PART III: CONSUMER INFORMATION

ESTRING*
(Estradiol Vaginal Ring)

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

ABOUT THIS MEDICATION

What this medication is used for:
ESTRING is used to relieve postmenopausal vaginal and urinary symptoms associated with estrogen deficiency.

If you still have your uterus, you should discuss progestin therapy with your doctor. The purpose of adding progestin therapy is to reduce the risk of endometrial hyperplasia (overgrowth of the lining of the uterus).

The maximum recommended duration of continuous treatment with ESTRING is 2 years.

ESTRING should be used only under the supervision of a doctor, with regular follow-up at least once a year to identify adverse effects associated with its use. 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 with your doctor. You and your doctor should talk regularly about whether you still need treatment with hormone replacement therapy.

What it does:
ESTRING (estradiol vaginal ring) contains a drug reservoir of 2 mg of estradiol (an estrogen medication) in its core. ESTRING releases estradiol into the vagina in a consistent, stable manner.

Estrogens are hormones made by the ovaries of women during their reproductive years. Between ages 45 and 55, the ovaries normally stop making estrogens. This leads to a drop in body estrogen levels which causes the "change of life" or meno-pause (the end of monthly menstrual periods). If both ovaries are removed during an operation before natural menopause takes place, the sudden drop in estrogen levels results in what is known as "surgically induced menopause".

The declining estrogen levels associated with menopause may result in urogenital atrophy (thinning and drying of the tissue of the urinary tract and vagina). Symptoms of urogenital atrophy include vaginal dryness, genital itching, burning and pain during intercourse, sensation of urinary urgency and pain on urination.

Drug Response
It will take about 2 to 3 weeks to restore the tissue of the vagina and urinary tract to a healthier condition and to feel the full effect of ESTRING in relieving vaginal and urinary symptoms. If your symptoms persist for more than a few weeks after beginning ESTRING therapy, contact your doctor or healthcare provider.

When it should not be used:

Do not use ESTRING if you:
- have a personal history of breast cancer or a personal or family history of endometrial cancer (cancer of the lining of the uterus)
- have been diagnosed with endometrial hyperplasia (overgrowth of the lining of the uterus)
- have experienced undiagnosed or abnormal genital bleeding
- have liver disease
- have or have had blood clot disorders including blood clots in the leg, lung or thrombophlebitis
- have vision loss due to a blood vessel disease
- are pregnant or think you may be pregnant
- are breast feeding
- have or had an allergic or unusual reaction to any of the ingredients of ESTRING. See **What the medicinal ingredient is** and **What the nonmedicinal ingredients are**, following this section for a list of ingredients.
- have or have had a stroke, heart attack, or coronary artery disease
- have or had porphyria
- have some types of congenital coagulation abnormalities (e.g. protein C, protein S, or antithrombin deficiency)

What the medicinal ingredient is:
17 β-Estradiol

What the nonmedicinal ingredients are:
Silicone elastomer, silicone fluid and barium sulfate.

What dosage forms it comes in:
Each ESTRING (estradiol vaginal ring) is individually packaged in a heat-sealed rectangular pouch. The pouch is provided with a tear-off notch on one side.

ESTRING (estradiol vaginal ring) is available in single units. Each unit contains 2 mg 17ß-estradiol

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 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 Women's Health Initiative (WHI) trial indicated no difference in the risk of breast cancer in post-menopausal women with prior hysterectomy taking oral 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 hormone replacement therapy (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 self-examination of the breast are recommended for all women. You should review the 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 postmenopausal 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. It is important to report any unusual vaginal bleeding to your doctor right away while you are using ESTRING. Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your doctor should check any unusual vaginal bleeding to find out the cause.
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
Use of oral estrogen alone and estrogen plus progestin therapies for 5 or more years has been associated with a small 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 postmenopausal women taking combined oral 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 postmenopausal women with prior hysterectomy taking oral *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 postmenopausal 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 postmenopausal 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 with 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 oral estrogens by post-menopausal women has been reported to increase the 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 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 postmenopausal women age 65 and over with prior hysterectomy taking oral *estrogen-alone* compared to women taking placebo.

Toxic Shock Syndrome
A few cases of toxic shock syndrome (TSS) have been reported in women using vaginal rings. TSS is a rare, but serious disease that may cause death. Warning signs of TSS include fever, nausea, vomiting, diarrhea, muscle pain, dizziness, faintness, or a sunburn-rash on face and body.

BEFORE you use ESTRING 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 been diagnosed with diabetes
- are pregnant or may be pregnant
- are breast feeding
- If you think you may have a vaginal infection
- smoke
- have been diagnosed with a rare disorder where you have a deficiency of enzymes involved in the production of heme known as porphyria
- have a history of high cholesterol or high levels of other fats (such as triglycerides) in the blood
- have a history of bone disease (this includes certain metabolic conditions or cancers that can affect blood levels of calcium and phosphorus)
- have had a hysterectomy (surgical removal of the uterus)
- have family history of angioedema

X-Ray Procedures
If any x-ray procedures of the lower abdominal tract take place, ESTRING should be removed since the barium sulphate containing core is visible on x-ray and could disturb the procedure or evaluation of x-rays.

INTERACTIONS WITH THIS MEDICATION

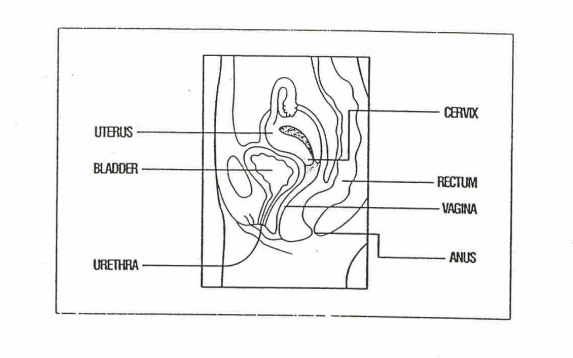
Some medications can interfere with the action of estrogens and estrogens can interfere with the effects of other medications. When you are using ESTRING it is important to let your doctor or pharmacist know if you are taking any other medications, including prescription medications, over-the-counter medications, vitamins and herbal products.

PROPER USE OF THIS MEDICATION

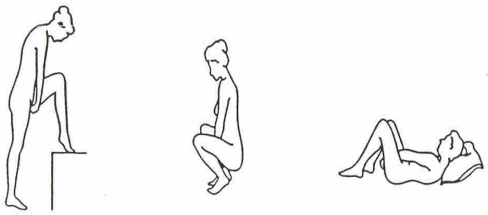
Usual Dose:
ESTRING can be inserted or removed by you or your doctor. ESTRING vaginal ring is to be worn continuously for 90 days.

A Guide to ESTRING Insertion and Removal:

FEMALE ANATOMY

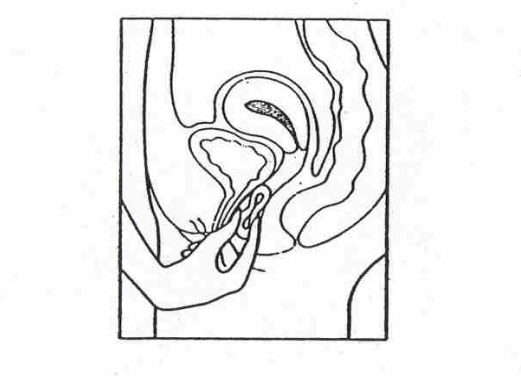


ESTRING INSERTION
ESTRING can be inserted and removed by you or your doctor. To insert ESTRING yourself, choose the position that is most comfortable for you: standing with one leg up, squatting, or lying down.



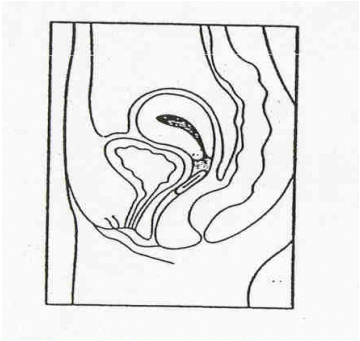
1. After washing and drying your hands, remove ESTRING from its pouch using the tear-off notch on the side. (Since the ring becomes slippery when wet, be sure your hands are dry before handling it).

2. Hold ESTRING between your thumb and index finger and press the opposite sides of the ring together as shown.



3. Gently push the compressed ring into your vagina as far as you can.

ESTRING PLACEMENT
The exact position of ESTRING is not critical, as long as it is placed in the upper third of the vagina.



When ESTRING is in place, you should not feel anything. If you feel uncomfortable, ESTRING is probably not far enough inside. Use your finger to gently push ESTRING further into your vagina. There is no danger of ESTRING being pushed too far up in the vagina or getting lost. ESTRING can only be inserted as far as the end of the vagina, where the cervix (the narrow, lower end of the uterus) will block ESTRING from going any further (*see diagram of* **Female Anatomy**).

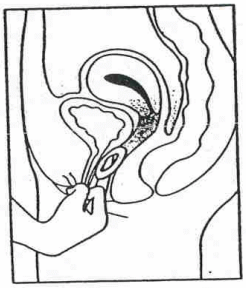
ESTRING USE
Once inserted, ESTRING should remain in place in the vagina for 90 days. Most women and their partners experience no discomfort with ESTRING in place during intercourse, so it is NOT necessary that the ring be removed. If ESTRING should cause you or your partner any discomfort, you may remove it prior to intercourse (*see* **ESTRING Removal**, *below*). Be sure to reinsert ESTRING as soon as possible afterwards. ESTRING may slide down into the lower part of the vagina as a result of the

abdominal pressure or straining that sometimes accompanies constipation. If this should happen, gently guide ESTRING back into place with your finger. There have been rare reports of ESTRING falling out in some women following intense straining or coughing. If this should occur, simply wash ESTRING with lukewarm (NOT hot) water and reinsert it.

ESTRING REMOVAL
After 90 days there will no longer be enough estradiol in the ring to maintain its full effect in relieving your vaginal or urinary symptoms. ESTRING should be removed at that time and replaced with a new ESTRING, if your doctor determines that you need to continue your therapy.

To remove ESTRING:
1. Wash and dry your hands thoroughly.
2. Assume a comfortable position, either standing with one leg up, squatting, or lying down.
3. Loop your finger through the ring and gently pull it out.
4. Discard the used ring in a waste receptacle.

(Do not flush ESTRING).



If you have any additional questions about removing ESTRING, contact your doctor or healthcare provider.

During treatment for vaginal infection with vaginal therapy: It is recommended that ESTRING be discontinued while other treatments are being used to treat a vaginal infection. Use of ESTRING can be resumed after termination of the other vaginal medication, and after first consulting with a physician.
The maximum recommended duration of continuous therapy is 2 years.

Overdose:
It is highly unlikely that overdosage would occur with ESTRING. In general excessive doses of estrogen may result in nausea, vomiting, abdominal cramps, headache, dizziness, breast tenderness, drowsiness/fatigue, withdrawal bleeding and general ill feeling (malaise). Call your doctor and/or your local Poison Control Centre if you suspect an overdose.

ADDITIONAL INFORMATION
- Some women have experienced moving or sliding of ESTRING within the vagina. If this happens, ESTRING can be gently pushed back into position using a clean finger. Instances of ESTRING slipping out of the vagina have been infrequent and were usually associated with moving the bowels, straining, or constipation within the first few weeks of treatment. If this occurs, ESTRING can be washed with lukewarm (NOT hot) water and reinserted. If this happens repeatedly, you should consult with your doctor or healthcare provider and determine whether continued treatment is appropriate for you.
- ESTRING may not be suitable for women with narrow, short, or stenosed (constricted) vaginas. A narrow vagina, vaginal stenosis (constriction), significant prolapse, and vaginal infections are conditions that make the vagina more susceptible to irritation or ulceration caused by ESTRING. Women with signs or symptoms of vaginal irritation should alert their doctor or healthcare provider.
- Vaginal infection is generally more common in postmenopausal women. Vaginal infections should be treated with appropriate therapy before initiation of ESTRING. If a vaginal infection develops during use of ESTRING, then ESTRING should be removed and reinserted only after the infection has been appropriately treated. See your doctor or healthcare provider if you have vaginal discomfort or suspect you have a vaginal infection.
- Cases of the rings sticking to the vaginal wall have occurred and have made removal difficult. Some cases have needed surgery to remove the rings.
- Your doctor has prescribed this drug for you and you alone. Do not give the drug to anyone else.
- Keep this and all drugs out of the reach of children.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medications, ESTRING (estradiol vaginal ring) may cause side effects. The most frequently reported side effect is increased vaginal secretions. Many of these vaginal secretions are like those that occur normally prior to menopause and indicate that ESTRING is working. Vaginal secretions that are associated with a bad odour, vaginal itching, or other signs of vaginal infection are NOT normal and may indicate a risk or a cause for concern. Other side effects may include vaginal discomfort, abdominal pain, or urogenital itching. The following adverse events were seen in studies with ESTRING:

- Vaginal bleeding/spotting (4%)
- Headache (13%)
- Breast tenderness (1%)
- Leg edema (swelling) (1-3%)

Other possible side effects (or post marketing experiences) reported with ESTRING are:

- Toxic shock syndrome
- adherence to the vagina making it difficult to remove the vaginal ring
- blockage of the bowel
- vaginal erosion/ vaginal ulceration

Cases of allergic reactions (e.g. itching, hives, swelling, vaginal discomfort/irritation, redness), including hospitalization, have been reported in women using vaginal rings.

In addition to the possible side effects noted above, the following have been reported with estrogen use:

- Breast tenderness or enlargement
- Retention of excess fluid. This may worsen some conditions such as asthma, epilepsy, migraine, heart disease or kidney disease
- Spotty darkening of the skin, particularly on the face

What are the additional possible side effects of estrogens?

Serious but less common side effects include**:** Breast cancer, cancer of the uterus, stroke, heart attack, blood clots, dementia, gallbladder disease, ovarian cancer, high blood pressure, liver problems, high blood sugar, and enlargement of benign tumors of the uterus ("fibroids").

Some of the warning signs of these serious side effects include: Breast lumps, unusual vaginal bleeding, dizziness and faintness, changes in speech, severe headaches, chest pain, shortness of breath, pains in your legs, changes in vision, vomiting, yellowing of the skin, eyes or nail beds.

Call your healthcare provider right away if you get any of these warning signs, or any other unusual symptom that concerns you.

Less serious but common side effects include: Headache, breast pain, irregular vaginal bleeding or spotting, stomach/abdominal cramps, bloating, nausea and vomiting, hair loss, fluid retention, vaginal yeast infection.

These are not all the possible side effects of estrogens. For more information, ask your healthcare provider or pharmacist.

SERIOUS SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Remove the ring and call your doctor or pharmacist
	Only if severe	In all cases	
Abnormal bleeding from the vagina		√	
Pain in the calves or chest, sudden shortness of breath or coughing blood			√
Severe headache or vomiting, dizziness, seizures, faintness, changes in vision or speech, visual disturbances, weakness or numbness of an arm or leg			√
Breast lumps		√	
Pain, swelling or tenderness in the abdomen		√	
Yellowing of the eyes and/or skin			√

Symptom / effect	Talk with your doctor or pharmacist		Remove the ring and call your doctor or pharmacist
	Only if severe	In all cases	
Toxic Shock Syndrome: warning signs include fever, nausea, vomiting, diarrhea, muscle pain, dizziness, faintness, or a sunburn-rash on face and body			√
Persistent sad mood			√
Allergic reaction (e.g. itching, hives, swelling, vaginal discomfort/irritation, redness)			√

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

HOW TO STORE IT

Store at controlled room temperature 15° to 30°C.
Keep out of reach of children and pets.

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** https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html
- **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 1908C
    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 https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist. 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: http://www.pfizer.ca or by contacting the distributor, Paladin Labs Inc., at 1-888-867-7426 (Medical Information).

This leaflet was prepared by Pfizer Canada Inc.

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