

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Pr[®]ESTROGEL

17 β -estradiol (as estradiol hemihydrate) transdermal gel

This Patient Medication Information is written for the person who will be taking **ESTROGEL**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **ESTROGEL**, talk to a healthcare professional.

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*.

(see Other warnings you should know about) for more information.

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 prevent 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 ESTROGEL is used for:

ESTROGEL is used for 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 it is taken with a progestin medication. ESTROGEL does not contain progestins.

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 ESTROGEL.

How ESTROGEL works:

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

During menopause, your body stops making estrogen. When your estrogen levels begin dropping, you may get symptoms, such as feelings of warmth in the face, neck, and chest, or sudden intense feeling of heat and sweating, trouble sleeping and vaginal dryness. In some women the symptoms are mild, but in other women, symptoms can be more severe.

ESTROGEL replaces the estrogens that are missing to help with these symptoms.

The ingredients in ESTROGEL are:

Medicinal ingredients: 17 β -estradiol (as estradiol hemihydrate)

Non-medicinal ingredients: Carbopol 980, ethanol, purified water and triethanolamine.

ESTROGEL comes in the following dosage forms:

Transdermal gel; 0.06% w/w

ESTROGEL comes in a metered-dose pump. It has 80 g of gel. One full pump actuation (pushing the pump all the way down) delivers 1.25 g of gel. This amount of gel has 0.75 mg of 17 β -estradiol. The pump contains 64 metered doses.

Do not use ESTROGEL if you:

- are allergic to 17 β -estradiol or any of the non-medicinal ingredients in ESTROGEL (see What are the ingredients in ESTROGEL?)
- 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 think you might be pregnant
- are breastfeeding
- 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
- have a known or suspected hormone dependant cancer

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

- have a history of liver tumours, jaundice (yellowing of the eyes and/skin), or itching related to estrogen use.
- 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 personal history of active thrombophlebitis (inflammation of veins)
- smoke
- have a history of high blood pressure
- have history of kidney problems, 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 depression
- have had a hysterectomy (surgical removal of the uterus) 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 been diagnosed with lupus
- have been diagnosed with hearing loss due to otosclerosis
- have Hepatitis C virus (HCV)

Other warnings you should know about:

Breast Cancer

- There is an increased risk for breast cancer in women taking menopausal hormone therapy (MHT) for many years. The risk increases the longer you take MHT and persists for more than 10 years after stopping treatment with both estrogen plus progestin therapy and estrogen-alone therapy.
- 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 disease, breast cancer or women with a history of breast lumps, breast biopsies or abnormal mammograms (breast x-rays) should talk to 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 exams by a healthcare professional and regular breast self-examinations are recommended for all women. You should review your technique for breast self-examination with your healthcare professional.

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 tell your healthcare professional about any unexpected or unusual vaginal bleeding.
- 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 healthcare professional 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

- 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 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 *estrogen-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 (allergic) reaction with continued use of the gel.

Children

- ESTROGEL should not be used by children.
- ESTROGEL can be accidentally transferred from the skin to other people.
- Do not allow others, especially children, to come into contact with the exposed area of your skin. If needed, cover the area, after the gel has dried.
- If a child comes in contact with the area of the skin where ESTROGEL was applied, wash the child's skin with soap and water as soon as possible.
- Young children who have been exposed to ESTROGEL may show signs of puberty that are not expected (for example breast budding). In most cases the symptoms will disappear when the child is no longer exposed.
- Talk to your healthcare professional if you see any signs or symptoms (such as breast development or other sexual changes) in a child that may have been exposed accidentally to ESTROGEL.

Blood Tests and Monitoring

- ESTROGEL should be used only under the supervision of a healthcare professional.
- You will have regular follow-ups, at least once a year to check for side effects. 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 also do blood tests. These will check your blood sugar levels, blood calcium, cholesterol and triglycerides and the health of your liver. They will decide when to do the tests and interpret the results.

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 ESTROGEL:

- barbiturates, medicines that cause you to relax and feel drowsy, used to treat anxiety and insomnia among other conditions
- anticonvulsant medicines used to prevent seizures, such as hydantoin, phenobarbital, carbamazepine, phenytoin, lamotrigine
- meprobamate, a tranquilizer used to treat anxiety
- rifampin, used to treat bacterial infections like tuberculosis
- atorvastatin, used to lower cholesterol
- antibiotics used to treat bacterial infections

- aminoglutethimide, used to treat problems with the adrenal gland such as Cushing's syndrome or cancer
- some herbal products, such as St. John's wort, used to treat depression
- medicines used to treat diabetes, such as troglitazone used to treat Type 2 diabetes
- vitamin C (ascorbic acid)
- acetaminophen, used to treat pain and fever
- oral birth control containing ethinyl estradiol
- the hormone progestin
- medicines used to treat Hepatitis C virus (HCV), such as the combination regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir as well as a regimen with glecaprevir/pibrentasvir
- anticoagulants, medicines used to thin the blood and prevent blood clots
- medicines used to lower high blood pressure
- ESTROGEL might interfere with certain blood tests. Before you have any blood tests tell the healthcare professional that you are using ESTROGEL.

How to take ESTROGEL:

- ESTROGEL is for topical use only.
- ESTROGEL contains alcohol. It may cause a burning sensation if it is applied to damaged skin.
- ESTROGEL is flammable until it is dry.
- ESTROGEL does not stain and has no odour.
- Your healthcare professional will prescribe the dose of ESTROGEL that is right for you. After two months, once you have developed your technique for applying the gel, your healthcare professional will do a blood test to see how much estradiol is in your blood. They may adjust your dose up or down. Breast tenderness or bleeding are signs that the dose is too high. If your menopausal symptoms are not being controlled, your dose might be too low. Do not change your dose without talking to your healthcare professional.
- ESTROGEL is applied in cycles. You can 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.
- If your periods have stopped, or are irregular, you can start taking ESTROGEL at any time. If your symptoms are not controlled during the treatment free interval talk to your healthcare professional. They may recommend a continuous application of ESTROGEL.
- ESTROGEL can be applied in the morning or evening but preferably at about the same time each day.
- **Do NOT apply ESTROGEL:**
 - **on the breasts**
 - **to the face**
 - **to irritated or damaged skin**

Using the ESTROGEL Pump

1. **Remove the pump cover.**
2. **Prime the pump.**
 - When you open a new pump, press on the pump once or twice in order to prime the pump.
 - Discard these doses.

3. To get your dose.

- Wash and dry your hands and the areas of skin where you will apply the gel.
- 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 clean, dry skin (at least 2,000 cm²). This is about 4 times the size of your hand.
- Repeat the steps above but apply the second amount of gel to a different part of your body.
- If you are applying ESTROGEL to your arms, use the opposite hand to apply the second amount of gel to the second arm.
- Allow the gel to dry for 2 minutes before covering the areas you have applied it with clothing.
- Always replace the pump cover after each use.



Usual 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.

Overdose:

If you think you, or a person you are caring for, have taken too much ESTROGEL, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

When someone accidentally takes too much ESTROGEL, the following symptoms may happen: nausea, breast discomfort, fluid retention, abdominal cramps, headache, dizziness, bloating or vaginal bleeding in women.

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 not sure, talk to your healthcare professional.

Possible side effects from using ESTROGEL:

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

Side effects may include:

- headaches
- breast tenderness/swelling
- water retention (bloating, swelling)
- nausea, vomiting, abdominal discomfort (cramps, pressure, pain)
- menstrual cramps
- vaginal itching/discharge
- pain during sexual intercourse
- change in sexual drive
- pain on urination or difficulty urinating
- premenstrual syndrome (PMS)
- brown, blotchy spots on exposed skin (also called mask of pregnancy)
- skin rash, tender red lumps or nodules or other skin reactions
- skin irritation where ESTROGEL has been applied
- loss of hair, excessive hair growth
- acne
- worsening of varicose veins (visible and bulging veins)
- nervousness, irritability
- fatigue, tiredness
- intolerance to contact lenses
- changes in appetite and body weight
- pain in the joints and muscles

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
COMMON			
Breast lump		✓	
Unexpected vaginal bleeding: bleeding or spotting between normal periods		✓	
UNCOMMON			
Migraine: severe headache often accompanied by nausea, vomiting and sensitivity to light			✓
Stroke: sudden severe headache or worsening of headache, vomiting, dizziness, fainting, disturbance of vision or speech, weakness or numbness in an arm, leg or face, sudden confusion, difficulty in walking or loss of balance or coordination			✓

RARE			
Myocardial infarction (heart attack): pressure or squeezing pain between the shoulder blades, in the chest, jaw, left arm or upper abdomen, shortness of breath, dizziness, fatigue, light-headedness, clammy skin, sweating, indigestion, anxiety, feeling faint and possible irregular heartbeat			✓
Hypertension (high blood pressure): shortness of breath, fatigue, dizziness or fainting, chest pain or pressure, swelling in your ankles and legs, blueish colour to your lips and skin, racing pulse or heart palpitations		✓	
Depression : persistent sad mood, difficulty sleeping or sleeping too much, changes in appetite or weight, feelings of worthlessness, withdrawal from social situations	✓		
Liver problems : yellowing of the skin or eyes (jaundice), right upper stomach pain or swelling, nausea or vomiting, unusual dark urine, unusual tiredness			✓
VERY RARE			
Endometrial hyperplasia (overgrowth of the lining of the uterus): heavier and/or longer than normal periods, bleeding between periods, vaginal bleeding after menopause		✓	
Heart palpitations : fast or irregular heartbeat, pounding heartbeat	✓		
UNKNOWN			
Deep vein thrombosis (blood clot in the deep veins of the leg or arm): pain, swelling, leg or arm may be warm to the touch and may appear red			✓
Pulmonary embolism (blood clot in the lung): sharp chest pain that may increase with deep breathing, cough, coughing blood, shortness of breath			✓

Blood clot in the eye: sudden partial or complete loss of vision			✓
Gallbladder problems: fever, nausea, vomiting, pain that radiates to your shoulder or back, severe pain in your upper right abdomen		✓	

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 (canada.ca/drug-device-reporting) 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:

ESTROGEL should be stored with the pump cover on securely and at room temperature (15-30°C). Keep out of reach and sight of children.

If you want more information about ESTROGEL:

- 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> or the Organon Canada website www.organon.ca or by calling Organon Canada at 1-844-820-5468.

This leaflet was prepared by Organon Canada Inc.

Date of Authorization: 2025-10-24

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