menopausal and post-menopausal symptoms (vasomotor symptoms like hot flushes 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 healthcare professional 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 for the prevention of osteoporosis is recommended only for women who are at risk of developing this condition. Talk to your healthcare professional 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 healthcare professional in addition to taking PREMARIN.

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

PREMARIN should not be used by women who still have their uterus unless it is taken with a progestin.

You should carefully discuss the risks and benefits of hormone replacement therapy (HRT) with your healthcare professional. You should regularly talk with your healthcare professional about whether you still need treatment with HRT.

How does PREMARIN work?

When taking PREMARIN women are using a hormone, estrogen (i.e. conjugated equine estrogen). 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, 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.

What are the ingredients in PREMARIN?

Medicinal ingredients: PREMARIN 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.

Non-medicinal ingredients: calcium phosphate tribasic, carnauba wax, FD&C Blue No. 2 (0.3 mg), FD&C Blue #2 aluminum lake (0.625 mg), FD&C Red #40 aluminum lake (0.625 mg), FD&C yellow #6 sunset yellow FCF aluminum lake (1.25 mg), hydroxypropyl cellulose, hypromellose, indigo carmine aluminum lake (0.3 mg), isopropyl alcohol, iron oxide black (1.25 mg), lactose monohydrate, macrogol, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate (1.25 mg), polysorbate 80 (0.3 mg), purified water, quinoline yellow lake (0.3 mg, 1.25 mg), sucrose, titanium dioxide.

PREMARIN comes in the following dosage forms:

sustained release tablets: 0.3 mg (green); 0.625 mg (maroon); 1.25 mg (yellow)

Do not use PREMARIN if you:

- are allergic to conjugated equine estrogens or to any of the non-medicinal ingredients in PREMARIN (see **What are the ingredients in PREMARIN?**)
- have a known, suspected, or past history of breast cancer
- have a known or suspected hormone-dependent cancer (e.g. endometrial cancer)
- have unexpected or unusual vaginal bleeding without a known cause
- have or have a history of blood clot disorders, including blood clots in the legs or lungs or inflammation of the veins (thrombophlebitis)
- have serious liver disease
- have active, or have a history of, heart disease, heart attacks or stroke
- are pregnant or suspect you may be pregnant. Talk to your healthcare professional immediately If you get pregnant while using PREMARIN. Since pregnancy may be possible early in the pre-menopause while you are still having spontaneous periods, you should talk to your healthcare professional about using non-hormonal birth control. 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 (endometrial hyperplasia)
- have a genetic condition that affects your blood clotting (e.g. protein C, protein S, or antithrombin deficiency)

- have, or have a history of, migraines with or without aura

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take PREMARIN. Talk about any health conditions or problems you may have, including if you:

- have a history of allergy or intolerance to any medications or other substances
- have a history of breast disease (including breast lumps) and/or breast biopsies, or a family history of breast cancer
- 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 high blood pressure
- have a family history of blood clots, heart disease or stroke
- have kidney problems
- have asthma
- have a history of 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 diabetes
- have porphyria (a disease of blood pigment)
- have otosclerosis (hearing loss due to a problem with the bones in your ear)
- have high cholesterol or high triglycerides
- have had a hysterectomy (surgical removal of the uterus)
- smoke
- have been told that you have a condition called hereditary or acquired 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 systemic lupus erythematous. This is a disease of the immune system that affects the joints, skin, kidneys, blood cells, brain, heart and lungs.
- have a history of depression
- have hypothyroidism. This is a condition in which your thyroid gland does not produce enough thyroid hormone.
- are breastfeeding
- are undergoing surgery or need long bed rest
- 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 warnings you should know about:

Cancer:

- **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 healthcare professional before starting HRT.

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

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

- **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.

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 healthcare professional. You should also report any unexpected or unusual vaginal bleeding to your healthcare professional.

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.

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 healthcare professional 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 sub-study 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.

Check-ups and Tests:

PREMARIN should be used only under the supervision of a healthcare professional, with regular follow-up visits, at least once a year, to check for 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 healthcare professional. Your healthcare professional may recommend some blood tests.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with PREMARIN:

- medicines used to treat pain and fever such as acetaminophen, salicylic acid
- anticoagulant medications used to thin the blood and prevent blood clots
- insulin and other medicines used to treat diabetes such as troglitazone
- medicines used to lower high blood pressure

- medicines used for the treatment of HIV and AIDS such as ritinovir
- some nutritional supplements such as vitamin C
- medicines used to lower cholesterol such as atorvastatin, clofibric acid
- medicines used for the treatment of epilepsy such as carbamazepine, lamotrigine, phenytoin, phenobarbital
- cimetidine, generally used to treat stomach problems
- cyclosporin, used to suppress the immune system
- corticosteroids used to treat joint pain and swelling such as dexamethasone, prednisolone
- medicines used to treat bacterial infections such as erythromycin, clarithromycin
- grapefruit juice
- herbal products containing St. John's Wort (*Hypericum perforatum*) used to treat depression and other conditions
- medicines used to treat fungal infections such as ketoconazole, itraconazole
- morphine, used for the treatment of severe pain
- oral birth control pills and other medicines containing estrogen
- rifampicin, used in the treatment of tuberculosis
- temazepam, used to treat insomnia
- theophylline, used to treat breathing problems such as asthma

Tell your healthcare professional that you are being treated with PREMARIN if you are going to have laboratory tests. Some laboratory tests, such as tests for glucose tolerance or thyroid function may be affected by PREMARIN therapy.

How to take PREMARIN:

- Take PREMARIN exactly as your healthcare professional tells you.
- PREMARIN can be taken with or without food.
- PREMARIN tablets are to be taken whole. Do not divide, crush, chew or dissolve the tablets in your mouth.
- Estrogens, like PREMARIN, should be taken at the lowest dose possible for only as long as you need them. You and your healthcare professional should discuss your dose and whether you still need treatment with PREMARIN regularly (i.e. every 3 to 6 months).
- Do not give PREMARIN to other people, even if they have the same symptoms as you. It may harm them.

Usual dose:

PREMARIN can be taken either continuously or in a cyclic regimen (i.e. 25 days on, 5 days off). Your healthcare professional will decide on the dose and schedule that is right for you.

Overdose:

Overdosage with estrogens may cause nausea and vomiting, breast discomfort, fluid retention, bloating or vaginal bleeding may occur in women. It may result in a period of amenorrhea (lack of menses) of a variable length and may be followed by irregular menses for several cycles.

If you think you, or a person you are caring for, have taken too much PREMARIN, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

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.

What are possible side effects from using PREMARIN?

These are not all the possible side effects you may have when taking PREMARIN. If you experience any side effects not listed here, tell your healthcare professional.

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

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Deep vein thrombosis (blood clot in the leg): pain or swelling			**√**

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
in the leg, difficulty standing or walking, feeling of warmth in the leg, red or discoloured skin			
Breast changes (breast lumps/ breast cancer): pain and tenderness, lumps, nipple discharge		**√**	
Edema: unusual swelling of the hands and/or feet	**√**		
High blood pressure: headaches, dizziness, vision problems, shortness of breath		**√**	
Depression: persistent sad mood that won't go away		**√**	
Unexpected or excessively heavy vaginal bleeding		**√**	
RARE			
Pulmonary embolism (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			**√**
Liver problems: yellowing of the skin or eyes, dark urine, light		**√**	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
coloured stool, 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 (lack of blood flow to the brain): visual disturbances, migraines, trouble speaking, paralysis or loss of consciousness			**√**
Gallbladder disease: 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			**√**
Heart palpitations	**√**		
Increased blood sugar: frequent urination, thirst, and hunger	**√**		
Worsening of asthma: wheezing, coughing, shortness of breath, difficulty breathing			**√**

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

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

Keep out of reach and sight of children.

If you want more information about PREMARIN:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website https://www.pfizer.ca/en, or by calling 1-800-463-6001.

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