PRODUCT MONOGRAPH

Pr ESTRING *
(17 β-Estradiol)

Vaginal Ring, 2 mg

Estrogen

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(17 β-Estradiol)

PART 1: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Vaginal	• Vaginal Ring, 2 mg	• Silicone elastomer • Barium sulphate • Silicone fluid

INDICATIONS AND CLINICAL USE

ESTRING (17 β-estradiol) is indicated for postmenopausal urogenital complaints due to estrogen deficiency such as feeling of dryness in the vagina (atrophic vaginitis) with or without pruritus vulvae, dyspareunia, dysuria and urinary urgency (atrophic mucosa in the urethra and trigonum).

ESTRING should be prescribed with an appropriate dosage of a progestin for women with intact uteri, in order to prevent endometrial hyperplasia/carcinoma**.**

The maximum recommended duration of continuous therapy is 2 years.

CONTRAINDICATIONS

- Known or suspected estrogen-dependent malignant neoplasia (e.g. endometrial cancer).
- Known, suspected, or past history of breast cancer.
- Undiagnosed abnormal genital bleeding.
- Known or suspected pregnancy.
- Known or suspected hypersensitivity to any component of the product. For a complete listing, see the Dosage Forms, Composition and Packaging section of the Product Monograph.
- Endometrial hyperplasia.
- Lactation
- Liver dysfunction or disease as long as liver function tests have failed to return to normal.
- Active or past history of arterial thromboembolic disease (e.g. stroke, myocardial infarction, coronary heart disease).
- Active or past history of confirmed venous thromboembolism (such as deep vein thrombosis or pulmonary embolism) or active thrombophlebitis.
- Partial or complete loss of vision due to ophthalmic vascular disease.
- Porphyria
- Known thrombophilic disorders (e.g., protein C, protein S, or antithrombin deficiency)

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

The Women's Health Initiative (WHI) trial examined the health benefits and risks of oral combined estrogen plus progestin therapy (n=16,608) and oral estrogen-alone therapy (n=10,739) in postmenopausal women aged 50 to 79 years.[1-3]

The estrogen plus progestin arm of the WHI trial (mean age 63.3 years) indicated an increased risk of myocardial infarction (MI), stroke, invasive breast cancer, pulmonary emboli and deep vein thrombosis in postmenopausal women receiving treatment with combined conjugated equine estrogens (CEE, 0.625 mg/day) and medroxyprogesterone acetate (MPA, 2.5 mg/day) for 5.2 years compared t o those receiving placebo.[1]

The estrogen-alone arm of the WHI trial (mean age 63.6 years) indicated an increased risk of stroke and deep vein thrombosis in hysterectomized women treated with CEE-alone (0.625 mg/day) for 6.8 years compared to those receiving placebo. [2]

Therefore, the following should be given serious consideration at the time of prescribing:
- Estrogens with or without progestins **should not** be prescribed for primary or secondary prevention of cardiovascular diseases.
-Estrogens with or without progestins should be prescribed at **the lowest effective dose** for the approved indication.
-Estrogens with or without progestins should be prescribed for the **shortest period possible** for the approved indication

General

Risks and benefits of treatment with ESTRING should be re-assessed at least annually. ESTRING should only be continued as long as the benefits outweigh the risks.

ESTRING is a vaginal administered estrogen product with low systemic absorption following continuous use for 3 months (see Action and Clinical Pharmacology – Pharmacokinetics – Absorption). It is expected that low systemic exposure to estradiol and estrone resulting from ESTRING use should elicit lower estrogen-dependent side effects. However, the following warnings and precautions associated with oral estrogen therapy should be considered in the absence of comparable data with other dosage forms of estrogens.

Carcinogenesis and Mutagenesis

Breast Cancer

Available epidemiological data indicate that the use of combined estrogen plus progestin by postmenopausal women is associated with an increased risk of invasive breast cancer.

In the estrogen plus progestin arm of the WHI trial, among 10,000 women over a one-year period, there were:
• 8 more cases of invasive breast cancer (38 on combined HRT versus 30 on placebo).[1]

The WHI study also reported that the invasive breast cancers diagnosed in the estrogen plus progestin group were similar in histology but were larger (mean [SD], 1.7 cm [1.1] vs 1.5 cm [0.9], respectively; P=0.04) and were at a more advanced stage compared with those diagnosed in the placebo group. The percentage of women with abnormal mammograms (recommendations for short-interval follow-up, a suspicious abnormality, or highly suggestive of malignancy) was significantly higher in the estrogen plus progestin group versus the placebo group. This difference appeared at year one and persisted in each year thereafter.[3]

In the oral estrogen-alone arm of the Women's Health Initiative (WHI) trial, there was no statistically significant difference in the rate of invasive breast cancer in hysterectomized women treated with conjugated equine estrogens versus women treated with placebo[2].

It is recommended that estrogens not be given to women with existing breast cancer or those with a previous history of the disease (see **CONTRAINDICATIONS**).
There is a need for caution in prescribing estrogens of any kind to women with a strong family history (first degree relative) of breast cancer or women who have nodules, fibrocystic disease or abnormal mammograms and/ or atypical hyperplasia at breast biopsy.

Other known risk factors for the development of breast cancer such as nulliparity, obesity, early menarche, late age at first full term pregnancy and at menopause should also be evaluated.

It is recommended that women undergo mammography prior to the start of HRT treatment and at regular intervals during treatment, as deemed appropriate by the treating physician and according to the perceived risks for each patient.

The overall benefits and possible risks of hormone replacement therapy should be fully considered and discussed with patients. It is important that the modest increased risk of being diagnosed with breast cancer after 4 years of treatment with HRT (as reported in the results of WHI-trial) be discussed with the patient and weighed against its known benefits.

Instructions for regular self-examination of the breasts should be included in this counselling.

Endometrial Hyperplasia & Endometrial Carcinoma
An increased risk of endometrial cancer has been reported with the use of unopposed estrogen therapy in women with a uterus. The reported endometrial cancer risk among unopposed estrogen users is about 2 to 12-times greater than in nonusers, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than 1 year. The greatest risk appears associated with prolonged use, with increased risks of 15 to 24 fold for 5 to 10 years or more. This risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued. There is no evidence that the use of natural estrogens result in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose. The endometrial safety of long-term or repeated intra-vaginal estrogen administration is uncertain. Adding a progestin to systemic estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Therefore, estrogen should be prescribed with an appropriate dosage of a progestin for women with intact uteri in order to prevent endometrial hyperplasia/carcinoma.

Clinical surveillance of all women taking estrogen plus progestin therapy is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding.

Ovarian cancer
Observational studies have found the use of hormone replacement therapy (estrogen-alone and estrogen plus progestin therapies), in particular for five or more years, has been associated with a small increase in the risk of ovarian cancer.

Liver tumour
In rare cases benign, and in even rarer cases malignant liver tumours leading in isolated cases to life-threatening intra-abdominal haemorrhage have been observed after the use of hormonal substances such as those contained in ESTRING. If severe upper abdominal complaints, enlarged liver or signs of intra-abdominal haemorrhage occur, a liver tumour should be considered in the differential diagnosis.

Cardiovascular
The results of the Heart and Estrogen/progestin Replacement Studies (HERS and HERS II) and the Women's Health Initiative (WHI) trial indicate that the use of continuous combined oral conjugated equine estrogens (CEE) and medroxyprogesterone acetate (MPA) is associated with an increased risk of coronary heart disease (CHD) in postmenopausal women. [1, 4, 5] The results of the WHI trial indicate that the use of oral estrogen-alone and oral estrogen plus progestin is associated with an increased risk of stroke in postmenopausal women. [1, 2]

WHI Trial Findings

In the combined *estrogen plus progestin* arm of the WHI trial, among 10 000 women over a one-year period, there were:

- 8 more cases of stroke (29 on combined HRT versus 21 on placebo)
- 7 more cases of CHD (37 on combined HRT versus 30 on placebo).[1]

In the *estrogen-alone* arm of the WHI trial of women with prior hysterectomy, among 10 000 women over a one-year period, there were/was:

- 12 more cases of stroke (44 on *estrogen-alone* therapy versus 32 on placebo)
- no statistically significant difference in the rate of CHD. [2]

HERS and HERS II Findings

In the Heart and Estrogen/progestin Replacement study (HERS) of postmenopausal women with documented heart disease (n = 2763, average age 66.7 years), a randomized placebo-controlled clinical trial of secondary prevention of coronary heart disease (CHD), treatment with 0.625 mg/day oral conjugated equine estrogen (CEE) plus 2.5 mg medroxyprogesterone acetate (MPA) demonstrated no cardiovascular benefit. Specifically, during an average follow-up of 4.1 years, treatment with CEE plus MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the hormone-treated group than in the placebo group in year 1, but not during the subsequent years. [4]

From the original HERS trial, 2 321 women consented to participate in an open label extension of HERS, known as HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. After 6.8 years, hormone therapy did not reduce the risk of cardiovascular events in women with CHD. [5]

Blood Pressure

Women using hormonal replacement therapy (HRT) sometimes experience increased blood pressure. Blood pressure should be monitored with HRT use. Elevation of blood pressure in previously normotensive or hypertensive patients should be investigated and HRT therapy may have to be discontinued.

Endocrine and Metabolism

Estrogen effects

Although uncommon with ESTRING, certain patients may develop undesirable manifestations of estrogenic stimulation, such as mastodynia.

Glucose and Lipid Metabolism

A worsening of glucose tolerance and lipid metabolism has been observed in a significant percentage of peri- and post-menopausal patients. Therefore, diabetic patients or those with a predisposition to diabetes should be observed closely to detect any alterations in carbohydrate or lipid metabolism, especially in triglyceride blood levels. The requirement for oral anti-diabetics or insulin can change as a result of the effect on glucose tolerance.

Women with familial hyperlipidemias need special surveillance. Lipid-lowering measures are recommended additionally, before treatment is started.

Hypertriglyceridemia

In patients with preexisting hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complication. These women should be followed closely during their estrogen replacement or hormone replacement therapy. Consider discontinuation of treatment if pancreatitis or other complications develop.

Heme metabolism
Women with porphyria need special surveillance.

Calcium and phosphorus metabolism
Because the prolonged use of estrogens influences the metabolism of calcium and phosphorus, estrogens should be used with caution in patients with metabolic and malignant bone diseases associated with hypercalcemia and in patients with renal insufficiency.

Hypocalcemia
Estrogens should be used with caution in individuals with severe hypocalcemia.

Hypercalcemia
Estrogen administration may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If hypercalcemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

Hypothyroidism
Patients who require thyroid hormone replacement therapy and who are also taking estrogen should have their thyroid function monitored regularly to assure that thyroid hormone levels remain in an acceptable range (see **Drug-Laboratory Test Interactions**).

Immune
Hypersensitivity
Cases of hypersensitivity reactions (e.g. pruritus, urticaria, inflammation, vulvovaginal discomfort, erythema), including hospitalization, have been reported in women using vaginal rings.

Angioedema
Exogenous estrogens may induce or exacerbate symptoms of angioedema, particularly in patients with hereditary angioedema.

Genitourinary
Some women may be unsuitable for treatment with ESTRING, in particular those with short narrow vaginas due to previous surgery or the effect of atrophy, or those with a degree of uterovaginal prolapse severe enough to prevent retention of the ring.

A potential problem related to the vaginal ring is a tendency in a limited number of patients for the ring to slide down, move or fall out. This was noticed primarily during the first 3 weeks of treatment and was the reason for withdrawal from treatment for 3% of the patients on their first ring.

Vaginal bleeding
Abnormal vaginal bleeding, due to its prolongation, irregularity or heaviness, occurring during therapy should prompt appropriate diagnostic measures to rule out the possibility of uterine malignancy and the treatment should be re-evaluated.

Women should be advised to inform their physician if irritation, pain, discharge, unusual or unexpected bleeding occur during treatment.

Although uncommon with ESTRING, certain patients may develop undesirable manifestations of estrogenic stimulation, such as abnormal uterine bleeding.

Location of ESTRING
Some women have experienced moving or gliding of ESTRING within the vagina. Instances of ESTRING being expelled from the vagina in connection with moving the bowels, strain, or constipation have been reported. If this occurs, ESTRING can be rinsed in lukewarm water and reinserted into the vagina by the patient.

Vaginal Irritation
ESTRING may not be suitable for women with narrow, short, or stenosed vaginas. Narrow vagina, vaginal stenosis, prolapse, and vaginal infections are conditions that make the vagina more susceptible to ESTRING-caused irritation or ulceration. Women with signs or symptoms of vaginal irritation should alert their physician.

In any woman experiencing persistent or severe discomfort due to the presence of the ring or excessive movement of the ring, treatment should be discontinued. Treatment should be discontinued in patients with signs of ulceration or severe inflammation due to unresponsive atrophic vaginitis.

Vaginal Adhesion
Cases of ring adherence to the vaginal wall, making ring removal difficult, have occurred. Some cases have required surgical removal of vaginal rings.

Uterine Leiomyomata
Pre-existing uterine leiomyomata may increase in size during estrogen use. Growth, pain or tenderness of uterine leiomyomata requires discontinuation of medication and appropriate investigation.

Exacerbation of endometriosis
Symptoms and physical findings associated with a previous diagnosis of endometriosis may reappear or become aggravated with estrogen use. A few cases of malignant transformation of residual endometrial implants have been reported in women treated post-hysterectomy with estrogen alone therapy. For patients known to have residual endometriosis post-hysterectomy, the addition of progestin should be considered.

Vaginal Infection
Vaginal infection is generally more common in postmenopausal women due to the lack of the normal flora of fertile women, especially lactobacillus, and the subsequent higher pH. Vaginal infections should be treated with appropriate antimicrobial 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.

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.

Hematologic
Venous Thromboembolism
Available epidemiological data indicate that use of oral estrogen with or without progestin by postmenopausal women is associated with an increased risk of developing venous thromboembolism (VTE).

In the *estrogen plus progestin* arm of the WHI trial, among 10 000 women on combined HRT over one-year period, there were 18 more cases of venous thromboembolism, including 8 more cases of pulmonary embolism.[1]

In the *estrogen-alone* arm of the WHI trial, among 10 000 women on estrogen therapy over a one-year period, there were 7 more cases of venous thromboembolism, although there was no statistically significant difference in the rate of pulmonary embolism. [2]

Generally recognized risk factors for VTE include a personal history, a family history (the occurrence of VTE in a direct relative at a relatively early age may indicate genetic predisposition), severe obesity (body mass index > 30 kg/m^2) and systemic lupus erythematosus. The risk of VTE also increases with age and smoking.

The risk of VTE may be temporarily increased with prolonged immobilization, major surgery or trauma. In women on HRT, attention should be given to prophylactic measures to prevent VTE following surgery. Also, patients with varicose veins should be closely supervised. The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, retinal thrombosis, cerebral embolism and pulmonary embolism). If these occur or are suspected, hormone therapy should be discontinued immediately, given the risks of long-term disability or fatality.

If feasible, estrogens should be discontinued at least 4 weeks before major surgery which may be associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

Hepatic/Biliary/Pancreatic
Gallbladder Disease
A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in women receiving postmenopausal estrogens has been reported.

Jaundice
Caution is advised in patients with a history of liver and/or biliary disorders. If cholestatic jaundice develops during treatment, the treatment should be discontinued and appropriate investigations carried out.

Liver Function Tests
Liver function tests should be done periodically in subjects who are suspected of having hepatic disease. For information on endocrine and liver function tests, see the section under **Monitoring and Laboratory Tests**.

Neurologic
Cerebrovascular insufficiency
Patients who develop visual disturbances, classical migraine, transient aphasia, paralysis, or loss of consciousness should discontinue medication.

Patients with a previous history of classical migraine and who develop a recurrence or worsening of migraine symptoms should be re-evaluated.

Dementia
Available epidemiological evidence indicates that the use of combined oral estrogen plus progestin in women aged 65 and over may increase the risk of developing probable dementia.

The Women's Health Initiative Memory Study (WHIMS), a clinical substudy of the WHI, was designed to assess whether postmenopausal hormone replacement therapy (oral *estrogen plus progestin* or oral *estrogen-alone*) reduces the risk of dementia in women aged 65 and over (age range 65-79 years) and free of dementia at baseline.[6,7]

In the *estrogen plus progestin* arm of the WHIMS (n = 4 532), women with an intact uteri were treated with daily 0.625 mg conjugated equine estrogens (CEE) plus 2.5 mg medroxyprogesterone acetate (MPA) or placebo for an average of 4.05 years . The results, when extrapolated to 10 000 women treated over a one-year period showed:

- 23 more cases of probable dementia (45 on combined HRT versus 22 on placebo). [6]

In the *estrogen-alone* arm of the WHIMS (n = 2947), women with prior hysterectomy were treated with daily 0.625 mg CEE or placebo for an average of 5.21 years. The results, when extrapolated to 10 000 women treated over a one-year period showed:

- 12 more cases of probable dementia (37 on estrogen-alone versus 25 on placebo), although this difference did not reach statistical significance.[7]

When data from the *estrogen plus progestin* arm of the WHIMS and the *estrogen-alone* arm of the WHIMS were combined, as per the original WHIMS protocol, in 10 000 women over a one-year period, there were:

- 18 more cases of probable dementia (41 on estrogen plus progestin or estrogen-alone versus 23 on placebo).[7]

Epilepsy
HRT may cause an exacerbation of epilepsy.

Renal

Fluid Retention

Estrogens may cause fluid retention. Therefore, particular caution is indicated in cardiac or renal dysfunction, epilepsy or asthma. If, in any of the above-mentioned conditions, a worsening of the underlying disease is diagnosed or suspected during treatment, the benefits and risks of treatment should be reassessed based on the individual case.

Special Populations

Pregnant Women: Estrogens should not be used during pregnancy. Any possibility of pregnancy must be ruled out before prescribing ESTRING. If pregnancy occurs during ESTRING treatment, ESTRING should be discontinued immediately. Women who may be at risk of pregnancy should be advised to adhere to non-hormonal contraceptive methods.

There appears to be little or no increased risk of birth defects in children born to women who have used estrogens and progestins as oral contraceptive inadvertently during early pregnancy.

Congenital lesions with malignant potential

Estrogen therapy during pregnancy is associated with an increased risk of fetal congenital reproductive tract disorders, and possibly other birth defects. Studies of women who received diethylstilbestrol (DES) during pregnancy have shown that female offspring have an increased risk of vaginal adenosis, squamous cell dysplasia of the uterine cervix and clear cell vaginal cancer later in life; male offspring have an increased risk of urogenital abnormalities and possibly testicular cancer later in life. Although some of these changes are benign, others are precursors of malignancy.

Nursing Women: Estrogens should not be used during lactation. ESTRING should not be prescribed to nursing mothers. Estrogens have been detected in the breast-milk of mothers receiving these drugs, and the effect on breast-fed infants has not been determined. Suppression of lactation may occur. Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the breast milk.

Pediatrics (< 18 years of age): ESTRING is not indicated for use in the pediatric population.

Geriatrics (> 65 years of age): There have not been sufficient numbers of geriatric patients involved in studies utilizing ESTRING to determine whether those over 65 years of age differ from younger subjects in their response to ESTRING.

In the estrogen alone substudy of the Women's Health Initiative (WHI) study, 46 percent (n = 4,943) of subjects were 65 years of age and older, while 7.1 percent (n = 767) of subjects were 75 years of age and older. There was a higher relative risk (daily CEE 0.625 mg versus placebo) of stroke in women less than 75 years of age compared to women 75 years and older.[1]

In the estrogen alone substudy of the Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, a population of 2,947 hysterectomized women, aged 65 to 79 years of age, was randomized to receive daily conjugated equine estrogens (CEE 0.625 mg daily) or placebo. After an average follow-up of 5.2 years, the relative risk (CEE versus placebo) of probable dementia was 1.49 (95 percent CI, 0.83-2.66). The absolute risk of developing probable dementia with estrogen alone was 37 versus 25 cases per 10,000 women-years compared with placebo.[6]

Of the total number of subjects in the estrogen plus progestin substudy of WHI, 44 percent (n = 7,320) were 65 years of age and older, while 6.6 percent (n = 1,095) were 75 years of age and older. In women 75 years of age and older compared to women less than 75 years of age, there was a higher relative risk of nonfatal stroke and invasive breast cancer in the estrogen plus progestin group versus placebo. In women greater than 75, the increased risk of nonfatal stroke and invasive breast cancer observed in the estrogen plus progestin group compared to placebo was 75 versus 24 per 10,000 women-years and 52 versus 12 per 10,000 women-years, respectively.[1,3]

In the estrogen plus progestin WHIMS substudy, a population of 4,532 postmenopausal women, aged 65 to 79 years, was randomized to receive CEE 0.625 mg/MPA 2.5 mg or placebo. In the estrogen plus progestin group, after an average follow-up of 4 years, the relative risk (CEE/MPA versus placebo) of probable dementia was 2.05 (95 percent CI, 1.21-3.48). The absolute risk of developing probable dementia with CEE/MPA was 45 versus 22 cases per 10,000 women-years compared with placebo.[6]

Seventy-nine percent of the cases of probable dementia occurred in women that were older than 70 for the CEE alone group, and 82 percent of the cases of probable dementia occurred in women who were older than 70 in the CEE/MPA group. The most common classification of probable dementia in both the treatment groups and placebo groups was Alzheimer's disease.[6]

When data from the two populations were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95 percent CI, 1.19-2.60). Since both substudies were conducted in women aged 65 to 79 years, it is unknown whether these findings apply to younger postmenopausal women.[6]

Conditions which need Supervision:
If any of the following conditions are present, have occurred previously, and/or have been aggravated during pregnancy or previous hormone treatment, the patient should be closely supervised. It should be taken into account that these conditions may recur or be aggravated during treatment with vaginal ring, in particular:

- Risk factors for estrogen dependent tumours, e.g. first degree heredity for breast cancer (see above)
- Diabetes mellitus with or without vascular involvement
- Migraine or (severe) headache
- Epilepsy
- A history of, or risk of factors for, thromboembolic disorders (see above)
- Systemic lupus erythematosus
- Liver disorders (e.g. liver adenoma)
- Otosclerosis
- Cholelithiasis
- Leiomyoma (uterine fibroids)
- Endometriosis
- A history of endometrial hyperplasia (see above)
- Hypertension
- Asthma

Reasons for immediate withdrawal of therapy:
Therapy should be discontinued in case a contra-indication is discovered and in the following situations:

- Jaundice or deterioration in liver function
- Significant increase in blood pressure
- New onset of migraine-type headache
- Pregnancy

Visual abnormalities: Discontinue medication pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, or diplopia. If examination reveals papilledema or retinal vascular lesions, estrogens should be discontinued.

Monitoring and Laboratory Tests
Before ESTRING (estradiol) is administered, the patient should have a complete physical examination including a blood pressure determination. Breasts and pelvic organs should be appropriately examined and a Papanicolaou smear should be performed. Endometrial biopsy should be done when indicated. Baseline tests should include mammography, measurements of blood glucose, calcium, triglycerides and cholesterol, and liver function tests.

Patients on long-term corticosteroid treatment or those with conditions causing poor skin integrity, e.g. Cushing's Disease, may be unsuitable for treatment as they may have vaginal atrophy unresponsive to estrogen therapy.

The first follow-up examination should be done within 3-6 months after initiation of treatment to assess response to treatment. Thereafter, examinations should be made at intervals at least once a year. Appropriate investigations should be arranged at regular intervals as determined by the physician.

The importance of regular self-examination of the breasts should be discussed with the patient.

Women treated with ESTRING should be advised to keep their regular medical checkups to assess the need for continuing therapy.

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.

Carcinogens, Mutagenesis, and Impairment of Fertility
Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testes and liver.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

See WARNINGS AND PRECAUTIONS regarding potential induction of malignant neoplasms and adverse effects similar to those of oral contraceptives.

The following adverse reactions have been reported with estrogen/progestin combination in general:

- **Reproductive System and Breast Disorders**
  Breakthrough bleeding; spotting; change in menstrual flow; dysmenorrhea; vaginal itching/discharge; dyspareunia; endometrial hyperplasia; pre-menstrual-like syndrome: reactivation of endometriosis; changes in cervical erosion and amount of cervical secretion, breast swelling and tenderness, vaginal adhesion (See WARNINGS AND PRECAUTIONS).
- **Blood and lymphatic system disorders**
  Altered coagulation tests (see **WARNINGS AND PRECAUTIONS**, **DRUG-LABORATORY TESTS INTERACTIONS**).
- **Cardiac disorders**
  Palpitations; coronary thrombosis; increase in blood pressure (see **WARNINGS AND PRECAUTIONS**).
- **Endocrine disorders**
  Increased blood sugar levels; decreased glucose tolerance.
- **Eye disorders**
  Neuro-ocular lesions (eg, retinal thrombosis, optic neuritis); visual disturbances; steepening of the corneal curvature; intolerance to contact lenses.
- **Gastrointestinal disorders**
  Nausea; vomiting; abdominal discomfort (cramps, pressure, pain, bloating).
- **General disorders and administration site conditions**
  Fatigue; changes in appetite; changes in body weight; change in libido.
- **Hepatobiliary disorders**
  Gallbladder disorder; asymptomatic impaired liver function; cholestatic jaundice.
- **Musculoskeletal and connective tissue disorders**
  Musculoskeletal pain including leg pain not related to thromboembolic disease (usually transient, lasting 3 to 6 weeks) may occur.
- **Nervous system disorders**
  Aggravation of migraine episodes; headaches, dizziness; neuritis.
- **Psychiatric disorders**
  Mental depression; nervousness; irritability.
- **Renal and urinary disorders**
  Cystitis; dysuria; sodium retention; edema.
- **Skin and subcutaneous tissue disorders**
  Chloasma or melasma, which may persist when drug is discontinued; erythema multiforme; erythema nodosum; haemorrhagic eruption; loss of scalp hair; hirsutism and acne.
- **Vascular Disorders**
  Isolated cases of: thrombophlebitis; thromboembolic disorders."

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse drug reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The biological safety of the silicone elastomer has been studied in various *in vitro* and *in vivo* test models. The results show that the silicone elastomer is non-toxic, non-pyrogenic, non-irritating, and non-sensitizing. Long-term implantation induced encapsulation equal to or less than the negative control (polyethylene) used in the USP test. No toxic reaction or tumour formation was observed with the silicone elastomer.

In general, ESTRING (estradiol vaginal ring) was well tolerated. In the two pivotal controlled studies, discontinuation of treatment due to an adverse event was required by 5.4% of patients receiving ESTRING and 3.9% of patients receiving conjugated estrogens vaginal cream. The most common reasons for withdrawal from ESTRING treatment due to an adverse event were vaginal discomfort and gastrointestinal symptoms.

The adverse events reported with a frequency of 3% or greater in the two pivotal controlled studies by patients receiving ESTRING or conjugated estrogens vaginal cream are listed in Table 1.

Table 1:Adverse Events Reported by 3% or More of Patients Receiving Either ESTRING or Conjugated Estrogens Vaginal Cream in Two Pivotal Controlled Studies		
	ESTRING (n=257)	Conjugated Estrogens Vaginal Cream (n=129)
ADVERSE EVENT	%	%
Musculoskeletal		
Back Pain	6	8
Arthritis	4	2
Arthralgia	3	5
Skeletal Pain	2	4
CNS/Peripheral Nervous System		
Headache	13	16
Psychiatric		
Insomnia	4	0
Gastrointestinal		
Abdominal Pain	4	2
Nausea	3	2
Respiratory		
Upper Respiratory Tract Infection	5	6
Sinusitis	4	3
Pharyngitis	1	3
Urinary		
Urinary Tract Infection	2	7
Female Reproductive		
Leukorrhea	7	3
Vaginitis	5	2
Vaginal Discomfort/Pain/Irritation	5	5
Vaginal Hemorrhage	4	5
Asymptomatic Genital Bacterial Growth	4	6
Breast Pain	1	7
Resistance Mechanisms		
Genital Moniliasis	6	7
Body as a Whole		
Flu-Like Symptoms	3	2
Hot Flushes	2	3
Allergy	1	4
Miscellaneous		
Family Stress	2	3

Other adverse events (listed alphabetically) occurring at a frequency of 1 to 3% in the two pivotal controlled studies by patients receiving ESTRING include: anxiety, bladder discomfort, bronchitis, chest pain, cystitis, dermatitis, diarrhea, dyspepsia, dysuria, flatulence, gastritis, genital eruption, urogenital pruritus, hemorrhoids, hyperhidrosis, leg edema, migraine, otitis media, skin hypertrophy, syncope, toothache, tooth disorder, urinary incontinence.

Less common clinical trial adverse reactions
The following additional adverse events were reported at least once by patients receiving ESTRING in the worldwide clinical program, which includes controlled and uncontrolled studies. A causal relationship with ESTRING has not been established.

Body as a Whole:	Allergic reaction
CNS/Peripheral Nervous System:	dizziness
Gastrointestinal:	enlarged abdomen, vomiting
Metabolic/Nutritional Disorders:	weight decrease or increase
Musculoskeletal:	arthropathy (including arthrosis)
Psychiatric:	depression, decreased libido, nervousness
Reproductive:	breast engorgement, breast enlargement, intermenstrual bleeding, genital edema, vulval disorder
Skin/Appendages:	pruritus, pruritus ani
Urinary:	micturition frequency, urethral disorder
Vascular:	thrombophlebitis
Vision:	abnormal vision

The following additional adverse reactions have been reported with estrogens:

Genitourinary system: increase in size of uterine leiomyomata; vaginitis, including vaginal candidiasis; changes in cervical ectropion; ovarian cancer; endometrial cancer

Breasts: pain, nipple discharge, galactorrhea; fibrocystic breast changes; breast cancer

Cardiovascular: pulmonary embolism; myocardial infarction; stroke

Gastrointestinal: pancreatitis, enlargement of hepatic hemangiomas

Skin: rash

Central Nervous System: mental depression; exacerbation of chorea; nervousness; mood disturbances; irritability; exacerbation of epilepsy, dementia

Miscellaneous: aggravation of porphyria; arthralgias; leg cramps; angioedema; anaphylactoid/anaphylactic reactions; hypocalcemia (preexisting condition); exacerbation of asthma; increased triglycerides.

If adverse symptoms persist, the prescription of HRT should be re-considered.

Post-Market Adverse Drug Reactions

A few cases of ring adherence to the vaginal wall, making ring removal difficult, have been reported. Vaginal wall ulceration or erosion has been reported in women using vaginal rings and should be carefully evaluated. If an ulceration or erosion has occurred, consideration should be given to leaving the ring out and not replacing it until healing is complete in order to prevent the ring from adhering to the healing tissue.

A few cases of bowel obstruction and vaginal ring use have been reported. Persistent abdominal complaints consistent with obstruction should be carefully evaluated.

A few cases of toxic shock syndrome have been reported in women using vaginal rings (see **WARNINGS AND PRECAUTIONS-Genitourinary- Toxic Shock Syndrome**).

Cases of hypersensitivity, including hospitalization, have been reported in women using vaginal rings (see **WARNINGS AND PRECAUTIONS**).

DRUG INTERACTIONS

Overview

ESTRING is a local vaginal estrogen therapy product. The following drug-interactions are based on the experience of systemic estrogen treatment.

Estrogens may diminish the effectiveness of anticoagulant, antidiabetic and antihypertensive agents.

Preparations inducing liver enzymes (e.g., barbiturates, hydantoins, carbamazepine, meprobamates, or rifampicin) can enhance estrogen metabolism, resulting in breakthrough bleeding or vaginal spotting.

Drug-Drug Interactions

No formal Drug-Drug Interaction studies with ESTRING have been conducted.

In vitro and in vivo studies have shown that systemic estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen metabolism.

Inducers of CYP3A4 such as phenobarbital, carbamazepine, and rifampin may reduce plasma concentrations of estrogens, possibly resulting in a decrease in systemic effects and/or changes in the uterine bleeding profile.

Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir may increase plasma concentrations of estrogens and may result in side effects.
Ritonavir and nelfinavir, although known as strong inhibitors, by contrast exhibit inducing properties when used concomitantly with steroid hormones.

Use of ESTRING should be discontinued during treatment with vaginal antimicrobial therapy (see **WARNINGS AND PRECAUTIONS-Genitourinary – Vaginal Infection**).

Drug-Food Interactions

Inhibitors of CYP3A4 such as grapefruit juice may increase plasma concentrations of estrogens and may result in side effects.

Drug-Herb Interactions

Inducers of CYP3A4 such as St. John's Wort preparations (Hypericum perforatum) may reduce plasma concentrations of estrogens, possibly resulting in a decrease in systemic effects and/or changes in the uterine bleeding profile.

It was found that some herbal products (e.g. St. John's Wort) which are available as over-the-counter (OTC) products might interfere with steroid metabolism and therefore alter the efficacy and safety of estrogen/progestin products.

Physicians and other health care providers should be aware of other non-prescription products concomitantly used by the patient, including herbal and natural products from health stores.

Drug-Laboratory Test Interactions

The results of certain endocrine and liver function tests may be affected by estrogen-containing products:

- Increased prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of anti-factor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity; increased norepinephrine-induced platelet aggregability.
- Increased thyroxine-binding globulin (TBG), leading to increased circulating total thyroid hormone levels, as measured by protein-bound iodine (PBI), T4 levels (by column or by radioimmunoassay) or T3 levels by radioimmunoassay. T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered. Patients on thyroid replacement therapy may require higher doses of thyroid hormone.
- Other binding proteins may be elevated in serum, (i.e., corticosteroid binding globulin [CBG], sex hormone-binding globulin [SHBG]), leading to increased circulating corticosteroid and sex steroids, respectively. Free hormone concentrations may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

- Increased plasma HDL and HDL2 cholesterol subfraction concentrations, reduced LDL cholesterol concentration, increased triglycerides levels, increased phospholipids concentration.

- Impaired glucose tolerance.

The results of the above laboratory tests should not be considered reliable unless therapy has been discontinued for two to four weeks.

The pathologist should be informed that the patient is receiving hormone replacement therapy (HRT) when relevant specimens are submitted.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Some women may be unsuitable for treatment with ESTRING, in particular those with short narrow vaginas due to previous surgery or the effect of atrophy, or those with a degree of utero-vaginal prolapse severe enough to prevent retention of the ring.

ESTRING should be prescribed with an appropriate dosage of a progestin for women with intact uteri in order to prevent endometrial hyperplasia/carcinoma. Progestin therapy is not required as part of hormone replacement therapy in women who have had a previous hysterectomy.

The maximum recommended duration of continuous therapy is 2 years**.**

Recommended Dose and Dosage Adjustment

One ESTRING (estradiol vaginal ring) is to be inserted as deeply as possible into the upper one-third of the vaginal vault. The ring is to remain in place continuously for three months, after which it is to be removed and, if continuation of therapy is deemed appropriate, replaced by a new ring. The need to continue treatment should be assessed at 3 or 6 month intervals.

Missed Dose

As ESTRING is a symptomatic treatment indicated for the postmenopausal urogenital complaints due to estrogen deficiency, ESTRING may be reintroduce at any time following a period without treatment (missed dose), as long as the patient is still an appropriate candidate for this product. The need to continue treatment should be assessed at 3- to 6-month intervals.

Administration

Instructions for Insertion

ESTRING (estradiol vaginal ring) insertion

The ring should be pressed into an oval and inserted into the upper third of the vaginal vault. The exact position is not critical. When ESTRING is in place, the patient should not feel anything. If the patient feels discomfort, ESTRING is probably not far enough inside. Gently push ESTRING further into the vagina.

ESTRING use
ESTRING should be left in place continuously for 90 days and then, if continuation of therapy is deemed appropriate, replaced by a new ESTRING. The patient should not feel ESTRING when it is in place and it should not interfere with sexual intercourse. Straining at defecation may make ESTRING move down in the lower part of the vagina. If so, it may be pushed up again with a finger. If ESTRING is expelled totally from the vagina, it should be rinsed in lukewarm water and reinserted by the patient (or doctor/nurse if necessary).

ESTRING removal
ESTRING may be removed by hooking a finger through the ring and pulling it out. For patient instructions, see **PATIENT INFORMATION**.

Retention of the ring for greater than 90-days does not represent overdosage but will result in progressively greater underdosage with the attendant risk of loss of efficacy and increasing risk of vaginal infections and/or erosions.

OVERDOSAGE

Symptoms of overdose

Numerous reports of ingestion of large doses of estrogen products and estrogen-containing oral contraceptives by young children have not revealed acute serious ill effects. Overdosage with estrogen may cause nausea and vomiting, breast discomfort and tenderness, abdominal pain, drowsiness/fatigue, fluid retention, bloating, withdrawal bleeding or vaginal bleeding in women.

Treatment of overdose

Treatment should be discontinued and symptomatic treatment administered.

It is highly unlikely that overdosage would occur with ESTRING (estradiol), as the principle of its release mechanism prevents overdose.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

ESTRING (estradiol vaginal ring) is a slightly opaque ring with a whitish core containing a drug reservoir of 2 mg estradiol. Estradiol, silicone polymers and barium sulfate are combined to form the ring. When placed in the vagina, ESTRING releases estradiol, approximately 7.5 μg/24 hours, in a consistent stable manner over 90 days. ESTRING has the following dimensions: outer diameter 55 mm; cross-sectional diameter 9 mm; core diameter 2 mm. One ESTRING should be inserted into the upper third of the vaginal vault, to be worn continuously for three months.

At menopause the ovaries cease to secrete estradiol (E_2), leading to symptoms of estrogen deficiency such as sweating, hot flushes and sleep disturbance. A couple of years after the actual menopause, increasing numbers of women also report symptoms of urogenital estrogen deficiency such as vaginal dryness, genital pruritus, dyspareunia, dysuria and urinary urgency. These latter symptoms respond well to vaginal estrogen replacement therapy.

Pharmacodynamics

The estradiol from ESTRING (estradiol vaginal ring) replaces the missing or decreasing endogenous estrogen production in the post-menopausal woman, and eliminates or reduces urogenital estrogen deficiency signs and symptoms. Substitution therapy with estradiol vaginal ring restores vaginal pH to pre-menopausal values and restores the histology and physiology of the vaginal and urethral epithelium to the pre-menopausal state.

In vivo, estrogens diffuse through cell membranes, distribute throughout the cell, bind to and activate the estrogen receptors, thereby eliciting their biological effects. Estrogen receptors have been identified in tissues of the reproductive tract, breast, pituitary, hypothalamus, liver and bone of women. ESTRING delivers estradiol constantly at a mean rate of 7.5 µg/24 hours for a period of up to 90 days. Its use in post-menopausal patients in Phase I and II studies showed no apparent effects on systemic levels of hepatic protein SHBG, or FSH. Lowering of the pretreatment vaginal pH from a mean of 6.0 to a mean of 4.6 (as found in fertile women) over the 12 to 48 week treatment period, and improvements evident in the vaginal mucosal epithelium seen in all studies attest to the local dynamic effects of estrogens.

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.

Pharmacokinetics

Absorption

Estrogens used in therapeutics are well absorbed through the skin, mucous membranes, and the gastrointestinal (GI) tract. The vaginal delivery of estrogens circumvents first-pass metabolism possibly reducing the induction of several other hepatic proteins.

In a Phase I study of 14 postmenopausal women, the insertion of ESTRING (estradiol vaginal ring) rapidly increased serum estradiol (E_2) levels attesting to the rapid absorption of estradiol via the vaginal mucosa. The time to attain peak serum estradiol levels (T_{max}) was 0.5 to 1 hour. Peak serum estradiol concentrations post-initial burst declined rapidly over the next 24 hours and were virtually indistinguishable from the baseline mean (range: 5 to 22 pg/mL). Serum levels of estradiol and estrone (E_1) over the following 12 weeks during which the ring was maintained in the vaginal vault remained relatively unchanged (see Table 2). The initial estradiol peak post-application of the second ring in the same women resulted in 38% lower C_{max}, apparently due to reduced systemic absorption via the revitalized vaginal epithelium. The relative systemic exposure from the initial peak of ESTRING accounted for approximately 4% of the total estradiol exposure over the 12 week period.

The constant and stable release of estradiol from ESTRING was demonstrated in a Phase II study of 166-222 post-menopausal women who inserted up to four rings consecutively at three month intervals. Low dose systemic delivery of estradiol from ESTRING resulted in mean steady state serum estradiol estimates of 7.8, 7.0, 7.0,8.1 pg/mL at weeks 12, 24, 36, and 48, respectively. Similar reproducibility is also seen in levels of estrone. Lower systemic exposure to estradiol and estrone is further supported by serum levels measured during a pivotal Phase III study.

In post-menopausal women, the mean dose of estradiol systemically absorbed unchanged from ESTRING is 8% [95% CI: 2.8-12.8%] of the daily amount released locally. Low systemic exposure to estradiol and estrone resulting from ESTRING should elicit lower estrogen-dependent effects.

After a brief initial peak (~50µg), estradiol vaginal ring releases a low and consistent amount of estradiol, approximately 7.5 µg/24 hours, during 90 days. Average *in vitro* release rates over 7 batches were:

Day 1	**Day 9**	**Day 16**	**Day 45**	**Day 90**
47.6±6.4	7.3±0.4	7.7±0.4	7.3±0.2	7.3±0.5

(in µg/24h)

The average *in vivo* release rate over an 88.4 day period was 9.0±0.06 µg/24h (n=215), calculated by subtracting the amount of estradiol in the ring at the end of the treatment period from the amount of estradiol measured in the ring before treatment, and averaging the amount over the treatment period. This gives a slightly higher value than is actually released, since it does not take the initial burst of estradiol into account.

Distribution

Circulating, unbound estrogens are known to modulate pharmacological response. Estrogens circulate in blood bound to sex-hormone binding globulin (SHBG) and albumin. A dynamic equilibrium exists between the conjugated and the unconjugated forms of estradiol and estrone, which undergo rapid interconversion.

Metabolism

Exogenously delivered or endogenously derived estrogens are primarily metabolized in the liver to estrone and estriol, which are also found in the systemic circulation. Estrogen metabolites are primarily excreted in the urine as glucuronides and sulphates. Of the several estrogen metabolites, urinary estrone and estrone sulphate (E_1S), post-ESTRING use, are in the normal post-menopausal range.

Excretion

Mean percent dose excreted in the 24-hour urine as estradiol, 4 and 12 weeks post-application of ESTRING in a Phase I study was 5 and 8%, respectively, of the daily released amount.

TABLE 2:PHARMACOKINETIC MEANS ESTIMATES FOLLOWING ESTRING APPLICATION

Estrogen	C_{max} (pg/mL)	$C_{ss\text{-}48\ hr}$ (pg/mL)	$C_{ss\text{-}4w}$ (pg/mL)	$C_{ss\text{-}12w}$ (pg/mL)
Estradiol (E_2)	63.2[a]	11.2	9.5	8.0
Baseline-adjusted E_2[b]	55.6	3.6	2.0	0.4
Estrone (E_1)	66.3	52.5	43.8	47.0
Baseline-adjusted E_1	20.0	6.2	-2.4	0.8

[a] n=14 [b] Based on means

Special Populations
ESTRING has not been studied in patients with hepatic or renal impairment.

STORAGE AND STABILITY

Store at room temperature (15-30ºC). Keep in a safe place out of the reach of children and pets.

SPECIAL HANDLING INSTRUCTIONS
Not applicable

DOSAGE FORMS, COMPOSITION AND PACKAGING

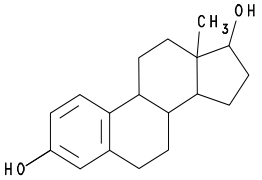
ESTRING is available by prescription only.

ESTRING (estradiol vaginal ring) is a slightly opaque ring, made of a silicone elastomer sheath surrounding a whitish silicone elastomer core, containing a drug reservoir of 2 mg estradiol, barium sulphate as a marker and silicone fluid as a dispersing agent. Each ring contains 2 mg estradiol which is released slowly, 7.5 µg/24 hours. One ring is individually packed in a heat-sealed rectangular pouch consisting of, from outside to inside: Polyester/aluminum foil/low density polyethylene. The pouch is provided with a tear-off notch on one side. Each pouch is packed into a cardboard carton containing a Patient Information Leaflet.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Trade Name	ESTRING
Proper Name	Estradiol
Chemical Names	Estra-1,3,5(10)-triene-3,17-diol.(17□) Estra-1,3,5(10)-triene-3, 1β-diol.
Molecular Formula	$C_{18}H_{24}O_2$
Structural Formula	
Molecular Weight	272.37
Physical Form	White crystalline powder. Almost insoluble in water, soluble in alcohol, dioxane and other organic solvents.
Melting point:	173 - 179°C: $[\alpha]^{25}$: +76° to 83° (dioxane).
Absorption	UV max: 225 and 280 nm.
pKa	10.30.

CLINICAL TRIALS

Two pivotal controlled studies have demonstrated the efficacy of ESTRING (estradiol vaginal ring) in the treatment of post-menopausal urogenital symptoms due to estrogen deficiency.

In a U.S. study where ESTRING was compared with conjugated estrogens vaginal cream, no difference in efficacy between the treatment groups was found with respect to improvement in the physician's global assessment of vaginal symptoms (83% and 82% of patients receiving ESTRING and cream, respectively) and in the patient's global assessment of vaginal symptoms (83% and 82% of patients receiving ESTRING and cream, respectively) after 12 weeks of treatment. In an Australian study, ESTRING was also compared with conjugated estrogens vaginal cream and no difference in the physician's assessment of improvement of vaginal mucosal atrophy (79% and 75% for ESTRING and cream, respectively) or in the patient's assessment of improvement in vaginal dryness (82% and 76% for ESTRING and cream, respectively) after 12 weeks of treatment.

In the U.S. study, symptoms of dysuria and urinary urgency improved in 74% and 65%, respectively, of patients receiving ESTRING as assessed by the patient. In the Australian study, symptoms of dysuria and urinary urgency improved in 90% and 71%, respectively, of patients receiving ESTRING as assessed by the patient.

In both studies, ESTRING and conjugated estrogens vaginal cream had a similar ability to reduce vaginal pH levels and to mature the vaginal mucosa (as measured cytologically using the maturation index and/or the maturation value) after 12 weeks of treatment. In supportive studies, ESTRING

was also shown to have a similar significant treatment effect on the maturation of the urethral mucosa.

Endometrial overstimulation, as evaluated in non-hysterectomized patients participating in the U.S. study by the progestogen challenge test and pelvic sonogram, was reported for none of the 58 (0%) patients receiving ESTRING and 4 of the 35 patients (11%) receiving conjugated estrogens vaginal cream.

Of the U.S. women who completed 12 weeks of treatment, 95% rated product comfort for ESTRING as excellent or very good compared with 65% of patients receiving conjugated estrogens vaginal cream, 95% of ESTRING patients judged the product to be very easy or easy to use compared with 88% of cream patients, and 82% gave ESTRING an overall rating of excellent or very good compared with 58% for the cream.

Clinical 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.

TOXICOLOGY

No toxicology studies have been performed on ESTRING. The biological safety of the silicone elastomer has been studied in various in vitro and in vivo test models.

Chronic Toxicity / Carcinogenicity
Fisher 344 rats were implanted with the silicone elastomer (Silastic Q7-4750) or a negative control (polyethylene USP) for 104 weeks. Sham-operated animals served as control. There were no differences in neoplasia incidence between implanted and sham-operated controls. Long-term implantation induced a chronic inflammatory reaction at the implantation sites with fibrous capsular formation that was comparable with that in the negative control group. No toxic reaction or tumour formation was observed with the silicone elastomer.

Special Toxicity
Silicone elastomer (Silastic Q7-4750) was implanted into the proximal vagina of six rabbits; 8 other rabbits served as sham-operated controls. The animals were sacrificed after 72 hours and the vaginas were examined. A slight to moderate local irritation of the vagina was observed in the treated animals compared to the controls. In one test animal, there was a small epithelial ulceration. The changes observed were most likely due to a reaction to the trauma caused by the implant.

Twelve rabbits were divided into 4 groups and received 4 intramuscular and 2 subcutaneous implants of the silicone elastomer (Silastic Q7-4750) and a negative control (polyethylene USP), and were observed after periods of either 3, 10, 30, or 90 days. No remarkable changes were observed in body organs examined from the animals killed after 10 and 90 days.

Intradermal injections of saline extracts of the silicone elastomer (Silastic Q7-4750) caused no reaction in 8 rabbits up to 72 hours after injection.

Silicone elastomer (Silastic Q7-4750) was applied to the epidermis 4 times in 10 days in 30 guinea pigs. No animals showed irritation or sensitization to the silicone elastomer at any test site.

Saline extracts of the silicone elastomer (Silastic Q7-4750) were not pyrogenic 3 hours after intravenous injection in 5 rabbits.

In vitro studies of the silicone elastomers (Silastic Q7-4750 and Q7-4735) and their saline extracts showed no cytotoxicity or hemolysis. Both silicone elastomers demonstrated a greater thrombogenic potential than the negative control, but ESTRING is not intended for direct contact with blood.

Reproduction
No reproduction toxicity studies have been performed with ESTRING.

Mutagenicity
Mutagenicity of the silastic elastomer is unknown.

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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

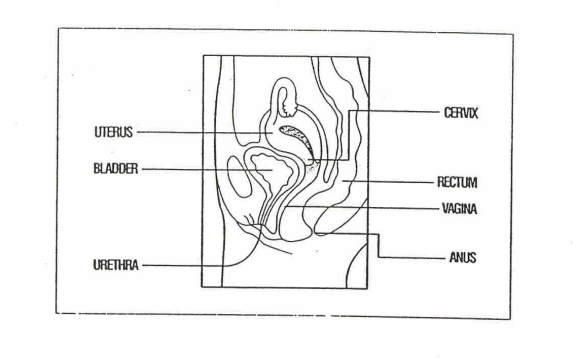
Some medications can interfere with the action of estrogens and estrogens can interfere with the effects of other medications. When you are using ESTRING it is important to let your doctor or pharmacist know if you are taking any other medications, including prescription medications, over-the-counter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

PROPER USE OF THIS MEDICATION

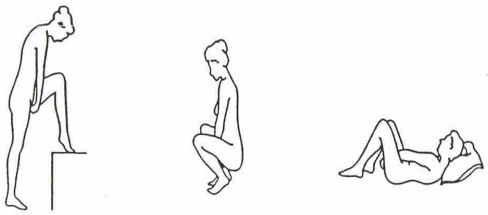
Usual Dose:
ESTRING can be inserted or removed by you or your doctor. ESTRING vaginal ring is to be worn continuously for 90 days.

A Guide to ESTRING Insertion and Removal:

FEMALE ANATOMY

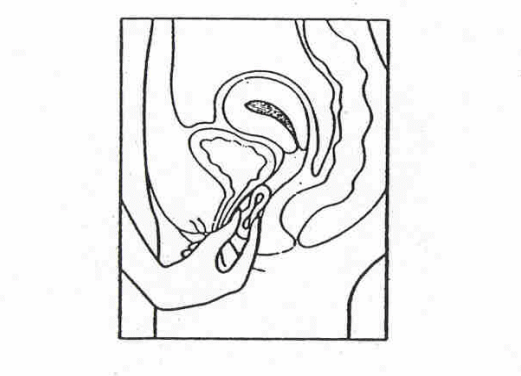


ESTRING INSERTION
ESTRING can be inserted and removed by you or your doctor. To insert ESTRING yourself, choose the position that is most comfortable for you: standing with one leg up, squatting, or lying down.



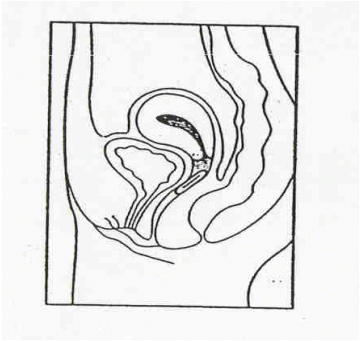
1. After washing and drying your hands, remove ESTRING from its pouch using the tear-off notch on the side. (Since the ring becomes slippery when wet, be sure your hands are dry before handling it).

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**).

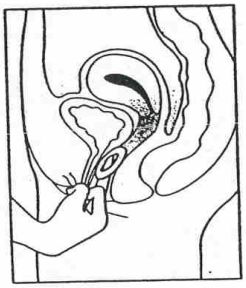
ESTRING USE
Once inserted, ESTRING should remain in place in the vagina for 90 days. Most women and their partners experience no discomfort with ESTRING in place during intercourse, so it is NOT necessary that the ring be removed. If ESTRING should cause you or your partner any discomfort, you may remove 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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