EVAMIST 11-2017

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use EVAMIST safely and effectively. See full prescribing information for EVAMIST.

EVAMIST(estradiol transdermal spray)

Initial U.S. Approval: 1975

WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, BREAST CANCER, PROBABLE DEMENTIA, AND UNINTENTIONAL SECONDARY EXPOSURE TO ESTROGEN

See full prescribing information for complete boxed warning.

Estrogen-Alone Therapy

- **There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens (5.2)**
- **Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia (5.1, 5.3)**
- **The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) (5.1)**
- **The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age and older (5.3)**

Estrogen Plus Progestin Therapy

- **Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia (5.1, 5.3)**
- **The WHI estrogen plus progestin substudy reported increased risks of stroke, DVT, pulmonary embolism (PE), and myocardial infarction (MI) (5.1)**
- **The WHI estrogen plus progestin substudy reported increased risks of invasive breast cancer (5.2)**
- **The WHIMS estrogen plus progestin ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age and older (5.3)**

Unintentional Secondary Exposure

- **Breast budding, breast masses, and gynecomastia have been reported in children following unintentional secondary exposure to Evamist (5.4)**

RECENT MAJOR CHANGES

- Warnings and Precautions Malignant Neoplasms (5.2) 11/2017

INDICATIONS AND USAGE

Evamist is an estrogen indicated for the treatment of moderate to severe vasomotor symptoms due to menopause (1.1)

DOSAGE AND ADMINISTRATION

- One spray once daily each morning to forearm as a starting dose (2.1)
- Increase to two or three sprays daily to forearm based upon clinical response (2.1)

DOSAGE FORMS AND STRENGTHS

- One spray consists of 90 mcL which contains 1.53 mg estradiol (3)

CONTRAINDICATIONS

- Undiagnosed abnormal genital bleeding (4)
- Known, suspected, or history of cancer of the breast (4, 5.2)
- Known or suspected estrogen-dependent neoplasia (4, 5.2)
- Active DVT, PE, or history of these conditions (4, 5.1)
- Active arterial thromboembolic disease (for example, stroke and MI), or history of these conditions (4, 5.1)
- Known anaphylactic reaction or angioedema with Evamist (4)
- Known liver impairment or disease (4, 5.10)
- Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders (4)
- Known or suspected pregnancy (4, 8.1)

WARNINGS AND PRECAUTIONS

- Estrogens increase the risk of gallbladder disease (5.5)
- Discontinue estrogens if severe hypercalcemia, loss of vision, severe hypertriglyceridemia or cholestatic jaundice occurs (5.6, 5.7, 5.10, 5.11)
- Monitor thyroid function in women on thyroid hormone replacement therapy (5.12, 5.21)

ADVERSE REACTIONS

Most common adverse reactions (≥5 percent) are: headache, breast tenderness and nipple pain, nausea, back pain, and nasopharyngitis (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Perrigo at 1-866-634-9120 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Inducers and inhibitors of CYP3A4 may affect estrogen drug metabolism (7.1)

USE IN SPECIFIC POPULATIONS

- Nursing Mothers: Estrogen administration to nursing women has been shown to decrease the quantity and quality of the breast milk (8.3)
- Geriatric Use: An increased risk of probable dementia in women over 65 years of age was reported in the Women's Health Initiative Memory ancillary studies of the Women's Health Initiative (5.3, 8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 08-2017

FULL PRESCRIBING INFORMATION: CONTENTS*

17 PATIENT COUNSELING INFORMATION

17.1 Vaginal Bleeding

17.2 Unintentional Secondary Exposure to Evamist

17.3 Possible Serious Adverse Reactions with Estrogen-Alone Therapy

17.4 Possible Less Serious but Common Adverse Reactions with Estrogen-Alone Therapy

PATIENT INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, BREAST CANCER, PROBABLE DEMENTIA AND UNINTENTIONAL SECONDARY EXPOSURE TO ESTROGEN

Estrogen-Alone Therapy

Endometrial Cancer

There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed and random endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal genital bleeding [see *Warnings and Precautions (5.2)*].

Cardiovascular Disorders and Probable Dementia

Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia *[see Warnings and Precautions (5.1, 5.3,* and *Clinical Studies (14.2, 14.3)].*

The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens (CE) [0.625 mg]-alone, relative to placebo [*see Warnings and Precautions (5.1),* and *Clinical Studies (14.2)]*.

The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE (0.625 mg)-alone, relative to placebo.

It is unknown whether this finding applies to younger postmenopausal women *[see Warnings and Precautions (5.3), Use in Specific Populations (8.5),* and *Clinical Studies (14.3)].*

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and other dosage forms of estrogens.

Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

Estrogen Plus Progestin Therapy

Cardiovascular Disorders and Probable Dementia

Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia *[see Warnings and Precautions (5.1, 5.3),* and *Clinical Studies (14.2)].*

The WHI estrogen plus progestin substudy reported increased risks of DVT, pulmonary embolism (PE), stroke and myocardial infarction (MI) in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral CE (0.625 mg) combined with medroxyprogesterone acetate (MPA) [2.5 mg], relative to placebo *[see Warnings and Precautions (5.1),* and *Clinical Studies (14.2)].*

The WHIMS estrogen plus progestin ancillary study of the WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CE (0.625mg) combined with MPA (2.5 mg), relative to placebo. It is unknown whether this finding applies to younger postmenopausal women *[see Warnings and Precautions (5.3), Use in Specific Populations (8.5),* and *Clinical Studies (14.3)].*

Breast Cancer

The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer *[see Warnings and Precautions (5.2),* and *Clinical Studies (14.2)].*

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and MPA and other combinations and dosage forms of estrogens and progestins.

Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

Unintentional Secondary Exposure

Breast budding and breast masses in prepubertal females and gynecomastia and breast masses in prepubertal males have been reported following unintentional secondary exposure to Evamist by women using this product. In most cases, the condition resolved with removal of Evamist exposure. Women should ensure that children do not come into contact with the site(s) where Evamist is applied. Healthcare providers should advise patients to strictly adhere to recommended instructions for use [see *Warnings and Precautions* (5.4)].

1 INDICATIONS AND USAGE

1.1 Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause.

2 DOSAGE AND ADMINISTRATION

Generally, when estrogen is prescribed for a postmenopausal woman with a uterus, a progestin should also be considered to reduce the risk of endometrial cancer. A woman without a uterus does not need a progestin. In some cases, however, hysterectomized women with a history of endometriosis may need a progestin *[see Warnings and Precautions (5.2, 5.15)]*.

Use of estrogen-alone, or in combination with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman. Postmenopausal women should be re-evaluated periodically as clinically appropriate to determine if treatment is still necessary.

2.1 Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause

Evamist therapy should be initiated with one spray per day. Dosage adjustment should be guided by the clinical response.

Before applying the first dose from a new applicator, the pump should be primed by spraying 3 sprays with the cover on. The container should be held upright and vertical for spraying.

One, two or three sprays are applied each morning to adjacent, non-overlapping areas on the inner surface of the forearm, starting near the elbow. Sprays should be allowed to dry for approximately 2 minutes before covering the site with clothing. The site should not be washed for at least one hour. Application of Evamist to other skin surfaces has not been adequately studied. Evamist should not be applied to skin surfaces other than the forearm.

Strict adherence to the following precautions is advised in order to minimize the potential for secondary exposure to estradiol from Evamist-treated skin. Women should cover the

Evamist application site with clothing if another person may come into contact with that area of skin after the spray dries. Additional precautions to minimize unintentional secondary exposure are outlined in Patient Counseling Information [*see Patient Counseling Information (17.2)*] and in the Patient Information Leaflet at the end of the prescribing information.

3 DOSAGE FORMS AND STRENGTHS

Evamist is an estradiol transdermal spray. One spray consists of 90 mcL that contains 1.53 mg of estradiol.

4 CONTRAINDICATIONS

Evamist is contraindicated in women with any of the following conditions:

- Undiagnosed abnormal genital bleeding
- Known, suspected, or history of cancer of the breast
- Known or suspected estrogen-dependent neoplasia
- Active DVT, PE, or history of these conditions
- Active arterial thromboembolic disease (for example, stroke and MI), or history of these conditions
- Known anaphylactic reaction or angioedema with Evamist
- Known liver impairment or disease
- Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders
- Known or suspected pregnancy

5 WARNINGS AND PRECAUTIONS

5.1 Cardiovascular Disorders

An increased risk of stroke and DVT has been reported with estrogen-alone therapy. An increased risk of PE, DVT, stroke, and MI has been reported with estrogen plus progestin therapy. Should any of these occur or be suspected, estrogen with or without progestin therapy should be discontinued immediately.

Risk factors for arterial vascular disease (for example, hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (VTE) (for example, personal history or family history of VTE, obesity, and systemic lupus erythematosus) should be managed appropriately.

Stroke

In the WHI estrogen-alone therapy substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg)-alone compared to women in the same age group receiving placebo (45 versus 33 per 10,000 women-years). The increase in risk was demonstrated in year 1 and persisted [*see Clinical Studies (14.2)*]. Should a stroke occur or be suspected, estrogen-alone therapy should be discontinued immediately.

Subgroup analyses of women 50 to 59 years of age suggest no increased risk of stroke for those women receiving CE (0.625 mg)-alone versus those receiving placebo (18 versus 21 per 10,000 women-years).[1]

In the WHI estrogen plus progestin substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women in the same age group receiving placebo (33 versus 25 per 10,000 women-years). [*see Clinical Studies (14.2)*]. The increase in risk was demonstrated after the first year and persisted.[1] Should a stroke occur or be suspected, estrogen plus progestin therapy should be discontinued immediately.

Coronary Heart Disease

In the WHI estrogen-alone substudy, no overall effect on coronary heart disease (CHD) events (defined as non-fatal MI, silent MI, or CHD death) was reported in women receiving estrogenalone compared to placebo2 [*see Clinical Studies (14.2*)].

In the WHI estrogen plus progestin substudy, there was a statistically non-significant increase risk of CHD events reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (41 versus 34 per 10,000 women-years)[1]. An increase in relative risk was demonstrated in year 1, and a trend toward decreasing relative risk was reported in years 2 through 5 [*see Clinical Studies (14.2*)].

Subgroup analysis of women 50 to 59 years of age suggest a statistically non-significant reduction in CHD events (CE [0.635 mg]-alone compared to placebo) in women with less than 10 years since menopause (8 versus 16 per 10,000 women-years)·1

In postmenopausal women with documented heart disease (n = 2,763, average 66.7 years of age), in a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study [HERS]), treatment with daily CE (0.625 mg) plus MPA (2.5 mg) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE plus MPA did not reduce the overall rate of CHD events in postmenopausal women with established CHD. There were more CHD events in the CE plus MPA-treated group than in the placebo group in year 1, but not during the subsequent years. Two thousand, three hundred and twenty-one (2,321) women from the original HERS trial agreed to participate in an

open label extension of HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE plus MPA group and the placebo group in HERS, HERS II, and overall.

Venous Thromboembolism

In the WHI estrogen-alone substudy, the risk of VTE (DVT and PE) was increased for women receiving daily CE (0.625 mg)-alone compared to placebo (30 versus 22 per 10,000 women-years), although only the increased risk of DVT reached statistical significance (23 versus 15 per 10,000 women-years). The increase in VTE risk was demonstrated during the first two years[3] [*see Clinical Studies (14.2)*]. Should a VTE occur or be suspected, estrogen-alone therapy should be discontinued immediately.

In the WHI estrogen plus progestin substudy, a statistically significant 2-fold greater rate of VTE was reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (35 versus 17 per 10,000 women-years). Statistically significant increases in risk for both DVT (26 versus 13 per 10,000 women-years) and PE (18 versus 8 per 10,000 women-years) were also demonstrated. The increase in VTE risk was observed during the first year and persisted[4] [*see Clinical Studies (14.2)*]. Should VTE occur or be suspected, estrogen plus progestin therapy should be discontinued immediately.

If feasible, estrogens should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

5.2 Malignant Neoplasms

Endometrial Cancer

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 an increased risk 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.

Clinical surveillance of all women using estrogen-alone or estrogen plus progestin therapy is important. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal genital bleeding. There is no evidence that the use of natural

estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose. Adding a progestin to postmenopausal estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

Breast Cancer

The most important randomized clinical trial providing information about breast cancer in estrogen-alone users is the WHI substudy of daily CE (0.625 mg)-alone. In the WHI estrogen-alone substudy, after an average follow-up of 7.1 years, daily CE-alone was not associated with an increased risk of invasive breast cancer (relative risk [RR] 0.80)[5] [*see Clinical Studies (14.2)*].

The most important randomized clinical trial providing information about breast cancer in estrogen plus progestin users is the WHI substudy of daily CE (0.625 mg) plus MPA (2.5 mg). After a mean follow-up of 5.6 years, the estrogen plus progestin substudy reported an increased risk of invasive breast cancer in women who took daily CE plus MPA. In this substudy, prior use of estrogen-alone or estrogen plus progestin therapy was reported by 26 percent of the women. The relative risk of invasive breast cancer was 1.24 and the absolute risk was 41 versus 33 cases per 10,000 women-years, for CE plus MPA compared with placebo [see Clinical Studies (14.2)]. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 versus 25 cases per 10,000 women-years, for CE plus MPA compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 versus 36 cases per 10,000 women-years for CE plus MPA compared with placebo. In the same substudy, invasive breast cancers were larger, were more likely to be node positive, and were diagnosed at a more advanced stage in the CE (0.625 mg) plus MPA (2.5 mg) group compared with the placebo group. Metastatic disease was rare, with no apparent difference between the two groups. Other prognostic factors, such as histologic subtype, grade and hormone receptor status did not differ between the groups[6] *[see Clinical Studies (14.2*)].

Consistent with the WHI clinical trial, observational studies have also reported an increased risk of breast cancer for estrogen plus progestin therapy, and a smaller increased risk for estrogen-alone therapy, after several years of use. The risk increased with duration of use, and appeared to return to baseline over about 5 years after stopping treatment (only the observational studies have substantial data on risk after stopping). 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. However, these studies have not found significant variation in the risk of breast cancer among different estrogens or among different estrogen plus progestin combinations, doses, or routes of administration.

The use of estrogen-alone and estrogen plus progestin has been reported to result in an increase in abnormal mammograms requiring further evaluation.

All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results.

Ovarian Cancer

The WHI estrogen plus progestin substudy reported a statistically non-significant increased risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE plus MPA versus placebo was 1.58 (95 percent CI, 0.77-3.24). The absolute risk for CE plus MPA versus placebo was 4 versus 3 cases per 10,000 women-years.[7] A meta-analysis of 17 prospective and 35 retrospective epidemiology studies found that women who used hormonal therapy for menopausal symptoms had an increased risk for ovarian cancer. The primary analysis, using case-control comparisons, included 12,110 cancer cases from the 17 prospective studies. The relative risks associated with current use of hormonal therapy was 1.41 (95% confidence interval [CI] 1.32 to 1.50); there was no difference in the risk estimates by duration of the exposure (less than 5 years [median of 3 years]vs. greater than 5 years [median of 10 years] of use before the cancer diagnosis). The relative risk associated with combined current and recent use (discontinued use within 5 years before cancer diagnosis) was 1.37 (95% CI 1.27-1.48), and the elevated risk was significant for both estrogen-alone and estrogen plus progestin products. The exact duration of hormone therapy use associated with an increased risk of ovarian cancer, however, is unknown.

5.3 Probable Dementia

In the WHIMS estrogen-alone ancillary study of the WHI, a population of 2,947 hysterectomized women 65 to 79 years of age was randomized to daily CE (0.625 mg)-alone or placebo.

After an average follow-up of 5.2 years, 28 women in the estrogen-alone group and 19 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE-alone versus placebo was 1.49 (95 percent CI, 0.83-2.66). The absolute risk of probable dementia for CE-alone versus placebo was 37 versus 25 cases per 10,000 womenyears[8] [*see Use in Specific Populations (8.5) and Clinical Studies (14.3)]*.

In the WHIMS estrogen plus progestin ancillary study, a population of 4,532 postmenopausal women 65 to 79 years of age was randomized to daily CE (0.625 mg) plus MPA (2.5 mg) or placebo. After an average follow-up of 4 years, 40 women in the CE plus MPA group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE plus MPA versus placebo was 2.05 (95 percent CI, 1.21-3.48). The

absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 cases per 10,000 women-years[8] *[see Use in Specific Populations (8.5) and Clinical Studies (14.3)*].

When data from the two populations in the WHIMS estrogen-alone and estrogen plus progestin ancillary studies 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 ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women8 [*see Use in Specific Populations (8.5) and Clinical Studies (14.3)*].

5.4 Unintentional Secondary Exposure to Estrogen

Postmarketing reports of breast budding and breast masses in prepubertal females and gynecomastia and breast masses in prepubertal males following unintentional secondary exposure to Evamist have been reported. In most cases, the condition resolved with removal of Evamist exposure.

Unexpected changes in breast tissue or other signs of abnormal sexual development in prepubertal children as well as the possibility of unintentional secondary exposure to Evamist should be brought to the attention of a physician. The physician should identify the cause of abnormal sexual development in the child. If unexpected breast development or changes are determined to be the result of unintentional exposure to Evamist, the physician should counsel the woman on the appropriate use and handling of Evamist when around children. Women should cover the Evamist application site with clothing if another person may come into contact with the site. Consideration should be given to discontinuing Evamist if conditions for safe use cannot be met [*see Patient Counseling Information (17.2)*].

5.5 Gallbladder Disease

A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving estrogens has been reported.

5.6 Hypercalcemia

Estrogen administration may lead to severe hypercalcemia in women 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.

5.7 Visual Abnormalities

Retinal vascular thrombosis has been reported in women receiving estrogens. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or a sudden

onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, estrogens should be permanently discontinued.

5.8 Addition of a Progestin When a Woman Has Not Had a Hysterectomy

Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer.

There are, however, possible risks that may be associated with the use of progestins with estrogens compared to estrogen alone regimens. These include an increased risk of breast cancer.

5.9 Elevated Blood Pressure

In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of estrogens on blood pressure was not seen.

5.10 Hypertriglyceridemia

In women with preexisting hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis. Consider discontinuation of treatment if pancreatitis occurs.

5.11 Hepatic Impairment and/or Past History of Cholestatic Jaundice

Estrogens may be poorly metabolized in women with impaired liver function. For women with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised, and in the case of recurrence, medication should be discontinued.

5.12 Hypothyroidism

Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Women with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T_4 and T_3 serum concentrations in the normal range. Women dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid hormone replacement therapy. These women should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

5.13 Fluid Retention

Estrogens may cause some degree of fluid retention. Women who have conditions that might be influenced by this factor, such as a cardiac or renal impairment, warrant careful observation when estrogen-alone is prescribed.

5.14 Hypocalcemia

Estrogen therapy should be used with caution in women with hypoparathyroidism as estrogen induced hypocalcemia may occur.

5.15 Exacerbation of Endometriosis

A few cases of malignant transformation of residual endometrial implants have been reported in women treated post-hysterectomy with estrogen alone therapy. For women known to have residual endometriosis post-hysterectomy, the addition of progestin should be considered.

5.16 Hereditary Angioedema

Exogenous estrogens may exacerbate symptoms of angioedema in women with hereditary angioedema.

5.17 Exacerbation of Other Conditions

Estrogen therapy may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus and hepatic hemangiomas and should be used with caution in women with these conditions.

5.18 Alcohol-Based Products are Flammable

Avoid fire, flame or smoking until the spray has dried.

5.19 Application of Sunscreen

When sunscreen is applied approximately one hour after application of Evamist, estradiol absorption was decreased by 11 percent. When sunscreen is applied approximately one hour before the application of Evamist, no significant change in estradiol absorption was observed.

5.20 Laboratory Tests

Serum follicle stimulating hormone (FSH) and estradiol levels have not been shown to be useful in the management of moderate to severe vasomotor symptoms.

5.21 Drug and Laboratory Test Interactions

Accelerated 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 antifactor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.

Increased TBG levels leading to increased circulating total thyroid hormone levels, as measured by protein-bound iodine (PBI), T_4 levels (by column or by radioimmunoassay) or T_3 levels by radioimmunoassay. T_3 resin uptake is decreased, reflecting the elevated TBG. Free T_4 and free T_3 concentrations are unaltered. Women on thyroid hormone replacement therapy may require higher doses of thyroid hormone.

Other binding proteins may be elevated in serum, for example, corticosteroid binding globulin (CBG), sex hormone binding globulin (SHBG), leading to increased total circulating corticosteroids and sex steroids, respectively. Free hormone concentrations, such as testosterone and estradiol, may be decreased. Other plasma proteins may be increased (angiotensinogen/rennin substrate, alpha-1-antitrypsin, ceruloplasmin).

Increased plasma high-density lipoprotein (HDL) and HDL_2 cholesterol subfraction concentrations, reduced low-density lipoprotein (LDL) cholesterol concentration, increased triglyceride levels.

Impaired glucose tolerance.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

Cardiovascular Disorders *[see Boxed Warning, Warnings and Precautions (5.1)]*

Malignant *Neoplasms [see Boxed Warning, Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In a 12-week, randomized, placebo-controlled trial of Evamist in 454 women, 80 to 90 percent of women randomized to active drug received at least 70 days of therapy and 75 to 85 percent randomized to placebo received at least 70 days of therapy.

The adverse reactions that occurred in at least 5 percent of women in any treatment group are shown in Table 1.

Table 1. Frequency of Adverse Reactions (≥5%) in Any Treatment Group in a Controlled Study of Evamist

System Organ Class Preferred Term	Frequency n (%)					
	1 Spray		2 Sprays		3 Sprays	
	Placebo (N = 77)	Evamist (N = 76)	Placebo (N = 76)	Evamist (N = 74)	Placebo (N = 75)	Evamist (N = 76)
Reproductive System and Breast Disorders						
Breast tenderness	0 (0)	4 (5)	4 (5)	5 (7)	0 (0)	4 (5)
Nipple pain	0 (0)	2 (3)	0 (0)	5 (7)	0 (0)	1 (1)
Gastrointestinal Disorders						
Nausea	5 (7)	1 (1)	1 (1)	2 (3)	4 (5)	2 (3)
Infections and Infestations						
Nasopharyngitis	1 (1)	4 (5)	2 (3)	3 (4)	1 (1)	1 (1)
Musculoskeletal and Connective Tissue Disorders						
Back pain	1 (1)	2 (3)	2 (3)	4 (5)	1 (1)	2 (3)
Arthralgia	1 (1)	1 (1)	4 (5)	1 (1)	0 (0)	3 (4)
Nervous system						
Headache	4 (5)	7 (9)	5 (7)	9 (12)	7 (9)	8 (11)

Application site reactions were reported in 3 out of 226 (1.3%) women treated with Evamist.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Evamist. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Breasts: Breast swelling, breast mass, breast enlargement

Cardiovascular: Heart rate increased

Central nervous system: Dizziness, dysgeusia, paresthesia, lethargy, hypoesthesia

Eyes: Eye irritation, ocular hyperemia

Gastrointestinal: Abdominal pain, diarrhea, constipation, abdominal distension, dry mouth, decreased appetite

Genitourinary system: Vaginal bleeding

Musculoskeletal: Muscle spasms, arthritis

Psychiatric: Insomnia, mood swings, anxiety, irritability, mood altered, depression

Respiratory tract: Cough, dyspnea, dry throat

Skin: Nipple and areola discoloration, usually on the same side of the body as the inner forearm on which Evamist is applied, rash, pruritus, alopecia, urticaria, dry skin, skin discoloration, chloasma

Miscellaneous: Weight increased, malaise, fatigue, asthenia

7 DRUG INTERACTIONS

No drug interaction studies have been conducted for Evamist.

7.1 Metabolic Interactions

In vitro and in vivo studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's wort (Hypericum perforatum) preparations, phenobarbital, carbamazepine, and rifampin may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Evamist should not be used during pregnancy [*see Contraindications (4)]*. There appears to be little or no increased risk of birth defects in children born to women who have used estrogens and progestins as an oral contraceptive inadvertently during early pregnancy.

8.3 Nursing Mothers

Evamist should not be used during lactation. Estrogen administration to nursing women has been shown to decrease the quantity and quality of the breast milk. Detectable amounts of estrogens have been identified in the milk of women receiving estrogen-alone therapy. Caution should be exercised when Evamist is administered to a nursing woman.

8.4 Pediatric Use

Evamist is not intended in children. Clinical studies have not been conducted in the pediatric population.

8.5 Geriatric Use

There have not been sufficient numbers of geriatric women involved in studies utilizing Evamist to determine whether those over 65 years of age differ from younger subjects in their response to Evamist.

The Women's Health Initiative Studies

In the WHI estrogen-alone substudy (daily CE [0.625 mg]-alone versus placebo), there was a higher relative risk of stroke in women greater than 65 years of age [see Clinical Studies (14.2)].

In the WHI estrogen plus progestin substudy (daily CE [0.625 mg] plus MPA [2.5 mg] versus placebo), there was a higher relative risk of nonfatal stroke and invasive breast cancer in women greater than 65 years of age *[see Clinical Studies (14.2)]*.

The Women's Health Initiative Memory Study

In the WHIMS ancillary studies of postmenopausal women 65 to 79 years of age, there was an increased risk of developing probable dementia in women receiving estrogen-alone or estrogen plus progestin when compared to placebo [*see Warnings and Precautions (5.3), and Clinical Studies (14.3)*].

Since both ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women[8] [see Warnings and Precautions (5.3), and Clinical Studies (14.3)].

8.6 Renal Impairment

The effect of renal impairment on the pharmacokinetics of Evamist has not been studied.

8.7 Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of Evamist has not been studied.

10 OVERDOSAGE

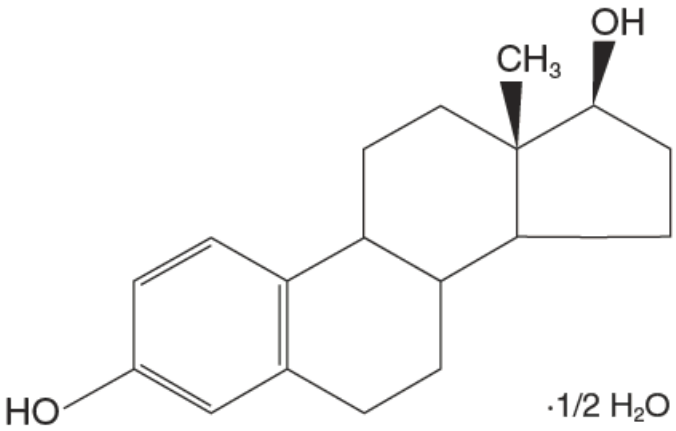
Overdosage of estrogen may cause nausea and vomiting, breast tenderness, abdominal pain, drowsiness and fatigue, and withdrawal bleeding may occur in women. Treatment of overdose consists of discontinuation of Evamist together with institution of appropriate symptomatic care.

11 DESCRIPTION

Evamist (estradiol transdermal spray) is designed to deliver estradiol to the blood circulation following topical application to the skin of a rapidly drying solution from a metered-dose pump.

Evamist is a homogeneous solution of 1.7% estradiol USP (active ingredient) in alcohol USP and octisalate USP formulated to provide sustained release of the active ingredient into the systemic circulation.

Estradiol USP is a white crystalline powder, chemically described as estra-1,3,5(10)-triene-3,17β-diol. It has an empirical formula of $C_{18}H_{24}O_2 \cdot 1/2\ H_2O$ and molecular weight of 281.4. The structural formula is



Each metered-dose pump contains 8.1 mL and is designed to deliver 56 sprays of 90 mcL each after priming. One spray of Evamist contains 1.53 mg estradiol. The metered-dose pump should be held upright and vertical for spraying. Before a new applicator is used for the first time, the pump should be primed by spraying 3 times with the cover on.

One, two or three sprays are applied daily each morning to adjacent non-overlapping 20 cm^2 areas on the inner surface of the arm between the elbow and the wrist and allowed to dry.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Endogenous estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estriol, at the receptor level.

The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 mcg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted

by the adrenal cortex, to estrone in the peripheral tissues. Thus, estrone and the sulfate conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.

Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. To date, two estrogen receptors have been identified. These vary in proportion from tissue to tissue.

Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH) and FSH, through a negative feed back mechanism. Estrogens act to reduce the elevated levels of these hormones seen in postmenopausal women.

12.2 Pharmacodynamics

There are no pharmacodynamic data for Evamist.

12.3 Pharmacokinetics

Absorption

In a multiple-dose study, 72 postmenopausal women were treated for 14 days with Evamist to the inner forearm. Serum concentrations of estradiol appeared to reach steady state after 7 to 8 days of application of one, two, or three 90 mcL sprays of Evamist per day (Figure 1).

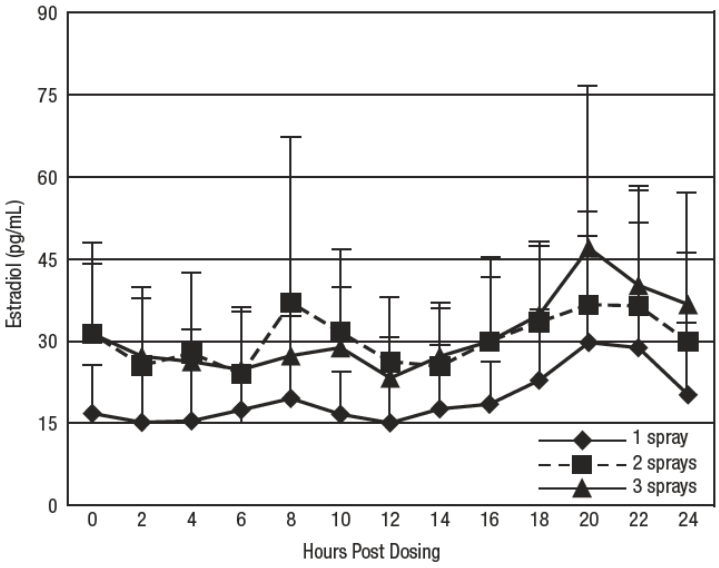


Figure 1. Mean (±SD) Serum Estradiol Concentrations on Day 14 Following Topical on for 14 Days of One, Two or Three Sprays of Evamist (Unadjusted for Baseline)

Pharmacokinetics parameters for estradiol from one, two, or three 90 mcL sprays of Evamist, as assessed on Day 14 of this study, are described in Table 2.

Table 2. Estradiol Pharmacokinetic Parameters on Day 14 (Unadjusted for Baseline)

PK Parameter	Number of Daily Sprays of Evamist		
	1 Spray (N = 24)	2 Sprays (N = 23)	3 Sprays (N = 24)
C_{max} (pg/mL)[a]	36.4 (62)	57.4 (4)	54.1 (50)
C_{min} (pg/mL)[a]	11.3 (52)	18.1 (51)	19.6 (27)
Cavg (pg/mL)[a]	19.6 (49)	30.7 (43)	30.9 (30)
AUC_{0-24} (pg*hr/mL)[a]	471 (4)	73 (43)	742 (30)
T_{max} (hours)[b]	20 (0–24)	18 (0-24)	20 (0-24)

[a] Values expressed are arithmetic means (%CV)
[b] Values expressed are medians (minimum-maximum)

Distribution

The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Estrogens circulate in blood largely bound to SHBG and albumin.

Metabolism

Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is a major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the intestine followed by reabsorption. In postmenopausal women, a significant proportion of the circulating estrogens exist as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens.

Excretion

Estradiol, estrone and estriol are excreted in the urine along with glucuronide and sulfate conjugates.

Use in Specific Populations

No pharmacokinetic studies were conducted with Evamist in specific populations, including women with renal or hepatic impairment.

Potential for Estradiol Transfer

The effect of estradiol transfer was evaluated in 20 healthy postmenopausal women who applied three 90-mcL sprays of Evamist to the inner forearm once daily. One hour after applying

Evamist, subjects held the dosed forearm against the inner forearm of a non-dosed (recipient) male subject for one 5-minute period of continual contact. A 4% increase in serum estradiol exposure was observed in persons who came in contact with the application site. The possibility of unintentional secondary exposure to Evamist should be brought to the attention of physicians and Evamist users.

Effect of Application Site Washing

Site washing with warm water and soap one hour after the application of three 90 mcL sprays to the inner forearm did not have a significant effect on average 24-hour serum concentrations of estradiol.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, 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, testis and liver.

14 CLINICAL STUDIES

14.1 Effects on Vasomotor Symptoms

In a 12-week, randomized, double-blind, placebo-controlled clinical trial, a total of 454 postmenopausal women (average 53 years of age, 70 percent Caucasian and 24 percent African-American) were randomized and received at least one dose of Evamist (one, two or three 90 mcL sprays) or placebo. Generally healthy postmenopausal women were enrolled with a mean total frequency of ≥56 moderate to severe vasomotor symptoms per week (≥ 8 per day).

Efficacy was determined as a statistically significant and clinically significant (at least two per day or 14 per week difference) reduction in hot flush frequency and a statistically significant reduction in severity for Evamist versus placebo. One, two or three daily sprays of Evamist were shown to be better than placebo for relief of frequency (Table 3) and severity (Table 4) of moderate to severe vasomotor symptoms at Week 4 and Week 12.

Table 3. Effect of Treatment on the Daily Frequency of Moderate to Severe Vasomotor Symptoms at Week 4 and Week 12
(Intent-To-Treat Population, LOCF)

	Mean Change from Baseline[a] (SD)		
Treatment (N)	**Baseline Mean (SD)**	**Week 4 Mean (SD)**	**Week 12 Mean (SD)**
1 Spray			
Evamist (N=76)	11.81 (4.07)	-6.26 (4.01)	-8.10 (4.02)
Placebo (N=77)	12.41 (5.59)	-3.64 (5.30)	-4.76 (5.84)

Difference[b]	—	-2.62	-3.34
p-value[c]	—	0.0010	0.0004
2 Sprays			
Evamist (N=74)	12.66 (7.33)	-7.30 (6.93)	-8.66 (6.65)
Placebo (N=76)	12.13 (6.10)	-4.74 (4.38)	-6.19 (5.77)
Difference[b]	—	-2.56	-2.47
p-value[c]	—	0.0027	0.0099
3 Sprays			
Evamist (N=76)	10.78 (3.58)	-6.64 (4.23)	-8.44 (4.50)
Placebo (N=75)	12.55 (11.94)	-4.54 (7.40)	-5.32 (6.30)
Difference[b]	—	-2.10	-3.12
p-value[c]	—	0.0002	<0.0001

[a] Mean change and difference based on raw data
[b] Evamist versus placebo
[c] Tests for pairwise differences using ANCOVA

Table 4. Effect of Treatment on the Weekly Severity of Moderate to Severe Vasomotor Symptoms at Week 4 and Week 12 (Intent-To-Treat Population, LOCF)[a]

	Mean Change from Baseline[b] (SD)		
Treatment (N)	**Baseline Mean (SD)**	**Week 4 Mean (SD)**	**Week 12 Mean (SD)**
1 Spray			
Evamist (N=76)	2.53 (0.25)	-0.47 (0.80)	-1.04 (1.01)
Placebo (N=77)	2.55 (0.25)	-0.19 (0.55)	-0.26 (0.60)
Difference[c]	—	-0.28	-0.78
p-value[d]	—	0.0573	<0.0001
2 Sprays			
Evamist (N=74)	2.54 (0.21)	-0.57 (0.83)	-0.92 (1.01)
Placebo (N=76)	2.54 (0.22)	-0.25 (0.64)	-0.54 (0.89)
Difference[c]	—	-0.32	0.38
p-value[d]	—	0.0160	0.0406
3 Sprays			
Evamist (N=76)	2.58 (0.25)	-0.43 (0.66)	-1.07 (1.01)
Placebo (N=75)	2.54 (0.24)	-0.13 (0.53)	-0.31 (0.75)
Difference[c]	—	-0.30	-0.76
p-value[d]	—	0.0031	<0.0001

[a]Severity score calculated as: (2 x number moderate +3 x number severe)/ number moderate + number severe)
[b] Mean change and difference based on raw data
[c] Evamist versus placebo
[d] Tests for pairwise differences using ANCOVA

14.2 Women's Health Initiative Studies

The WHI enrolled approximately 27,000 predominantly healthy postmenopausal women in two substudies to assess the risks and benefits of daily oral CE (0.625 mg)-alone or in combination with MPA (2.5 mg) compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of CHD (defined as nonfatal MI, silent MI and CHD death), with invasive breast cancer as the primary adverse outcome. A "global index" included the

earliest occurrence of CHD, invasive breast cancer, stroke, PE, endometrial cancer (only in the CE plus MPA substudy), colorectal cancer, hip fracture, or death due to other cause. These substudies did not evaluate the effects of CE-alone or CE plus MPA on menopausal symptoms

WHI Estrogen-Alone Substudy

The WHI estrogen-alone substudy was stopped early because an increased risk of stroke was observed, and it was deemed that no further information would be obtained regarding the risks and benefits of estrogen-alone in predetermined primary endpoints. Results of the estrogen-alone substudy, which included 10,739 women (average 63 years of age, range 50 to 79 years of age; 75.3 percent White, 15.1 percent Black, 6.1 percent Hispanic, 3.6 percent Other), after an average follow-up of 7.1 years are presented in Table 5

Table 5. Relative and Absolute Risk Seen in the Estrogen Alone Substudy of WHI[a]

Event	Relative Risk CE vs. Placebo (95% nCI[b])	CE (n = 5,310)	Placebo (n = 5,429)
		Absolute Risk per 10,000 Women-Years	
CHD events[c]	0.95 (0.78-1.16)	54	57
Non-fatalMI[cc]	*0.91 (0.73-1.14)*	*40*	*43*
CHD death [c]	*1.01 (0.71-1.43)*	*16*	*16*
All strokes[c]	1.33 (1.05-1.68)	45	33
Ischemic stroke [c]	*1.55 (1.19-2.01)*	*38*	*25*
Deep vein thrombosis[c,d]	1.47 (1.06-2.06)	23	15
Pulmonary embolism[c]	1.37 (0.90-2.07)	14	10
Invasive breast cancer[c]	0.80 (0.62-1.04)	28	34
Colorectal cancer [e]	1.08 (0.75-1.55)	17	16
Hip fracture[c]	0.65 (0.45-0.94)	12	19
Vertebral fractures[c,d]	0.64 (0.44-0.93)	11	18
Lower arm/wrist fractures[c,d]	0.58 (0.47-0.72)	35	59
Total fractures[c,d]	0.71 (0.64-0.80)	144	197
Death due to other causes [e,f]	1.08 (0.88-1.32)	53	50
Overall mortality[c,d]	1.04 (0.88-1.22)	79	75
Global index[g]	1.02 (0.92-1.13)	206	201

[a] Adapted from numerous WHI publications. WHI publications can be viewed at www.nhlbi.nih.gov/whi.
[b] Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.
[c] Results are based on centrally adjudicated data for an average follow-up of 7.1 years.
[d] Not included in "global index".
[e] Results are based on an average follow-up of 6.8 years.
[f] All deaths, except from breast or colorectal cancer, definite or probable CHD, PE or cerebrovascular disease.
[g] A subset of the events was combined in a "global index", defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, PE, endometrial cancer, colorectal cancer, hip fracture, or death due to other causes.

For those outcomes included in the WHI "global index" that reached statistical significance, the absolute excess risk per 10,000 women-years in the group treated with CE-alone was 12 more strokes, while the absolute risk reduction per 10,000 women-years was 7 fewer hip fractures.[9]

The absolute excess risk of events included in the "global index" was a non-significant 5 events per 10,000 women-years. There was no difference between the groups in terms of all-cause mortality.

No overall difference for primary CHD events (nonfatal MI, silent MI and CHD death) and invasive breast cancer incidence in women receiving CE-alone compared to placebo was reported in final centrally adjudicated results from the estrogen-alone substudy, after an average follow-up of 7.1 years.

Centrally adjudicated results for stroke events from the estrogen-alone substudy, after an average follow-up of 7.1 years, reported no significant differences in distribution of stroke subtypes or severity, including fatal strokes, in women receiving CE-alone compared to placebo. Estrogen-alone increased the risk for ischemic stroke, and this excess risk was present in all subgroups of women examined. [10]

Timing of the initiation of estrogen-alone therapy relative to the start of menopause may affect the overall risk benefit profile. The WHI estrogen-alone substudy stratified by age showed in women 50 to 59 years of age a non-significant trend toward reduced risk for CHD [hazard ratio (HR) 0.63 (95 percent CI, 0.36-1.09)] and overall mortality [HR 0.71 (95 percent CI, 0.46-1.11)].

WHI Estrogen Plus Progestin Substudy

The WHI estrogen plus progestin substudy was stopped early. According to the predefined stopping rule, after an average follow-up of 5.6 years of treatment, the increased risk of invasive breast cancer and cardiovascular events exceeded the specified benefits included in the "global index". The absolute excess risk of events included in the "global index" was 19 per 10,000 women-years.

For those outcomes included in the WHI "global index" that reached statistical significance after 5.6 years of follow-up, the absolute excess risks per 10,000 women-years in the group treated with CE plus MPA were 7 more CHD events, 8 more strokes, 10 more PEs, and 8 more invasive breast cancers, while the absolute risk reduction per 10,000 women-years were 6 fewer colorectal cancers and 5 fewer hip fractures.

Results of the CE plus MPA substudy which included 16,608 women (average 63 years of age; range 50 to 79 years of age: 83.9 percent White, 6.5 percent Black, 5.4 percent Hispanic, 3.9 percent Other) are presented in Table 6. These results reflect centrally adjudicated data after an average follow-up of 5.6 years.

Table 6. Relative and Absolute Risk Seen in the Estrogen Plus Progestin Substudy of WHI at an Average of 5.6 Years[a,b]

Event	Relative Risk CE/MPA vs. Placebo (95% nCI[c])	CE/MPA (n = 8,506)	Placebo (n = 8,102)
		Absolute Risk per 10,000 Women-Years	
CHD events	1.23 (0.99-1.53)	41	34
Non-fatalMI	*1.28 (1.00-1.63)*	*31*	*25*
CHD death [c]	*1.10 (0.70-1.75)*	*8*	*8*
All strokes	1.31 (1.03-1.68)	33	25
Ischemic stroke	*1.44 (1.09-1.90)*	*26*	*18*
Deep vein thrombosis[d]	1.95 (1.43-2.67)	26	13
Pulmonary embolism	2.13 (1.45-3.11)	18	8
Invasive breast cancer[e]	1.24 (1.01-1.54)	41	33
Colorectal cancer	0.61 (0.42-0.87)	10	16
Endometrial cancer[d]	0.81 (0.48-1.36)	6	7
Cervical cancer[d]	1.44 (0.47-4.42)	2	1
Hip fracture	0.67 (0.47-0.96)	11	16
Vertebral fractures[d]	0.65 (0.46-0.92)	11	17
Lower arm/wrist fractures[d]	0.71 (0.59-0.85)	44	62
Total fractures[d]	0.76 (0.69-0.83)	152	199
Overall mortality[f]	1.00 (0.83-1.19)	52	52
Global index[g]	1.13 (1.02-1.25)	184	165

[a] Adapted from numerous WHI publications, WHI publications can be viewed at www.nhlbi.nih.gov/whi
[b] Results are based on centrally adjudicated data.
[c] Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.
[d] Not included in "global index".
[e] Includes metastatic and non-metastatic breast cancer, with the exception of in situ breast cancer.
[f] All deaths, except from breast or colorectal cancer, definite or probably CHD, PE or cerebrovascular disease.
[g] A subset of the events was combined in a "global index", defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, PE, endometrial cancer, colorectal cancer, hip fracture, or death due to other causes.

Timing of the initiation of estrogen plus progestin therapy relative to the start of menopause may affect the overall risk benefit profile. The WHI estrogen plus progestin substudy stratified by age showed in women 50 to 59 years of age a non-significant trend toward reduced risk for overall mortality [HR 0.69 (95 percent CI, 0.44-1.07)].

14.3 Women's Health Initiative Memory Study

The WHIMS estrogen-alone ancillary study of the WHI, enrolled 2,947 predominantly healthy hysterectomized postmenopausal women 65 to 79 years of age (45 percent were 65 to 69 years of age, 36 percent were 70 to 74 years of age, and 19 percent were 75 years of age and older) to evaluate the effects of daily CE (0.625 mg) on the incidence of probable dementia (primary outcome) compared to placebo

After an average follow-up of 5.2 years, the relative risk of probable dementia for CE-alone versus placebo was 1.49 (95 percent CI, 0.83-2.66). The absolute risk of probable dementia for CE-alone versus placebo was 37 versus 25 cases per 10,000 women-years. Probable dementia as defined in this study included Alzheimer's disease (AD), vascular dementia (VaD) and mixed type (having features of both AD and VaD). The most common classification of probable dementia in the treatment group and the placebo group was AD. Since the ancillary study was conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women [*see Warnings and Precautions (5.3) and Use in Specific Populations (8.5)]*.

The WHIMS estrogen plus progestin ancillary study enrolled 4,532 predominantly healthy postmenopausal women 65 years of age and older (47 percent were 65 to 69 years of age, 35 percent were 70 to 74 years of age, and 18 percent were 75 years of age and older) to evaluate the effects of daily CE (0.625 mg) plus MPA (2.5 mg) on the incidence of probable dementia (primary outcome) compared to placebo.

After an average follow-up of 4 years, the relative risk of probable dementia for CE plus MPA versus placebo was 2.05 (95 percent CI, 1.12-3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 per 10,000 women-years. Probable dementia as defined in this study included AD, VaD and mixed type (having features of both AD and VaD). The most common classification of probable dementia in the treatment group and the placebo group was AD. Since the ancillary study was conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women [*see Warnings and Precautions (5.3), and Use in Specific Populations (8.5)]*.

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). Differences between groups became apparent in the first year of treatment. It is unknown whether these findings apply to younger postmenopausal women [*see Warnings and Precautions (5.3*), *and Use in Specific Populations (8.5)*].

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16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Evamist (NDC 0574-2067-27) is supplied as a homogeneous solution of estradiol USP, octisalate USP and alcohol USP. The liquid formulation of Evamist is packaged in a glass vial fitted with a metered-dose pump. The unit is encased in a plastic housing with a conical bell opening that controls the distance, angle, and area of application of the metered-dose spray. Each metered-dose pump contains 8.1 mL and is designed to deliver 56 sprays of 90 mcL after priming. One spray contains 1.53 mg estradiol.

16.2 Storage and Handling

Keep out of reach of children.

Alcohol and alcohol-based liquids are flammable. Avoid fire, flame or smoking until the spray has dried.

Store at room temperature 20°C to 25°C (68°F to 77°F); excursion permitted between 15°C to 30°C (59°F to 86°F). Do not freeze.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information and Instructions for Use)

17.1 Vaginal Bleeding

Inform postmenopausal women of the importance of reporting unusual vaginal bleeding to their healthcare provider as soon as possible [*see Warnings and Precautions (5.2)*].

17.2 Unintentional Secondary Exposure to Evamist

Provide the following information about secondary exposure to Evamist:

- **Apply Evamist as directed and keep children from contacting exposed application site(s).** If direct contact with the application site occurs, the contact area should be washed thoroughly with soap and water. Women should cover the Evamist application site, after the 2 minute drying period, with clothing if another person may come in contact with that area of skin. [See FDA-Approved Patient Information Leaflet at the end of the prescribing information.]
- **Look for signs of unexpected sexual development, such as breast mass or increased breast size in prepubertal children.**
- If signs of unintentional secondary exposure are noticed:
  - Have children evaluated by a healthcare provider.
  - Discontinue Evamist until the cause(s) is identified for any unexpected sexual development in children under their care.
  - Women should contact their healthcare provider and discuss the appropriate use and handling of Evamist when around children.
  - If conditions for safe use cannot be met, Evamist should be discontinued and alternative treatments for menopausal signs and symptoms should be considered.
- Pets may also be unintentionally exposed to Evamist if above precautions are not followed.

17.3 Possible Serious Adverse Reactions with Estrogen-Alone Therapy

Inform postmenopausal women of the possible serious adverse reactions of estrogen-alone therapy including Cardiovascular Disorders, Malignant Neoplasms, and Probable Dementia [*see Warnings and Precautions (5.1, 5.2, 5.3)]*.

17.4 Possible Less Serious but Common Adverse Reactions with Estrogen-Alone Therapy

Inform postmenopausal women of possible less serious but common adverse reactions of estrogen-alone therapy such as headache, breast pain and tenderness, nausea and vomiting.

Manufactured by DPT Laboratories, Ltd San Antonio, TX 78215

Manufactured For

Perrigo®

Minneapolis, MN 55427

6X200 RC J3 Rev 11-17 C

Patient Information

EVAMIST (EE-vuh-mist)
(estradiol transdermal spray)

Read this Patient Information before you start using EVAMIST and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your menopausal symptoms or your treatment.

What is the most important information I should know about EVAMIST (an estrogen hormone)?

- Using estrogen-alone may increase your chance of getting cancer of the uterus (womb). Report any unusual vaginal bleeding right away while you are using EVAMIST. Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find the cause.
- Do not use estrogen-alone to prevent heart disease, heart attacks, strokes or dementia (decline in brain function).
- Using estrogen-alone may increase your chances of getting strokes or blood clots.
- Using estrogen-alone may increase your chance of getting dementia, based on a study of women 65 years or older.
- Do not use estrogens with progestins to prevent heart disease, heart attack, strokes, or dementia.
- Using estrogens with progestins may increase your chances of getting heart attacks, strokes, breast cancer, or blood clots.
- Using estrogens with progestins may increase your chance of getting dementia, based on a study of women 65 years and older.
- The estrogen in EVAMIST spray can transfer from the area of skin where it was sprayed to other people. Do not allow others, especially children, to come into contact with the area of your skin where you sprayed EVAMIST. Young children who are accidentally exposed to

estrogen through contact with women using EVAMIST may show signs of puberty that are not expected (for example, breast budding).
- You and your healthcare provider should talk regularly about whether you still need treatment with EVAMIST.

What is EVAMIST?

EVAMIST is a prescription medicine spray that contains estradiol (an estrogen hormone).

What is EVAMIST used for?

EVAMIST spray is used after menopause to:

- **Reduce moderate to severe hot flashes**

  Estrogens are hormones made by a woman's ovaries. The ovaries normally stop making estrogens when a woman is between 45 and 55 years old. This drop in body estrogen levels causes the “change of life” or menopause (the end of monthly menstrual periods). Sometimes, both ovaries are removed during an operation before natural menopause takes place. The sudden drop in estrogen levels causes “surgical menopause.”

  When the estrogen levels begin dropping, some women get very uncomfortable symptoms, such as feelings of warmth in the face, neck, and chest, or sudden strong feelings of heat and sweating (“hot flashes” or “hot flushes”). In some women, the symptoms are mild, and they will not need to use estrogens. In other women, symptoms can be more severe. You and your healthcare provider should talk regularly about whether you still need treatment with EVAMIST.

Who should not use EVAMIST?

Do not start using EVAMIST if you:

- **have unusual vaginal bleeding**

  Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause.

- **currently have or have had certain cancers**

  Estrogens may increase the chance of getting certain types of cancers, including cancer of the breast or uterus. If you have or have had cancer, talk with your healthcare provider about whether you should use EVAMIST.

- **had a stroke or heart attack**
- **currently have or have had blood clots**
- **currently have or have had liver problems**
- **have been diagnosed with a bleeding disorder**
- **are allergic to EVAMIST or any of its ingredients**

  See the list of ingredients in EVAMIST at the end of this leaflet

- **think you may be pregnant**

  EVAMIST is not for pregnant women. If you think you may be pregnant, you should have a pregnancy test and know the results. Do not use EVAMIST if the test is positive and talk to your healthcare provider.

What should I tell my healthcare provider before I use EVAMIST?

Before you use EVAMIST, tell your healthcare provider if you:

- **have any unusual vaginal bleeding**

  Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any vaginal bleeding to find out the cause.

- **have any other medical conditions**

  Your healthcare provider may need to check you more carefully if you have certain conditions, such as asthma (wheezing), epilepsy (seizures), diabetes, migraine, endometriosis, lupus, angioedema (swelling of face and tongue), or problems with your heart, liver, thyroid, kidneys, or have high calcium levels in your blood.

- **are going to have surgery or will be on bed rest**

  Your healthcare provider will let you know if you need to stop using EVAMIST.

- **are breast feeding**

  The hormone in EVAMIST can pass into your breast milk.

Tell your healthcare provider about all the medicines you take including prescription and nonprescription medicines, vitamins and herbal supplements. Some medicines may affect how EVAMIST works. EVAMIST may also affect how your other medicines work. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I use EVAMIST?

For detailed instructions, see the step-by-step instructions for using EVAMIST at the end of this Patient Information.

- Use EVAMIST exactly as your healthcare provider tells you to use it.
- EVAMIST is for skin use only.
- Apply EVAMIST at the same time each day.
- If you use sunscreen 1 hour after you use EVAMIST, it may reduce the amount of EVAMIST absorbed by your skin.
- The estrogen in EVAMIST spray can transfer from the area of skin where it was sprayed to other people or pets. **Do not** allow other people, especially children to come into contact with the area of your skin where you have sprayed EVAMIST.
- If another person accidentally touches the area of your skin where you have sprayed EVAMIST, that area of their skin should be washed with soap and water right away.
- **Do not** let pets lick or touch your arm where you have sprayed EVAMIST, especially small pets. EVAMIST may harm them. Cover your skin with clothing where you have sprayed EVAMIST if you think a pet could come in contact with that area of your skin.
- If a pet accidentally comes in contact with the area of your skin where you have sprayed EVAMIST, the area of the pet's skin should be washed with soap and water right away.
- Young children who are accidentally exposed to estrogen through contact with women using EVAMIST may show signs and symptoms of puberty that are not expected. Signs and symptoms in children of exposure to EVAMIST may include:
  - breast budding or breast lumps
  - other signs of abnormal sexual development

  If a child shows signs and symptoms of accidental exposure to EVAMIST:

  - have the child checked right away by their healthcare provider.
  - stop using EVAMIST and call your healthcare provider right away.
  - talk to your healthcare provider about the correct use of EVAMIST when around children.
- Talk to your healthcare provider about other treatments for your menopause symptoms if accidental exposure to EVAMIST cannot be avoided.
- You and your healthcare provider should talk regularly (for example, every 3 to 6 months) about the dose you are taking and whether you still need treatment with EVAMIST.

What should I avoid while using EVAMIST?

- **Do not** allow others to make contact with the area of skin where you have applied the EVAMIST spray.
- EVAMIST contains alcohol, which is flammable. Avoid fire, flame, or smoking until the area of your skin where you have applied EVAMIST has dried.

What are the possible side effects of EVAMIST?

Side effects are grouped by how serious they are and how often they happen when you are treated.

Serious, but less common side effects include:

- heart attack
- stroke
- blood clots
- dementia
- breast cancer
- cancer of the lining of the uterus (womb)
- cancer of the ovary
- high blood pressure
- high blood sugar
- gallbladder disease
- liver problems
- changes in your thyroid hormone levels
- enlargement of benign tumors of the uterus (“fibroids”)

Call your healthcare provider right away if you get any of the following warning signs or any other unusual symptoms that concern you:

- new breast lumps
- unusual vaginal bleeding
- changes in vision or speech
- sudden new severe headaches
- severe pains in your chest or legs with or without shortness of breath, weakness and fatigue

Less serious, but common side effects include:

- headache
- breast pain
- irregular vaginal bleeding or spotting

- stomach or abdominal cramps, bloating
- nausea and vomiting
- hair loss
- fluid retention
- vaginal yeast infection

These are not all the possible side effects of EVAMIST. For more information, ask your healthcare provider or pharmacist. Tell your healthcare provider if you have any side effect that bothers you or does not go away. You may report side effects to Perrigo at 1-866-634-9120 or to FDA at 1-800-FDA-1088.

What can I do to lower my chances of a serious side effect with EVAMIST?

- Talk with your healthcare provider regularly about whether you should continue using EVAMIST.
- If you have a uterus, talk with your healthcare provider about whether the addition of a progestin is right for you.
- The addition of a progestin is generally recommended for women with a uterus to reduce the chance of getting cancer of the uterus.
- See your healthcare provider right away if you get vaginal bleeding while using EVAMIST.
- Have a pelvic exam, breast exam, and mammogram (breast X-ray) every year unless your healthcare provider tells you something else.
- If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram, you may need to have breast exams more often.
- If you have high blood pressure, high cholesterol (fat in the blood), diabetes, weight, or if you use tobacco, you may have a higher chance of getting heart disease.

Ask your healthcare provider for ways to lower your chances of getting heart disease.

How should I store EVAMIST?

- Store EVAMIST at room temperature 68°F to 77°F (20°C to 25°C)
- **Do not** freeze.
- Safely throw away medicine that is out of date or no longer needed.

Keep EVAMIST and all medicines out of the reach of children.

General information about the safe and effective use of EVAMIST.

Medicines are sometimes prescribed for conditions other than those listed in patient information leaflets. Do not use EVAMIST for conditions for which it was not prescribed. Do not give EVAMIST to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about EVAMIST. If you would like more information, talk with your healthcare provider or pharmacist. You can ask for information about EVAMIST that is written for health professionals.

For more information, go to www.Evamist.com or call Perrigo at 1-866-634-9120.

What are the ingredients in EVAMIST?

Active ingredient: estradiol

Inactive ingredients: octisalate, alcohol

Instructions for Use

EVAMIST (EE-vuh-mist)

(estradiol transdermal spray)

Read this Instructions for Use before you start using EVAMIST and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your menopausal symptoms or your treatment.

The parts of your EVAMIST applicator

EVAMIST comes in a spray applicator that delivers a measured amount of estradiol to your skin with each spray (see Figure A).

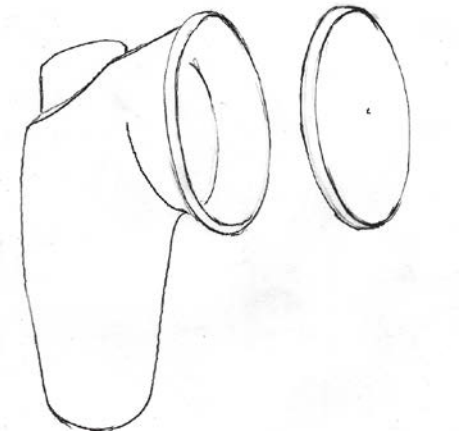

Figure A

Step 1. Priming your EVAMIST

- **Before you use your EVAMIST applicator for the first time, the applicator must be primed.**
- Hold the EVAMIST applicator upright. Keep the cover on. Fully press down the pump button 3 times with your thumb or index finger (see Figure B). After priming, the EVAMIST applicator is ready to use.
- **The EVAMIST applicator should be primed only 1 time when you first start using a new applicator. Do not** prime the EVAMIST applicator before your dose each day.

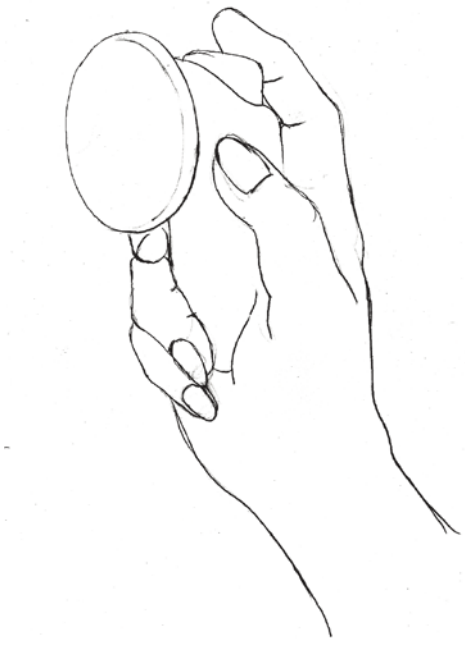

Figure B

Step 2. Using your EVAMIST

- Remove the plastic cover.
- Apply EVAMIST to a clean, dry, unbroken skin area on the inside of your forearm between the elbow and the wrist (see Figure C). This area must be clean, dry, and the skin must be without open wounds, cuts, abrasions, or rashes.
- Hold the EVAMIST applicator upright and rest the plastic cone flat against your skin. You may need to change the position of your arm or the position of the cone on your arm so that the cone is flat against your skin and there are no gaps between the cone and your skin (see Figure C).
- Press the pump button down fully 1 time (see Figure C).

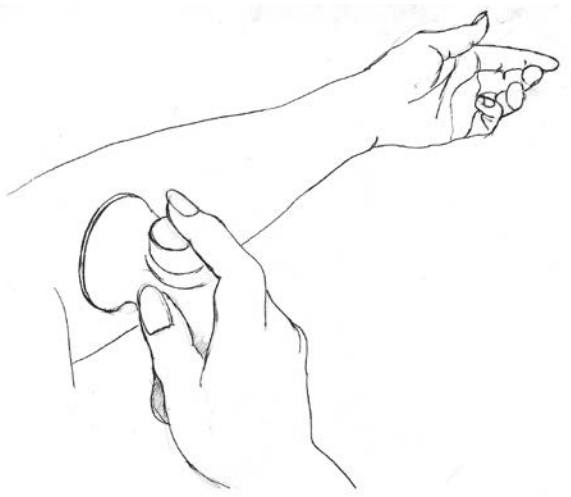

Figure C

If your healthcare provider tells you to increase your dose to 2 or 3 sprays, move the cone before applying the second or third spray to an area of your skin next to but not touching the area of the previous spray (see Figure D).

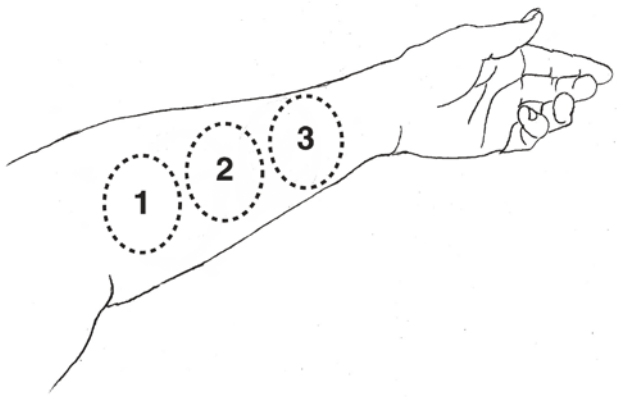

Figure D

- **Do not** apply EVAMIST to your breasts or in and around your vagina.
- **Do not** massage or rub EVAMIST into your skin.
- Let EVAMIST spray dry on your skin for at least:
  - 2 minutes before you cover your skin with clothing.
  - 1 hour before you wash your skin.

Step 3. After you use EVAMIST

- Place the plastic cover back on the EVAMIST applicator cone.
- EVAMIST is flammable until dry. Avoid fire, flame, or smoking until the area of your skin where you have applied EVAMIST has completely dried.

Step 4. Throwing away used EVAMIST applicators

- Your EVAMIST applicator contains enough medicine to allow for initial priming of the pump with 3 sprays and application of 56 sprays.
- **Do not** use your EVAMIST applicator for more than 56 application sprays even though the bottle may not be completely empty. You may not get the correct dose.
- Always replace the cover over the cone of your EVAMIST applicator before you throw it away to prevent accidental exposure to other people or pets.

This Patient Information and Instructions for Use have been approved by the U.S. Food and Drug Administration.

Manufactured by
DPT Laboratories. Ltd
San Antonio, TX 78215

Perrigo®
Pharmaceuticals

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