PART III: CONSUMER INFORMATION

ESTROGEL®

17β-estradiol, as estradiol hemihydrate

IMPORTANT PLEASE READ:
This leaflet is part III of a three-part "Product Monograph" published when ESTROGEL® (17β-estradiol) was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ESTROGEL®.

Please read this leaflet carefully before you start taking ESTROGEL® and each time you have your prescription refilled. It contains information regarding possible risks of hormone replacement therapy obtained from the results of the Women's Health Initiative Study.

This information leaflet does not take the place of talking to your health professional about your medical condition or your treatment. If you have any questions or concerns, consult your doctor or your pharmacist.

ABOUT THIS MEDICATION

What the medication is used for:
ESTROGEL® is approved for use in the following situation:

- replacement of estrogen in menopausal women with symptoms of menopause, which may include hot flushes, disturbed sleep and vaginal dryness.

ESTROGEL® should not be used by women who have not had a hysterectomy (surgical removal of the uterus) unless prescribed in association with a progestin medication.

ESTROGEL® 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:
ABOUT MENOPAUSE
Menopause is not a disease. Menopause is a natural, pre-determined point in a women's life when the ovaries decrease their production of the female hormones, estrogen and progesterone. In most women, this occurs between the ages of 45 and 55 or sooner if the ovaries have been removed by surgery.

The symptoms associated with menopause vary for every woman. The most common symptom is hot flushes/flashes. Other symptoms some women may develop after menopause include insomnia (reduced quality of sleep) and vaginal atrophy (dryness). Your doctor can provide you with further information on menopause.

The active ingredient in ESTROGEL® is estradiol, a natural female hormone. In healthy women of childbearing age, estradiol is the main estrogen produced by the ovaries.

ESTROGEL® does not contain progestins.

When it should not be used:
Do not use ESTROGEL® if you:

- have liver disease;
- have a personal history of breast cancer or endometrial cancer (cancer of the uterus);
- have been diagnosed with endometrial hyperplasia (overgrowth of the lining of the uterus);
- have experienced undiagnosed or unexpected vaginal bleeding;
- are pregnant or suspect you may be pregnant;
- are breast-feeding;
- have a history of coronary heart disease (including heart attack) or stroke;
- experience migraine headaches;
- have a history of blood clots;
- have active thrombophlebitis (inflammation of the veins);
- have had partial or complete loss of vision due to blood vessel disease of the eye;
- known or suspected hormone dependant cancer;
- have had an allergic or unusual reaction to ESTROGEL® or to any of its ingredients.

What the medicinal ingredient is:
The medicinal ingredient in ESTROGEL® is 17β-estradiol.

What the nonmedicinal ingredients are:
Carbopol 980, ethanol, purified water and triethanolamine.

What dosage forms it comes in:
ESTROGEL® comes in a metered-dose pump. It has 80 g of gel.

Each gram of gel contains 0.6 mg of 17β-estradiol

One full pump actuation (pushing the pump all the way down) delivers 1.25 grams of gel. This amount of gel has 0.75 mg of 17β-estradiol.

Two full pump actuations (pushing the pump all the way down two times) delivers 2.5 grams of gel. This amount of gel has 1.5 milligram of the 17β-estradiol.

The gel should be applied to the skin over a large area (>2000 cm2). It will be quickly absorbed into the underlying layers of the skin. Over time, the estradiol will be slowly released into your bloodstream.

The pump contains 64 metered-doses. That is enough gel for about 1 month of use if you use two full pump actuations per day. After that, the amount of gel delivered may be lower. It is recommended to change the pump after one month.

WARNINGS AND PRECAUTIONS

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 to 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 post-menopausal 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 postmenopausal 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-examinations 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
In some studies the use of *estrogen-alone* therapy 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 estrogen therapy by post menopausal women has been associated with an increased-risk of gallbladder disease requiring surgery.

Dementia (loss of memory and intellectual function)
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 postmenopausal 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 e*strogen-alone* compared to women taking placebo.

Contact Sensitization
Products applied onto the skin may result in sensitization. Although it is extremely rare, skin sensitization may evolve into severe hypersensitivity reaction with continued use of the gel.

BEFORE you use ESTROGEL® talk to your doctor or pharmacist if you:

- have a history of liver disease, liver tumours, or jaundice (yellowing of the eyes and/or skin) or itching related to estrogen use or during pregnancy;
- have a personal history of breast disease (including breast lumps) and/or breast biopsies, or a family history of breast cancer;
- have a history of endometrial hyperplasia (overgrowth of the lining of the uterus);
- have experienced undiagnosed or unusual vaginal bleeding;
- have experienced pressure or pain in your abdomen or pelvis;
- have a history of uterine fibroids (abnormally thick tissue in the uterus) or endometriosis (disorder of the uterine lining);
- have a history of heart disease or stroke or family history of blood clots;
- have a history of migraine headaches;
- have a personal history of active thrombophlebitis (inflammation of veins);
- have had a partial or complete loss of vision due to blood vessel disease of the eye;
- are pregnant or may be pregnant;
- have a history of allergy or intolerance to ESTROGEL® or any of its ingredients, or to any medications or other substances;
- smoke;
- have a history of high blood pressure;
- have 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 (disease of blood pigments);
- have a history of high cholesterol or high triglycerides (a type of fat in the blood);
- have a history of depression;
- have had a hysterectomy (surgical removal of the uterus);
- 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 been diagnosed with hearing loss due to otosclerosis;
- breastfeeding.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with ESTROGEL® include:

Barbiturates, hydantoins, carbamazepine, meprobamate, phenylbutazone or rifampin, atorvastatin, antibiotics, aminoglutethimide, some herbal products (e.g. St. John's wort), phenobarbital, phenytoin troglitazone, ascorbic acid, acetaminophen, oral contraceptives containing ethinyl estradiol, progestin.

Estrogens may diminish the effectiveness of anticoagulant (substance that prevents coagulation), antidiabetic (drugs treating diabetes mellitus) and antihypertensive agents (drugs treating high blood pressure).

Tell your doctor or pharmacist if you are taking any other medications, including prescription medications, over-the-counter medications, vitamins or herbal products.

PROPER USE OF THIS MEDICATION

Do NOT apply ESTROGEL®

- on the breasts. This may cause unwanted side effects and discomfort.
- to the face
- to irritated or damaged skin.

Estrogel is for topical use only.

Apply ESTROGEL:

- in cycles. Use it on one of these schedules:
    - Each calendar month: Use it from day 1 to day 25.
    - Each 28-day cycle: Use it from day 1 to day 21.
- after washing. It can be in the morning or evening but preferably at about the same time each day.
- using clean hands
- onto clean, dry skin
- to both arms, the abdomen or to the inner thighs. The illustrations show you where to use it. It is not necessary to rotate the site of use.
- allow the gel to dry for 2 minutes before covering with clothes. ESTROGEL does not stain and does not smell.

If your periods have stopped, or are irregular, you can start using ESTROGEL® at any time.

Usual adult dose: 2.5 g of gel each day. To get this dose, take two full pump actuations. This means you push the pump all the way down twice.

Your doctor will prescribe the dose of Estrogel to meet your individual needs. After two months your doctor may adjust your dose up or down. Breast tenderness or bleeding are signs that the dose is too high. However, if the selected dose fails to control your menopausal symptoms, follow up with your doctor who may increase your dose, if appropriate.

You and your doctor should talk regularly about whether you still need treatment with estrogen.

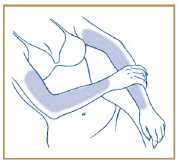
Using the ESTROGEL® Pump
Remove the pump cover.

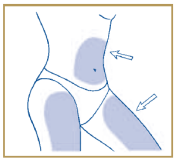
I- Priming the pump
When you open a new pump, press on the pump once or twice in order to prime the pump. Discard these doses.

II- To get your dose
Press firmly on the pump for one full pump actuation (pushing the pump all the way down)
Collect the gel in one hand.

- Apply the gel over a large area of skin (at least 2,000 cm^2). This is about 4 times the size of your hand.
- Repeat but apply the second amount of gel to a different part of your body.
- If applying to your arms, use the opposite hand to apply the second amount of gel to the second arm.
- Always replace the pump cover after each use.

Once you have developed your gel use technique, the doctor can test how much estradiol is in your blood. They can do this at your regular follow-up visit or after about two months of treatment. The lowest effective dose should be used.





Overdose:

For management of a suspected drug overdose, contact your regional Poison Control Centre.

When someone accidentally takes too much ESTROGEL®, the following symptoms may arise: nausea (urge to vomit), breast discomfort, fluid retention, abdominal cramps, headache, dizziness, bloating or vaginal bleeding in women.

In case of accidental overdosage or ingestion of ESTROGEL®, contact your doctor and/or your local Poison Control Centre.

Missed dose:
If a dose of this medication has been missed, it should be taken as soon as possible. However, if it is almost time for the next dose, skip the missed dose and go back to the regular dosing schedule. Do not double dose. If you are in doubt, contact your healthcare provider.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Very rarely, skin irritation can occur with ESTROGEL®. Depending on the dosage of estrogen and the sensitivity of the patient, the following side effects are possible

- genital bleeding or spotting (minor vaginal bleeding) in between the normal periods,
- headaches or depressive mood;
- breast tenderness/swelling;
- water retention (bloating, swelling);
- endometrial hyperplasia (overgrowth of the lining of the uterus);
- nausea (urge to vomit), abdominal discomfort (cramps, pressure, pain);
- gallbladder disorder, impaired liver function;
- menstrual cramps;
- vaginal itching/discharge;
- pain during sexual intercourse;
- pain on urination or difficulty urinating;
- premenstrual syndrome (PMS);
- inflammation of the bladder;
- brown, blotchy spots on exposed skin (pregnancy mask);
- skin rash, tender red lumps or nodules or other skin reactions;
- loss of hair, hairiness;
- acne;
- palpitations (unpleasant sensation of irregular and/or forceful beating of the heart);
- worsening of varicose veins (visible and bulging veins);
- nervousness;
- fatigue (tiredness);
- irritability;
- intolerance to contact lenses;
- changes in appetite and body weight;
- change in sexual drive;
- pain in the joints and muscles, usually lasting only 3-6 weeks.

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 call your doctor or pharmacist
		Only if severe	In all cases	
	Abnormal increase in blood clotting;			√
	Increase in blood pressure;		√	
	Abdominal pain, nausea or vomiting		√	
	Breast lump		√	
	Crushing chest pain or heaviness			√
	Pain or swelling in the leg			√
	Persistent sad mood			√
	Sharp pain in the chest, coughing blood or sudden shortness of breath			√
	Sudden partial or complete loss of vision			√
	Migraine			√
	Sudden severe headache or worsening of headache, vomiting, dizziness, fainting, disturbance of vision or speech or weakness or numbness in an arm or leg			√
	Unexpected vaginal bleeding		√	
	Yellowing of the skin or eyes (jaundice)			√

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

HOW TO STORE IT

ESTROGEL® should be stored with the pump cover on securely and at room temperature (15-30ºC).

Keep out of reach of children.

GENERAL THINGS TO REMEMBER

1. This medication has been prescribed only for your current medical problem. Do not use it for other medical problems.
2. Do not allow other people to use your medications and do not use medications meant for other people.
3. Tell any doctor treating you what medications you are taking. Always carry a medical information card stating which medications you are using. This can be very important in case you are involved in an accident.
4. Return unused medications to the pharmacy for safe disposal.
5. Make sure that other people you live with or who look after you read this information.

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:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701D
    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 at: www.organon.ca or by contacting the sponsor, Organon Canada Inc., at 1-844-820-5468.

This leaflet was prepared by Organon Canada Inc.

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