Product Monograph

Including Patient Medication Information

PrESTRING *

(17 β-Estradiol)

Vaginal Ring, 2 mg

Estrogen

Pfizer Canada ULC
17,300 Trans-Canada Highway
Kirkland, Quebec H9J 2M5

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Pfizer Canada ULC, Licensee

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Recent Major Label Changes

7. Warnings and Precautions, Carcinogenesis and Genotoxicity	01/2026

Table of Contents

Certain sections or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

Part 1: Healthcare Professional Information

1. Indications

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.

1.1. Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2. Geriatrics

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 (See 7 Warnings and Precautions: Special Populations: Geriatrics).

2. 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)

3. Serious Warnings and Precautions Box

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.

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.

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.

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

4. Dosage and Administration

4.1. 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**.**

4.2. 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.

4.4. 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 healthcare professional if necessary).

ESTRING removal

ESTRING may be removed by hooking a finger through the ring and pulling it out. For patient instructions, see Patient Medical 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.

4.5. Missed Dose

As ESTRING is a symptomatic treatment indicated for the postmenopausal urogenital complaints due to estrogen deficiency, ESTRING may be reintroduced 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.

5. Overdose

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.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6. Dosage Forms, Strengths, Composition, and Packaging

Description

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.

7. Warnings and Precautions

See 3 Serious Warnings and Precautions Box.

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 Genotoxicity

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).

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.

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.

It is recommended that estrogens not be given to women with existing breast cancer or those with a previous history of the disease (see 2 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**.**

Epidemiological data/meta-analysis: A large meta-analysis of prospective cohort studies based on 108, 647 postmenopausal women who developed breast cancer at mean age of 65 years old, also reported an increased risk of developing breast cancer in women treated with estrogen plus progestin therapy or estrogen alone therapy. Not only the risk of breast cancer increases with the duration of use, but also the risk could last up to >10 years after discontinuation of treatment. Observational studies also suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen plus progestin therapy as compared to estrogen-alone therapy. These studies have not generally found significant variation in the risk of breast cancer among different estrogen plus progestin combinations, doses, or routes of administration.

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.

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.

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. 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.

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).

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.

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.

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.

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 9 Drug Interactions: Drug-Laboratory Test Interactions).

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.

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.

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 7 Warnings and Precautions: Monitoring and Laboratory Tests.

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.

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.

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.

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).

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.

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).

Epilepsy

HRT may cause an exacerbation of epilepsy.

Perioperative Considerations

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.

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.

7.1. Special Populations

7.1.1. Pregnancy

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.

7.1.2. Breastfeeding

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.

7.1.3. Pediatrics

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

7.1.4. Geriatrics

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.

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.

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.

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.

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.

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.

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.

8. Adverse Reactions

8.1. Adverse Reaction Overview

See 7 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 7 Warnings and Precautions).
- **Blood and lymphatic system disorders**
  Altered coagulation tests (see 7 Warnings and Precautions: Drug-Laboratory Test Interactions)
- **Cardiac disorders**
  Palpitations; coronary thrombosis; increase in blood pressure (see 7 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.

8.2. Clinical Trial Adverse 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.

8.3. 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.

8.4. Post-Market Adverse 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 7 Warnings and Precautions: Genitourinary).

Cases of hypersensitivity, including hospitalization, have been reported in women using vaginal rings (see 7 Warnings and Precautions).

9. Drug Interactions

9.2. 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.

9.4. 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 7 Warnings and Precautions: Genitourinary).

9.5. Drug-Food Interactions

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

9.6. 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.

9.7. 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.

10. Clinical Pharmacology

10.1. 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.

10.2. 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.

10.3. 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.

Elimination

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 and conditions

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

11. Storage, Stability, and Disposal

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

Part 2: Scientific Information

12. Pharmaceutical Information

Drug Substance

Trade name: ESTRING

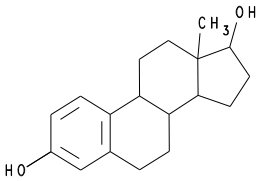
Proper name: Estradiol

Chemical name: Estra-1,3,5(10)-triene-3,17-diol.(17)

Estra-1,3,5(10)-triene-3, 1β-diol.

Molecular formula and molecular mass: $C_{18}H_{24}O_2$ 272.37 g/mol

Structure (for biologics)/Structural formula:



Physicochemical properties:

- 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.

13. Clinical Trials

13.1. Clinical Trials by Indication

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.

14. Microbiology

ESTRING is not an antimicrobial drug.

15. Non-Clinical 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.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrESTRING *

Estradiol Vaginal Ring

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

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

Serious warnings and precautions box

In postmenopausal women taking estrogen with progestin (another female hormone), there is an increased risk of:

- breast cancer
- heart attack
- stroke
- blood clots in both lungs and large veins

In postmenopausal women taking estrogen-alone who had prior surgery to remove the uterus (called a hysterectomy), there is an increased risk of:

- stroke
- blood clots in the deep veins of the leg or arm

Estrogens, like that in ESTRING, should:

- not be used for the prevention of heart disease or stroke.
- be used at the **lowest effective dose** and for the **shortest period of time** possible. You should have regular medical check-ups.

What ESTRING is used for:

ESTRING is used to relieve menopausal vaginal and urinary symptoms caused by low estrogen. Symptoms include vaginal dryness, genital itching, burning and pain during intercourse, sensation of urinary urgency and pain on urination.

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

The maximum recommended time you should be taking ESTRING continuously is 2 years.

How ESTRING works:

ESTRING is a vaginal ring that contains estradiol, which is a type of estrogen. At menopause, the body stops making estrogens. The declining estrogen levels associated with menopause may result in thinning and drying of the tissue of the urinary tract and vagina. ESTRING releases estradiol into the vagina in a consistent, stable manner.

ESTRING restores levels of estrogen to relieve the symptoms of menopausal women.

The ingredients in ESTRING are:

Medicinal ingredient(s): 17 β-Estradiol

Non-medicinal ingredients: Silicone elastomer, silicone fluid and barium sulfate.

ESTRING comes in the following dosage form(s):

Ring: 2 mg

Do not use ESTRING if you:

- have (or have had) a history of known or suspected estrogen-dependency cancer. An example is cancer of the uterus (endometrial cancer).
- have excessive thickening of the womb lining (endometrial hyperplasia)
- have (or have had) a history of known or suspected breast cancer
- have experienced undiagnosed or abnormal vaginal bleeding
- have liver disease
- have (or have had) blood clot disorders. This including blood clots in the legs, lungs or veins.
- have partial or complete loss of vision due to blood vessel disease in the eye
- are pregnant or think you may be pregnant
- are breast feeding
- are allergic to any of the ingredients of ESTRING or its container
- have or have had a stroke, heart attack, or coronary artery disease
- have or had been diagnosed with a rare disorder where you have a deficiency of enzymes involved in the production of heme known as porphyria
- have known blood disorders that may give you a greater risk of blood clots (e.g. protein C, protein S, or antithrombin deficiency)

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

- have a history of allergy or intolerance to any medications or other substances
- are taking thyroid hormone replacement therapy
- have a short or narrow vagina, vaginal stenosis, vaginal prolapse
- have a history of uterine fibroids or endometriosis
- have a history of jaundice (yellowing of the eyes and/or skin) or itching related to estrogen use
- have a history of migraine headache
- have a history of high blood pressure
- have a personal or family history of blood clots
- have a history of kidney disease, asthma or epilepsy (seizures)
- have been diagnosed with diabetes
- think you may have a vaginal infection
- smoke
- 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

Other warnings you should know about:

- **Overgrowth of the lining of the uterus and cancer of the uterus:** Taking estrogen-only HRT (hormone replacement therapy) will increase your risk of excessive thickening of the lining of the womb (endometrial hyperplasia) and cancer of the womb (endometrial cancer). If you still have your uterus, your healthcare professional will prescribe a progestin (another hormone drug) for a certain number of days of each month to reduce the risk of endometrial hyperplasia (abnormal growth of the lining of the uterus). This will reduce the risk of developing these side effects. You should discuss progestin therapy and risk factors for endometrial hyperplasia and endometrial cancer with your healthcare professional. You should also report any unexpected or unusual vaginal bleeding to your healthcare professional.

    - If you have had your uterus removed, you are not at risk of developing endometrial hyperplasia or endometrial cancer. Progestin therapy is not generally required in women who have had a hysterectomy (surgical removal of the uterus).

- **Ovarian Cancer:** Taking hormone replacement therapy [HRT] for five years or more may increase your risk of developing ovarian cancer.

- **Abnormal Blood Clotting*:*** Taking estrogen can increase your risk of developing blood clots. You should discuss risk factors for blood clots with your healthcare professional since blood clots can be life threatening or cause serious disability. Consult your healthcare professional if:
    - you or a family member have a history of blood clots
    - you smoke
    - you are severely overweight

  The risk of blood clots also can temporarily increase:

    - if you are inactive for long periods of time
    - following major surgery.

- **Dementia:** Your risk of developing dementia (memory loss) is increased if you are a woman aged 65 and over taking estrogen with progestin.

- **Gallbladder Disease:** Your risk of developing gallbladder disease that requires surgery is increased when taking estrogens.

- **Breast Cancer**:
    - Estrogens should not be taken by women who have a personal history of breast cancer.
    - Talk to your healthcare professional before starting hormone therapy if you have a personally history, family history of breast cancer or have had breast lumps, breast biopsies or abnormal mammograms (breast x-rays)

- There is an increased risk for breast cancer in women taking menopausal hormone therapy (MHT) for many years. The risk increases the longer you take MHT and persists for more than 10 years after stopping treatment with both estrogen plus progestin therapy and estrogen-alone therapy.

- **Check-ups and testing:** You will have regular visits with your healthcare profession, before and during your treatment. They will:
  - Complete a physical examination on you before you begin treatment. Your visit may include a blood pressure check, a breast exam, a Pap smear and pelvic exam. You should have a mammogram before starting treatment and at regular intervals as recommended by your healthcare professional. Your healthcare professional may recommend some blood tests
  - Conduct regular follow-up examinations at least once a year to identify side effects associated with the use of ESTRING. Your first follow-up visit should be within 3 to 6 months of starting treatment.
  - Advise you to regularly check your own breasts. Speak to your healthcare professional if you are uncertain on the technique to perform a breast self-examination

- **X-rays:** You should remove ESTRING before any x-ray procedures of the lower abdominal tract. The barium sulphate containing core is visible on x-ray and could disturb the procedure or evaluation of x-rays.

- **During treatment for vaginal infection with vaginal therapy**: It is recommended that you speak to your healthcare professional about stopping your ESTRING treatment while using other medications to treat a vaginal infection. Use of ESTRING can continue after ending your treatment with other vaginal medication and after first speaking with your healthcare professional.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with ESTRING:

- Antimicrobial vaginal medications
- Anticonvulsants used in the treatment of epilepsy such as hydantoins, phenobarbital or carbamazepine
- Antibiotic medications such rifampicin, rifampin, erythromycin, clarithromycin
- Medications used to treat HIV such as ritonavir and nelfinavir
- Antifungal medications such as ketoconazole, itraconazole
- Blood thinner medications
- Diabetic medications
- High blood pressure medications
- Meprobamate, a medication used to treat anxiety disorders
- Barbiturates, a sedative-hypnotic medication

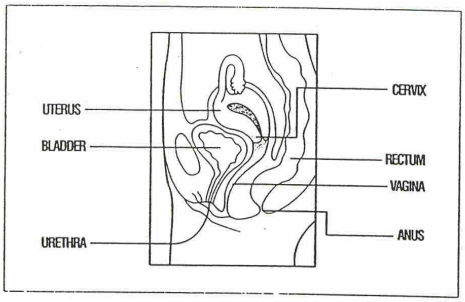
How to use ESTRING:

- Read these instructions about the right way to insert, remove, clean, and dispose of (throw away) ESTRING.
- Use ESTRING exactly as your healthcare professional tells you to use it. Speak to your healthcare professional if you have any questions on how to use ESTRING.
- ESTRING can be inserted or removed by you or your doctor.
- The maximum recommended time to continuously use ESTRING is 2 years.

Usual dose:
ESTRING vaginal ring is to be worn continuously for 90 days. 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.

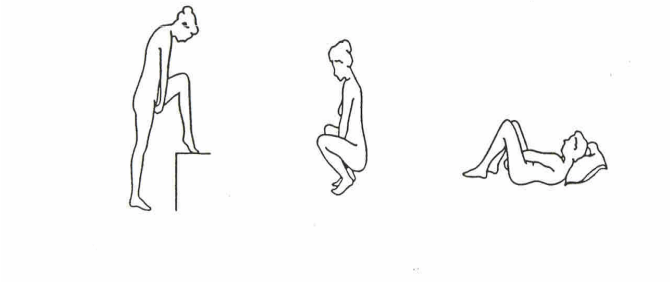
A Guide to ESTRING Insertion and Removal:

FEMALE ANATOMY



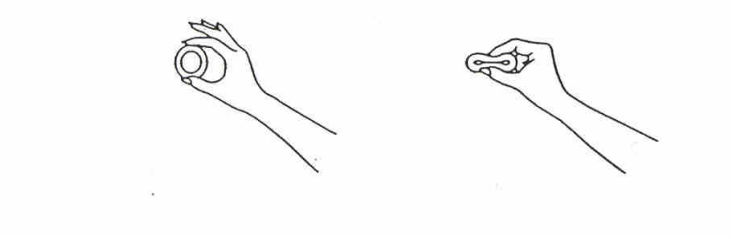
How to insert ESTRING

To insert ESTRING yourself, choose the position that is most comfortable for you: standing with one leg up, squatting, or lying down.

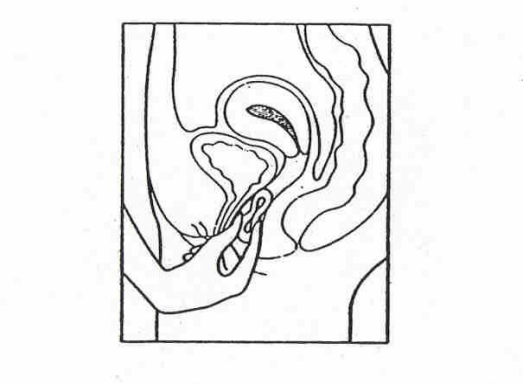


1. After washing and drying your hands, remove ESTRING from its pouch using the tear-off notch on the side. Since the ring becomes slippery when wet, be sure your hands are dry before handling it.

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

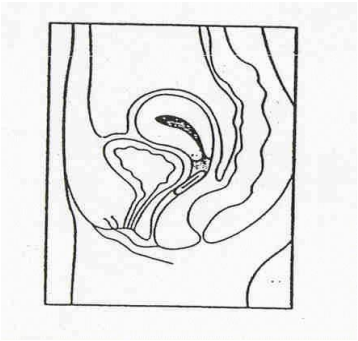


3. Gently push the compressed ring into your vagina as far as you can.



Placement of ESTRING

- 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**).

Using ESTRING

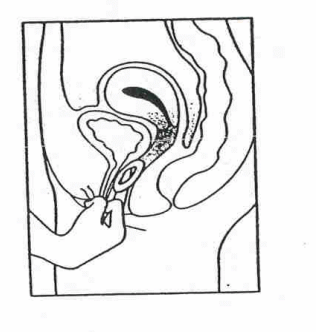
- It is NOT necessary to remove ESTRING during intercourse as most women and their partners experience no discomfort. You may remove ESTRING before sex if it causes you or your partner any discomfort. Be sure to reinsert ESTRING as soon as possible afterwards (See **How to remove ESTRING** below).
- 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.
- ESTRING may fall out following intense straining or coughing. If this should occur, simply wash ESTRING with lukewarm (NOT hot) water and reinsert it.

How 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 (See figure under **How to insert ESTRING**).

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.

Overdose:

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.

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

Missed dose:
ESTRING may be reintroduced at any time following a period without treatment (missed dose), as long as your healthcare professional considers treatment with ESTRING is still appropriate for you.

Possible side effects from using ESTRING:

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

- Breast pain
- Feeling bloated
- Hair loss
- Headache
- Nausea
- Vomiting

Serious side effects and what to do about them

Side Effect/Symptom	Talk to your healthcare professional		Remove the ring and call your healthcare professional
	Only if severe	In all cases	
Vaginal hemorrhage (Vaginal bleeding): Abnormal bleeding or spotting from the vagina		√	
Venous thromboembolism (blood clots in veins): Pain in the calves or chest, sudden shortness of breath or coughing blood			√
Migraine with visual disturbances: Severe headache or vomiting, dizziness, seizures, faintness, changes in vision or speech, visual disturbances			√
Stroke (bleeding or blood clot in the brain): sudden numbness, weakness or tingling of the face, arm, or leg, particularly on one side of the body, sudden headache, blurry vision, difficulty swallowing or speaking, or lethargy, dizziness, fainting, vomiting, trouble understanding, trouble with walking and loss of balance			√
Abdominal pain: Pain, swelling or tenderness in the abdomen		√	
Liver problems: yellowing of your skin and eyes (jaundice), right upper stomach area pain or swelling, nausea or vomiting, unusual dark urine, unusual			√

Side Effect/Symptom	Talk to your healthcare professional		Remove the ring and call your healthcare professional
	Only if severe	In all cases	
tiredness, unexplained loss of appetite			
Toxic Shock Syndrome (life threatening infection)**:** fever, nausea, vomiting, diarrhea, muscle pain, dizziness, faintness, or a sunburn-rash on face and body			√
Depression (Persistent sad mood): difficulty sleeping or sleeping too much, changes in appetite or weight, feelings of worthlessness, guilt, regret, helplessness or hopelessness, withdrawal from social situations			√
Vaginal yeast infection (inflammation of the vagina): itching, burning, or discharge from the vagina		√	
Hyperglycemia: (high blood sugar): increased thirst, frequent urination, dry skin, headache, blurred vision and fatigue			√
Hypertension (high blood pressure): shortness of breath, fatigue, dizziness or fainting, chest pain or pressure, swelling in your ankles and legs, bluish colour to your lips and skin, racing pulse or heart palpitations			√
Ovarian cancer: Abdominal bloating or swelling, quickly feeling full when eating, weight loss, discomfort in the pelvic area, fatigue, back pain, changes in bowel habits, frequent need to urinate			√
Gallbladder disease: abdominal pain, nausea and vomiting, fever, and yellowing of the skin (jaundice)			√
Dementia: memory loss, problems communicating or finding words,			√

Side Effect/Symptom	Talk to your healthcare professional		Remove the ring and call your healthcare professional
	Only if severe	In all cases	
confusion, personality changes, anxiety, agitation, paranoia, hallucinations			
Endometrial hyperplasia/cancer (abnormal growth or cancer of the lining of the uterus): vaginal bleeding not associated with a period or after menopause; menstrual bleeding that is heavier or lasts longer than normal; abnormal blood-tinged discharge from the vagina; pain in the pelvis			√
Heart Attack: Crushing chest pain or chest heaviness			√
Hypersensitivity (allergic reaction): Itching, hives, swelling, vaginal discomfort/irritation, redness			√
Peripheral edema (swelling of the legs or hands caused by fluid retention): swollen or puffy legs or hands, feeling heavy, achy or stiff			√
Difficulty removing ring: Ring attaches to vaginal wall or is difficult to remove			√
Intestinal obstruction (blockage that stops or impairs passage of contents of intestines): cramping pain in abdomen that may begin suddenly, bloating, loss of appetite, pain that comes and goes but will then last, nausea and vomiting, constipation or diarrhea			√
Vaginal mucosal erosion/ulceration (small wounds that can form on your vagina): burning sensation, fever, itchiness, painful urination, vaginal discharge			√
Breast abnormalities (including breast cancer): Lumps or discharge from the breast, changes in the nipple, breast enlargement or tenderness		√	

Side Effect/Symptom	Talk to your healthcare professional		Remove the ring and call your healthcare professional
	Only if severe	In all cases	
Edema (fluid retention): unusual swelling of the arms, hands, legs, feet and ankles, face or airway passages			√
Skin Hyperpigmentation (areas of the skin darker than others): brown, black, gray, red or pink spots or patches on skin			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting side effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

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

If you want more information about ESTRING:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.pfizer.ca ; or by calling the distributor Paladin Pharma Inc., at 1-888-867-7426.

This leaflet was prepared by Pfizer Canada ULC.

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