

## PART III: CONSUMER INFORMATION

### **Premplus® conjugated estrogen tablets CSD and medroxyprogesterone acetate tablets USP (Continuous therapy)**

#### **IMPORTANT: PLEASE READ**

This leaflet is part III of a three-part "Product Monograph" published when Premplus® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Premplus®. 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.

Use of Premplus® is to be considered in light of other available therapies for the prevention of postmenopausal osteoporosis. Adequate diet, calcium and vitamin D intake, cessation of smoking as well as regular physical weight bearing exercise should be discussed with your doctor or pharmacist in addition to the administration of Premplus®.

Use of Premplus® tablets for the prevention of osteoporosis is recommended only for women who are at risk of developing this condition. If you use Premplus® only to prevent osteoporosis from menopause, talk with your healthcare provider about whether a different treatment or medicine without estrogens might be better for you.

- To treat vulva and vaginal atrophy associated with menopause (itching, burning, dryness in or around the vagina, difficulty or burning on urination)

If you use Premplus® 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.

Premplus® 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 Premplus®, women are using a combination of two hormones, an estrogen (i.e. conjugated equine estrogens tablets) and a progestin (i.e. medroxyprogesterone acetate tablets). Premplus® replaces the hormones in your body, which naturally decrease at menopause.

Premplus® has been shown to provide the benefits of estrogen replacement therapy while lowering the frequency of a possible precancerous condition of the uterine lining with the addition of the progestin. This therapy is not intended for women who have had a hysterectomy (surgical removal of the uterus).

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

When a woman is between 45 and 55 years old, the ovaries normally stop making estrogens. This leads to a drop in body estrogen levels and marks the beginning of menopause or the "change of life" (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 get very uncomfortable symptoms, such as feelings of warmth in the face, neck and chest, or sudden strong feelings of heat and sweating ("hot flashes" or "hot flushes"). In some women the symptoms are mild, and they will not need to take estrogens. In other women, symptoms can be more severe. These symptoms may last only a few months or longer. Taking Premplus® can alleviate these symptoms. You and your healthcare provider should talk regularly about whether you still need treatment with Premplus®.

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.

##### **When it should not be used:**

Estrogens and progestins should not be used to prevent heart disease, heart attacks, or strokes. You and your healthcare provider should talk regularly about the duration of your treatment with Premplus®.

Before using Premplus® be sure to tell your doctor if you have any of the following medical problems, as Premplus® should not be used under these conditions:

- **Known, suspected, or past history of breast cancer.**
- **Known or suspected hormone-dependent 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 Premplus®.
- **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).**
- **Serious liver disease**
- **Active or past history of heart disease, heart attacks or stroke.**
- **If you are allergic to Premplus® or any of its ingredients, or have had any unusual reactions to its ingredients (see What the medicinal ingredients are and What the nonmedicinal ingredients are).**
- **If you are pregnant or suspect you may be pregnant.**  
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.
- If you have partially or completely lost vision due to blood vessel disease of the eye.
- If you have overgrowth of the lining of the uterus.

**What the medicinal ingredients are:**

Conjugated equine estrogens and medroxyprogesterone acetate.

**What the nonmedicinal ingredients are:**

*Non-Medicinal Ingredients of Premplus®*

**Each Conjugated Estrogens Tablet contains the following inactive ingredients:**

Calcium sulfate, carnauba wax, edible ink, erythrosine aluminum lake, FD&C blue No. 2, FD&C yellow No. 6, glyceryl monooleate, lactose, magnesium stearate, methyl cellulose, microcrystalline cellulose, pharmaceutical glaze, polyethylene glycol, povidone, sodium benzoate, stearic acid, sucrose, and titanium dioxide.

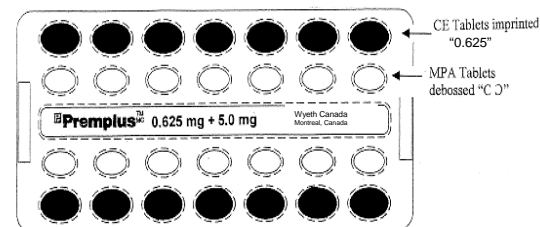
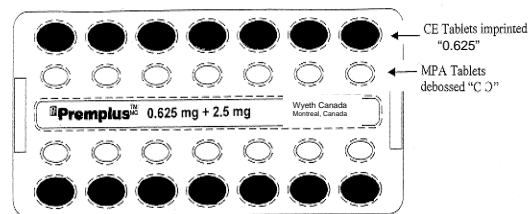
**Each Medroxyprogesterone Acetate Tablet contains the following inactive ingredients:**

Lactose, microcrystalline cellulose, methylcellulose and magnesium stearate. In addition, each Medroxyprogesterone Acetate 5.0 mg Tablet contains D&C blue No. 1 aluminum lake and D&C red No. 30 aluminum lake.

**What dosage forms it comes in:**

Premplus® is available as tablets, as follows:

Premplus®: conjugated estrogens tablets, 0.625 mg, and medroxyprogesterone acetate tablets, 2.5 mg, and 5.0 mg



**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 with or without progestins 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).

The purpose of adding a progestin medication to estrogen therapy is 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***

In some studies, the use of *estrogen-alone* and *estrogen plus progestin* therapies for 5 or more years has been associated with an increased risk of ovarian cancer.

### ***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 Premplus® 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 a history of high cholesterol or high triglycerides
- are pregnant or may be pregnant
- have had a hysterectomy (surgical removal of the uterus)
- smoke

Other existing conditions you should discuss with your health professional include lupus, 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.

### INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist if you are taking any other medications, including prescription medications, over-the-counter medications, vitamins or herbal products (such as St. John’s wort). Some medications (such as medications for high blood pressure, diabetes, blood clots, sleeping, anxiety, seizures, pain-relief and tuberculosis) may affect how Premplus® works. Premplus® may also affect how other medicines work.

### PROPER USE OF THIS MEDICATION

#### Usual dose:

Premplus® - take by mouth one maroon tablet (conjugated estrogens) and one white or purple tablet (progestin) at the same time each day, depending on the strength of the progestin you were prescribed.

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 Premplus®.

Take Premplus® only as directed by your doctor or pharmacist.

#### Overdose:

Contact your physician or local Poison Control Center in case of accidental ingestion of high doses of Premplus®.

Overdosage with Premplus® may cause nausea and vomiting, breast discomfort, fluid retention, bloating, or vaginal bleeding.

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. No cases of overdosage in male patients have been reported.

#### 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.

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not take Premplus® for conditions for which they were not prescribed. Do not give Premplus® to other people, even if they have the same symptoms you have. It may harm them.

### SIDE EFFECTS AND WHAT TO DO ABOUT THEM

**Possible side effects may include, but are not necessarily limited to, those listed in this section.**

In clinical trials for Premplus®, lasting 13 cycles, in which 1,724 patients participated, the most common adverse effects experienced by the participants are listed below. The adverse effects are ordered by frequency (percentage of participants experiencing adverse effect):

For the patients taking Premplus® in the study, the most frequent side effect was breast pain, reported by approximately one third of the patients. Headache was the second most common event for these patients. The most common side effects from the study are listed below, along with the frequencies.

- Breast pain – 32 to 36%
- Headache – 16 to 26%
- Abdominal pain – 11 to 16%
- Flatulence – 7 to 8%
- Nausea – 6 to 8%
- Painful menstrual cramps – 5 to 13%
- Back pain – 5 to 7%
- Depression – 4 to 8%
- Itching of the skin – 4 to 6%
- Genital bleeding/spotting – 3 to 6%
- Weight gain – 3%

Patients may have reported two or more different side effects during the study. The addition of progestin to estrogen replacement therapy may contribute to breast pain as a greater percentage of patients on Premplus® reported breast pain than those on Premarin alone.

The following self-limiting side effects, in the table below, are listed by frequency and body categories. These include side effects from the clinical study as well as those gathered during the marketing of Premplus®:

- Very Common: ≥10%
- Common: ≥1% and <10%
- Uncommon: ≥0.1% and <1%
- Rare: ≥0.01% and <0.1%
- Very rare: <0.01%

Body System	Side effects
<i>Reproductive system and breast disorders</i>	
Very common	Breast pain
Common	Breakthrough bleeding/ painful periods; spotting
Uncommon	Change in menstrual flow;

Rare	A spontaneous flow of milk from the nipple
<i>Gastrointestinal disorders</i>	
Uncommon	Nausea; bloating; abdominal pain
Rare	Vomiting
<i>Nervous system disorders</i>	
Uncommon	Dizziness; headache (including migraine)
<i>Musculoskeletal, connective tissue and bone disorders</i>	
Common	Joint pain
<i>Psychiatric disorders</i>	
Uncommon	Changes in libido; mood disturbances
Rare	Irritability
<i>Skin and subcutaneous tissue disorders</i>	
Uncommon	Acne; hair loss; itching
Rare	Rash
Very rare	Tender red nodules on the shins and legs
<i>Infections and Infestations</i>	
Common	Inflammation of the vagina
<i>Immune system disorders</i>	
Rare	Hives
<i>Respiratory, thoracic and mediastinal disorders</i>	
Rare	Worsening of asthma
<i>Investigations</i>	
Common	Changes in weight (increase or decrease)
Very rare	Increase in blood pressure

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Frequency (common or uncommon)	Symptom / possible side effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Uncommon	Abdominal pain, nausea or vomiting	✓		
Rare	Breast lump, unusual discharge		✓	
Rare	Shortness of breath, weakness, unusual fatigue, cold sweat, dizziness, sleep disturbance, indigestion, anxiety		✓	
Uncommon	Pain or swelling in the leg			✓
Common	Persistent sad mood		✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
		Talk with your doctor or pharmacist		
Rare	Sharp pain in the chest, coughing blood or sudden shortness of breath			✓
Very rare	Sudden partial or complete loss of vision			✓
Rare	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	Unexpected vaginal bleeding, difficult/painful urination		✓	
Very rare	Yellowing of the skin or eyes		✓	
Uncommon	Memory loss, poor concentration, problems learning new ideas or skills		✓	

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

#### HOW TO STORE IT

Store Premplus® at 15° C to 25° C (room temperature).

Keep out of reach of children.

## **REPORTING SUSPECTED SIDE EFFECTS**

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance:

By toll-free telephone: 866-234-2345

By toll-free fax: 866-678-6789

On-line: [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)

By email: [CanadaVigilance@hc-sc.gc.ca](mailto:CanadaVigilance@hc-sc.gc.ca)

By regular mail:

Canada Vigilance National Office  
Marketed Health Products Safety and  
Effectiveness Information Division  
Marketed Health Products Directorate  
Health Products and Food Branch  
Health Canada  
Tunney's Pasture, AL 0701C  
Ottawa ON K1A 0K9

*NOTE: Before contacting Canada Vigilance, you should contact your physician or pharmacist.*

## **MORE INFORMATION**

This document plus the full product monograph, prepared for health professionals can be found at: <http://www.wyeth.ca/en> or by contacting the sponsor,

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This leaflet was prepared by WYETH CANADA

Last revised: April 30, 2008