



NDA 22-014/S-001

**APPROVAL LETTER**

KV Pharmaceutical Company  
Attention: Alison Parks  
Manager, Regulatory Labeling  
2503 South Hanley Road  
St. Louis, MO 63144-2255

Dear Ms. Parks:

Please refer to your supplemental new drug application dated September 27, 2007, received September 28, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Evamist™ (estradiol transdermal spray).

We also acknowledge receipt of your submissions dated March 24, 26, 31, and April 9, 2008.

This "Changes Being Effected in 30 days" supplemental new drug application provides for revisions to the labeling to include new marketer and distributor information and updating of the estrogen class labeling of the Package Insert and Patient Package Insert.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html> that is identical to the enclosed, agreed-upon labeling (text for the package insert and patient package insert in PLR format). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "**SPL for approved NDA 22-014/S-001.**"

The final printed labeling (FPL) must be identical to the enclosed package insert and patient package insert.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved supplement NDA 22-014/S-001.**" Approval of this submission by FDA is not required before the labeling is used.

We request that you submit a labeling supplement for the carton and container labels that is consistent with the revisions in the enclosed labeling.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call George Lyght, R.Ph., Sr. Regulatory Health Project Manager, at (301) 796-0948.

Sincerely,

*{See appended electronic signature page}*

Scott Monroe, M.D.  
Director  
Division of Reproductive and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure: Agreed upon labeling

## 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, AND PROBABLE DEMENTIA**

*See full prescribing information for complete boxed warning.*

- There is an increased risk of endometrial cancer in women with a uterus who use unopposed estrogens (5.2)
- Women's Health Initiative substudies reported increased risks of stroke, deep vein thrombosis, pulmonary embolism, invasive breast cancer, myocardial infarction, and probable dementia (14.4, 14.5)
- Estrogens with or without progestins should not be used for the prevention of cardiovascular disease or dementia (5.1, 5.3)
- Use estrogens with or without progestins at the lowest dose and for the shortest duration consistent with treatment goals and individual risks (2)

### **INDICATIONS AND USAGE**

Evamist is an estrogen indicated for the treatment of moderate to severe vasomotor symptoms due to menopause (1)

### **DOSAGE AND ADMINISTRATION**

- One spray once daily to forearm as a starting dose (2.2)
- Increase to two or three sprays daily to forearm based upon clinical response (2.2)

### **DOSAGE FORMS AND STRENGTHS**

- One spray delivers 90 mcL which contains 1.53 mg estradiol

### **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 deep vein thrombosis, pulmonary embolism, or history of these conditions (4, 5.1)

## **FULL PRESCRIBING INFORMATION: CONTENTS\***

### **WARNING - ENDOMETRIAL CANCER, CARDIOVASCULAR AND OTHER RISKS**

#### **1 INDICATIONS AND USAGE**

#### **2 DOSAGE AND ADMINISTRATION**

- 2.1 General Dosing Information
- 2.2 Treatment of Moderate to Severe Vasomotor Symptoms

#### **3 DOSAGE FORMS AND STRENGTH**

#### **4 CONTRAINDICATIONS**

#### **5 WARNINGS AND PRECAUTIONS**

- 5.1 Cardiovascular Disorders
- 5.2 Malignant Neoplasms
- 5.3 Dementia
- 5.4 Gallbladder Disease
- 5.5 Hypercalcemia
- 5.6 Visual Abnormalities
- 5.7 Addition of a Progestin When a Woman Has Not Had a Hysterectomy
- 5.8 Elevated Blood Pressure
- 5.9 Hypertriglyceridemia
- 5.10 Impaired Liver Function and Past History of Cholestatic Jaundice
- 5.11 Hypothyroidism
- 5.12 Fluid Retention
- 5.13 Hypocalcemia
- 5.14 Exacerbation of Endometriosis
- 5.15 Exacerbation of Other Conditions
- 5.16 Alcohol-Based Products are Flammable
- 5.17 Application of Sunscreen
- 5.18 Laboratory Tests
- 5.19 Drug and Laboratory Test Interactions

- Active or recent (within the past year) arterial thromboembolic disease (for example, stroke and myocardial infarction) (4, 5.1)
- Known liver dysfunction or disease (4, 5.9)
- Known or suspected pregnancy (4, 8.1)

### **WARNINGS AND PRECAUTIONS**

- An increased risk of stroke, deep vein thrombosis, pulmonary embolism, myocardial infarction, and probable dementia has been reported with the use of estrogens with or without progestins (5.1, 5.3)
- An increased risk of invasive breast cancer has been reported with the use of estrogens plus progestins (5.2)
- Estrogens increase the risk of gallbladder disease (5.4)
- Discontinue estrogens if severe hypercalcemia, loss of vision, severe hypertriglyceridemia or cholestatic jaundice occurs (5.5, 5.6, 5.9, 5.10)
- Monitor thyroid function in women on thyroid hormone replacement therapy (5.11, 5.19)

### **ADVERSE REACTIONS**

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

To report SUSPECTED ADVERSE REACTIONS, contact Ther-Rx Corporation at 1-877-567-7676 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### **DRUG INTERACTIONS**

- Estrogen products may interact with inducers and inhibitors of CYP3A4 (7.1)

### **USE IN SPECIFIC POPULATIONS**

- Nursing Mothers: Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the breast milk (8.2)
- Geriatric Use: An increased risk of probable dementia in women over 70 years of age was reported in the two substudies of the Women's Health Initiative Memory Study (8.4)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 04/2008

## **6 ADVERSE REACTIONS**

- 6.1 Clinical Study Experience
- 6.2 Additional Adverse Reactions Reported With Estrogen and/or Progestin Therapy

## **7 DRUG INTERACTIONS**

- 7.1 Metabolic Interactions

## **8 USE IN SPECIFIC POPULATIONS**

- 8.1 Pregnancy
- 8.2 Nursing Mothers
- 8.3 Pediatric Use
- 8.4 Geriatric Use

## **10 OVERDOSAGE**

## **11 DESCRIPTION**

## **12 CLINICAL PHARMACOLOGY**

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

## **13 NONCLINICAL TOXICOLOGY**

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

## **14 CLINICAL STUDIES**

- 14.1 Effects on Vasomotor Systems
- 14.2 Effect of Application Site Washing
- 14.3 Potential for Estradiol Transfer
- 14.4 Women's Health Initiative Studies
- 14.5 Women's Health Initiative Memory Study

## **15 REFERENCES**

## **16 HOW SUPPLIED/STORAGE AND HANDLING**

## **17 PATIENT COUNSELING INFORMATION**

- 17.1 Vaginal Bleeding
- 17.2 Common Adverse Reactions with Estrogen
- 17.3 FDA-Approved Patient Labeling

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

## FULL PRESCRIBING INFORMATION

### WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR AND OTHER RISKS

#### ENDOMETRIAL CANCER

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 [see *Warnings and Precautions* (5.2)].

#### CARDIOVASCULAR AND OTHER RISKS

Estrogens with or without progestins should not be used for the prevention of cardiovascular disease or dementia [see *Warnings and Precautions* (5.1) and (5.3) and *Clinical Studies* (14.4 and 14.5)].

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 6.8 years and 7.1 years, respectively, of treatment with daily oral conjugated estrogens (CE 0.625 mg), relative to placebo [see *Warnings and Precautions* (5.1) and *Clinical Studies* (14.4)].

The estrogen plus progestin WHI substudy reported increased risk of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and DVT 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 (5.2) and *Clinical Studies* (14.4)].

The Women's Health Initiative Memory Study (WHIMS), a substudy of the WHI, reported 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 and during 4 years of treatment with daily CE 0.625 mg 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* (8.4) and *Clinical Studies* (14.5)].

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. Because of these risks, 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.

## 1 INDICATIONS AND USAGE

Evamist (estradiol transdermal spray) is an estrogen indicated for the treatment of moderate to severe vasomotor symptoms due to menopause.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 General Dosing Information

When estrogen is prescribed for a postmenopausal woman with a uterus, generally, a progestin should also be initiated to reduce the risk of endometrial cancer. A woman without a uterus does not need progestin.

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 (for example at 3-month to 6-month intervals) to determine if treatment is still necessary.

### 2.2 Treatment of Moderate to Severe Vasomotor Symptoms

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 and the site should not be washed for 30 minutes. Application of Evamist to other skin surfaces has not been adequately studied. Evamist should not be applied to skin surfaces other than the forearm.

## 3 DOSAGE FORM AND STRENGTH

Evamist is an estradiol transdermal spray. One spray delivers 90 mcL which contains 1.53 mg of estradiol.

## 4 CONTRAINDICATIONS

Evamist should not be used 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 deep vein thrombosis, pulmonary embolism, or history of these conditions
- Active or recent (within the past year) arterial thromboembolic disease (for example, stroke and myocardial infarction)
- Known liver dysfunction or disease
- Known or suspected pregnancy

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Cardiovascular Disorders

An increased risk of stroke and deep vein thrombosis (DVT) has been reported with estrogen alone therapy. An increased risk of stroke, DVT, pulmonary embolism, and myocardial infarction has been reported with estrogen plus progestin therapy. Should any of these occur or be suspected, estrogens with or without progestins should be discontinued immediately.

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

#### Stroke

In the Women's Health Initiative (WHI) estrogen alone substudy, a statistically significant increased risk of stroke was reported in women receiving daily conjugated estrogens (CE 0.625 mg) compared to placebo (45 versus 33 per 10,000 women-years). The increase in risk was demonstrated in year 1 and persisted<sup>1</sup> [see *Clinical Studies* (14.4)].

In the estrogen plus progestin substudy of WHI, a statistically significant increased risk of stroke was reported in women receiving daily CE 0.625 mg plus medroxyprogesterone acetate (MPA 2.5 mg) compared to placebo (31 versus 24 per 10,000 women-years). The increase in risk was demonstrated after the first year and persisted [see *Clinical Studies* (14.4)].

#### Coronary heart disease

In the estrogen alone substudy of WHI, no overall effect on coronary heart disease (CHD) events (defined as non-fatal myocardial infarction [MI], silent MI, or CHD death) was reported in women receiving estrogen alone compared to placebo<sup>2</sup> [see *Clinical Studies* (14.4)].

In the estrogen plus progestin substudy of the WHI, no statistically significant increase of CHD events was reported in women receiving CE/MPA compared to women receiving placebo (39 versus 33 per 10,000 women-years). 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* (14.4)].

In postmenopausal women with documented heart disease (n = 2,763, average age 66.7 years), 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/MPA 2.5 mg demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE/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 CE/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/MPA group and the placebo group in HERS, HERS II, and overall.

#### *Venous Thromboembolism (VTE)*

In the estrogen alone substudy of WHI, the risk of VTE (DVT and pulmonary embolism [PE]) was reported to be increased for women receiving daily CE 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<sup>3</sup> [see *Clinical Studies* (14.4)].

In the estrogen plus progestin substudy of WHI, a statistically significant two-fold greater rate of VTE was reported in women receiving daily CE/MPA 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 [see *Clinical Studies* (14.4)].

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 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. 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 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 this issue in estrogen alone users is the Women's Health Initiative (WHI) substudy of daily conjugated estrogens (CE 0.625 mg). In the estrogen alone substudy of WHI, after an average of 7.1 years of follow-up, daily CE 0.625 mg was not associated with an increased risk of invasive breast cancer (relative risk [RR] 0.80, 95 percent nominal confidence interval [nCI] 0.62-1.04) [see *Clinical Studies* (14.4)].

The most important randomized clinical trial providing information about this issue in estrogen plus progestin users is the Women's Health Initiative (WHI) substudy of daily CE 0.625 mg plus medroxyprogesterone acetate (MPA 2.5 mg). In the estrogen plus progestin substudy, after a mean follow-up of 5.6 years, the WHI substudy reported an increased risk of breast cancer in women

who took daily CE/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 (95 percent nCI 1.01-1.54), and the absolute risk was 41 versus 33 cases per 10,000 women-years, for estrogen plus progestin compared with placebo, respectively. 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 estrogen plus progestin 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 estrogen plus progestin compared with placebo. In the same substudy, invasive breast cancers were larger and diagnosed at a more advanced stage in the CE/MPA 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 [see *Clinical Studies* (14.4)].

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 estrogen plus progestin substudy of the WHI reported that daily CE/MPA increased the risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE/MPA versus placebo was 1.58 (95 nCI, 0.77-3.24) but was not statistically significant. The absolute risk for CE/MPA vs. placebo was 4.2 versus 2.7 cases per 10,000 women-years. In some epidemiologic studies, the use of estrogen-only products, in particular for 10 or more years, has been associated with an increased risk of ovarian cancer. Other epidemiologic studies have not found these associations.

## **5.3 Dementia**

In the estrogen alone Women's Health Initiative Memory Study (WHIMS), a substudy of the WHI, a population of 2,947 hysterectomized women 65 to 79 years of age was randomized to daily conjugated estrogens (CE 0.625 mg) or placebo. In the estrogen plus progestin WHIMS substudy, a population of 4,532 postmenopausal women 65 to 79 years of age was randomized to daily CE 0.625 mg plus medroxyprogesterone acetate (MPA 2.5 mg) or placebo.

In the estrogen alone substudy, after an average follow-up of 5.2 years, 28 women in the CE 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 women-years [see *Use in Specific Populations* (8.4) and *Clinical Studies* (14.5)].

In the estrogen plus progestin substudy, after an average follow-up of 4 years, 40 women in the CE/MPA group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE/MPA versus placebo was 2.05 (95 percent CI, 1.21-3.48). The absolute risk of probable dementia for CE/MPA versus placebo was 45 versus 22 cases per 10,000 women-years [see *Use in Specific Populations* (8.4) and *Clinical Studies* (14.5)].

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). Since both substudies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women [see *Use in Specific Populations (8.4) and Clinical Studies (14.5)*].

#### **5.4 Gallbladder Disease**

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

#### **5.5 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.

#### **5.6 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.

#### **5.7 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 a possible increased risk of breast cancer, adverse effects on lipoprotein metabolism (lowering HDL, raising LDL), and impairment of glucose tolerance.

#### **5.8 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. Blood pressure should be monitored at regular intervals with estrogen use.

#### **5.9 Hypertriglyceridemia**

In women with preexisting hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications. Consider discontinuation of treatment if pancreatitis or other complications develop.

#### **5.10 Impaired Liver Function and 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.

#### **5.11 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<sub>4</sub> and T<sub>3</sub> 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.

#### **5.12 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 dysfunction, warrant careful observation when estrogens are prescribed.

#### **5.13 Hypocalcemia**

Estrogens should be used with caution in women with preexisting severe hypocalcemia.

#### **5.14 Exacerbation of Endometriosis**

Endometriosis may be exacerbated with administration of estrogens. 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.

#### **5.15 Exacerbation of Other Conditions**

Estrogens 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.

#### **5.16 Alcohol-Based Products are Flammable**

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

#### **5.17 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.

#### **5.18 Laboratory Tests**

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

#### **5.19 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<sub>4</sub> levels (by column or by radioimmunoassay) or T<sub>3</sub> levels by radioimmunoassay. T<sub>3</sub> resin uptake is decreased, reflecting the elevated TBG. Free T<sub>4</sub> and free T<sub>3</sub> concentrations are unaltered. Women on thyroid hormone replacement therapy may require higher doses of thyroid hormone.

Other binding proteins may be elevated in serum [ corticosteroid binding globulin (CBG), SHBG], leading to increased total circulating corticosteroids and sex steroids, respectively. Free hormone concentrations, such as testosterone and estradiol, may be decreased. As with other transdermal estradiol products, a slight increase in SHBG was seen with Evamist active drug compared with baseline.

Increased plasma HDL and HDL<sub>2</sub> cholesterol subfraction concentrations, reduced LDL cholesterol concentration, increased triglyceride levels.

Impaired glucose tolerance.

### **6 ADVERSE REACTIONS**

#### **6.1 Clinical Study 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 practice.

In a 12-week, randomized, placebo-controlled trial of Evamist in 454 women, 80-90 percent of women randomized to active drug received at least 70 days of therapy and 75-85 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)
<b>Reproductive System and Breast Disorders</b>						
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)
<b>Gastrointestinal Disorders</b>						
Nausea	5 (7)	1 (1)	1 (1)	2 (3)	4 (5)	2 (3)
<b>Infections and Infestations</b>						
Nasopharyngitis	1 (1)	4 (5)	2 (3)	3 (4)	1 (1)	1 (1)
<b>Musculoskeletal and Connective Tissue Disorders</b>						
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)
<b>Nervous system</b>						
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 Additional Adverse Reactions Reported With Estrogen and/or Progestin Therapy

The following additional adverse reactions have been reported with estrogen and/or progestin therapy.

### Genitourinary System

Abnormal uterine bleeding/spotting, dysmenorrhea/pelvic pain, increase in size of uterine leiomyomata, vaginitis including vaginal candidiasis, change in amount of cervical secretion, changes in cervical ectropion, ovarian cancer, endometrial hyperplasia, endometrial cancer.

### Breasts

Tenderness, enlargement, pain, nipple discharge, galactorrhea, fibrocystic breast changes, breast cancer.

### Cardiovascular

Deep and superficial venous thrombosis, pulmonary embolism, thrombophlebitis, myocardial infarction, stroke, increase in blood pressure.

### Gastrointestinal

Nausea, vomiting, abdominal cramps, bloating, cholestatic jaundice, increased incidence of gallbladder disease, pancreatitis, enlargement of hepatic hemangiomas.

### Skin

Chloasma or melasma, that may persist when drug is discontinued; erythema multiforme, erythema nodosum, hemorrhagic eruption, loss of scalp hair, hirsutism, pruritus, rash.

### Eyes

Retinal vascular thrombosis, intolerance to contact lenses.

### Central Nervous System

Headache, migraine, dizziness, mental depression, exacerbation of chorea, nervousness, mood disturbances, irritability, exacerbation of epilepsy, dementia.

### Miscellaneous

Increase or decrease in weight, glucose intolerance, aggravation of porphyria, edema, arthralgias, leg cramps, changes in libido, urticaria, angioedema, anaphylactoid/anaphylactic reactions, hypocalcemia (preexisting condition), exacerbation of asthma, increased triglycerides.

## 7 DRUG INTERACTIONS

No formal 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 preparations (Hypericum perforatum), 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.

### 8.2 Nursing Mothers

Evamist should not be used during lactation. Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk. Detectable amounts of estrogens have been identified in the milk of mothers receiving this drug.

### 8.3 Pediatric Use

Evamist is not intended for pediatric use and no clinical data have been collected in children.

### 8.4 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.

In the estrogen alone substudy of the Women's Health Initiative (WHI) study, 46 percent (n = 4,943) of women were 65 years of age and older, while 7.1 percent (n = 767) of women were 75 years of age and older. There was a higher relative risk (daily conjugated estrogens [CE 0.625 mg] versus placebo) of stroke in women less than 75 years of age compared to women 75 years of age 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, 65 to 79 years of age, was randomized to receive daily conjugated estrogens (CE 0.625 mg) or placebo. After an average follow-up of 5.2 years, the relative risk (CE 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 to placebo.

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 Spray (N = 23)	3 Spray (N = 24)
C <sub>max</sub> (pg/mL) <sup>1</sup>	36.4 (62)	57.4 (94)	54.1 (50)
C <sub>min</sub> (pg/mL) <sup>1</sup>	11.3 (52)	18.1 (51)	19.6 (27)
C <sub>avg</sub> (pg/mL) <sup>1</sup>	19.6 (49)	30.7 (43)	30.9 (30)
AUC <sub>0-24</sub> (pg*hr/mL) <sup>1</sup>	471 (49)	736 (43)	742 (30)
T <sub>max</sub> (hours) <sup>2</sup>	20 (0-24)	18 (0-24)	20 (0-24)

<sup>1</sup> Values expressed are arithmetic means (%CV)

<sup>2</sup> 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 sex hormone binding globulin (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.

### 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  $\geq 56$  moderate to severe vasomotor symptoms per week ( $\geq 8$  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 <sup>a</sup> (SD)	
Treatment (N)	Baseline Mean (SD)	Week 4 Mean (SD)	Week 12 Mean (SD)
<b>1 Spray</b>			
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 <sup>b</sup>	—	-2.62	-3.34
p-value <sup>c</sup>	—	0.0010	0.0004
<b>2 Sprays</b>			
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 <sup>b</sup>	—	-2.56	-2.47
p-value <sup>c</sup>	—	0.0027	0.0099
<b>3 Sprays</b>			
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 <sup>b</sup>	—	-2.10	-3.12
p-value <sup>c</sup>	—	0.0002	<0.0001

<sup>a</sup> Mean change and difference based on raw data

<sup>b</sup> Evamist versus placebo

<sup>c</sup> 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)<sup>a</sup>**

		Mean Change from Baseline <sup>b</sup> (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 <sup>c</sup>	—	-0.28	-0.78
p-value <sup>d</sup>	—	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 <sup>c</sup>	—	-0.32	-0.38
p-value <sup>d</sup>	—	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 <sup>c</sup>	—	-0.30	-0.76
p-value <sup>d</sup>	—	0.0031	<0.0001

<sup>a</sup> Severity score calculated as: (2 x number moderate + 3 x number severe) / number moderate + number severe)

<sup>b</sup> Mean change and difference based on raw data

<sup>c</sup> Evamist versus placebo

<sup>d</sup> Tests for pairwise differences using ANCOVA

## 14.2 Effect of Application Site Washing

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

## 14.3 Potential for Estradiol Transfer

The effect of estradiol transfer was evaluated in 20 healthy postmenopausal women who applied three 90 mL 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. No significant transfer of estradiol was observed in persons who came in contact with the application site of estradiol-treated individuals.

## 14.4 Women's Health Initiative Studies

The Women's Health Initiative (WHI) enrolled approximately 27,000 predominantly healthy postmenopausal women in two substudies to assess the risks and benefits of either the use of daily oral conjugated estrogens (CE 0.625 mg) alone or in combination with medroxyprogesterone acetate (MPA 2.5 mg) compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of coronary heart disease (CHD) (nonfatal myocardial infarction [MI], silent MI and CHD death), with invasive breast cancer as the primary adverse outcome studied. A "global index" included the earliest occurrence of CHD, invasive breast cancer, stroke, pulmonary embolism (PE), endometrial cancer (only in the CE/MPA substudy), colorectal cancer, hip fracture, or death due to other cause. These substudies did not evaluate the effects of CE or CE/MPA on menopausal symptoms.

The 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 6.8 years are presented in Table 5.

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 6 fewer hip fractures. The absolute excess risk of events included in the "global index" was a non-significant 2 events per 10,000 women-years. There was no difference between the groups in terms of all-cause mortality [see *Warnings and Precautions* (5)].

Final centrally adjudicated results for CHD events and centrally adjudicated results for invasive breast cancer incidence from the estrogen alone substudy, after an average follow-up of 7.1 years, reported 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 (see Table 5).<sup>2,4</sup>

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 (see Table 5).<sup>1</sup>

The estrogen plus progestin substudy was also stopped early. According to the predefined stopping rule, after an average follow-up of 5.2 years of treatment, the increased risk of 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 (relative risk [RR] 1.15, 95 percent nCI, 1.03-1.28).

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/MPA were 6 more CHD events, 7 more strokes, 10 more PEs, and 8 more invasive breast cancers, while the absolute risk reduction per 10,000 women-years were 7 fewer colorectal cancers and 5 fewer hip fractures [see *Warnings and Precautions* (5)].

Results of the estrogen plus progestin 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 5. Relative and Absolute Risk Seen in the Estrogen Alone Substudy of WHI**

Event	Relative Risk CE vs. Placebo (95% nCI <sup>a</sup> )	Placebo (n = 5,429)	CE (n = 5,310)
		Absolute Risk per 10,000 Women-Years	
CHD events <sup>b</sup>	0.95 (0.79-1.16)	56	53
Non-fatal MI <sup>b</sup>	0.91 (0.73-1.14)	43	40
CHD death <sup>b</sup>	1.01 (0.71-1.43)	16	16
Stroke <sup>b</sup>	1.37 (1.09-1.73)	33	45
Ischemic <sup>b</sup>	1.55 (1.19-2.01)	25	38
Deep vein thrombosis <sup>b,d</sup>	1.47 (1.06-2.06)	15	23
Pulmonary embolism <sup>b</sup>	1.37 (0.90-2.07)	10	14
Invasive breast cancer <sup>b</sup>	0.80 (0.62-1.04)	34	28
Colorectal cancer <sup>c</sup>	1.08 (0.75-1.55)	16	17
Hip fracture <sup>c</sup>	0.61 (0.41-0.91)	17	11
Vertebral fractures <sup>c,d</sup>	0.62 (0.42-0.93)	17	11
Total fractures <sup>c,d</sup>	0.70 (0.63-0.79)	195	139
Death due to other causes	1.08 (0.88-1.32)	50	53
Overall mortality <sup>c,d</sup>	1.04 (0.88-1.22)	78	81
Global index <sup>c,f</sup>	1.01 (0.91-1.12)	190	192

<sup>a</sup> Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.

<sup>b</sup> Results are based on centrally adjudicated data for an average follow-up of 7.1 years.

<sup>c</sup> Results are based on an average follow-up of 6.8 years.

<sup>d</sup> Not included in global index.

<sup>e</sup> All deaths, except from breast or colorectal cancer, definite/probable CHD, PE or cerebrovascular disease.

<sup>f</sup> A subset of the events was combined in a “global index,” defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture, or death due to other causes.

#### 14.5 Women’s Health Initiative Memory Study

The estrogen alone Women’s Health Initiative Memory Study (WHIMS), a substudy of the WHI, enrolled 2,947 predominantly healthy postmenopausal women 65 years of age and older (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 conjugated estrogen (CE 0.625 mg) on the incidence of probable dementia (primary outcome) compared to placebo.

After an average follow-up of 5.2 years, 28 women in the estrogen alone group (37 per 10,000 women-years) and 19 in the placebo group (25 per 10,000 women-years) were diagnosed with probable dementia. The relative risk of probable dementia in the estrogen alone group was 1.49 (95 percent CI, 0.83-2.66) compared to placebo. It is unknown whether these findings apply to younger postmenopausal women [see *Warnings and Precautions* (5.3) and *Use in Specific Populations* (8.4)].

The estrogen plus progestin WHIMS substudy 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 medroxyprogesterone acetate (MPA 2.5 mg) on the incidence of probable dementia (primary outcome) compared to placebo.

After an average follow-up of 4 years, 40 women in the estrogen plus progestin group (45 per 10,000 women-years) and 21 in the placebo group (22 per 10,000 women-years) were diagnosed with probable dementia. The relative risk of probable dementia in the hormone therapy group was 2.05 (95

percent CI, 1.21- 3.48) compared to placebo.

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* (8.4)].

**Table 6. Relative and Absolute Risk Seen in the Estrogen Plus Progestin Substudy of WHI at an Average of 5.6 Years<sup>a</sup>**

Event	Relative Risk CE/MPA vs. Placebo (95% nCI <sup>b</sup> )	Placebo (n = 8,102)	CE/MPA (n = 8,506)
		Absolute Risk per 10,000 Women-Years	
CHD events	1.24 (1.00-1.54)	33	39
Non-fatal MI	1.28 (1.00-1.63)	25	31
CHD death	1.10 (0.70-1.75)	8	8
All strokes	1.31 (1.02-1.68)	24	31
Ischemic stroke	1.44 (1.09-1.90)	18	26
Deep vein thrombosis	1.95 (1.43-2.67)	13	26
Pulmonary embolism	2.13 (1.45-3.11)	8	18
Invasive breast cancer <sup>c</sup>	1.24 (1.01-1.54)	33	41
Invasive colorectal cancer	0.56 (0.38-0.81)	16	9
Endometrial cancer	0.81 (0.48-1.36)	7	6
Cervical cancer	1.44 (0.47-4.42)	1	2
Hip fracture	0.67 (0.47-0.96)	16	11
Vertebral fractures	0.65 (0.46-0.92)	17	11
Lower arm/wrist fractures	0.71 (0.59-0.85)	62	44
Total fractures	0.76 (0.69-0.83)	199	152

<sup>a</sup> Results are based on centrally adjudicated data. Mortality data was not part of the adjudicated data; however, data at 5.2 years of follow-up showed no difference between the groups in terms of all-cause mortality (RR 0.98, 95 percent nCI, 0.82-1.18).

<sup>b</sup> Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.

<sup>c</sup> Includes metastatic and non-metastatic breast cancer, with the exception of in situ breast cancer.

## 15 REFERENCES

- Hendrix, SL, et al. Effects of Conjugated Equine Estrogen on Stroke in the Women’s Health Initiative. *Circulation*. 2006;113:2425-2434.
- Hsia J, et al. Conjugated Equine Estrogens and Coronary Heart Disease. *Arch Int Med*. 2006;166:357-365.
- Curb JD, et al. Venous Thrombosis and Conjugated Equine Estrogen in Women Without a Uterus. *Arch Int Med*. 2006; 166:772-780.
- Stefanick ML, et al. Effects of Conjugated Equine Estrogens on Breast Cancer and Mammography Screening in Postmenopausal Women With Hysterectomy. *JAMA*. 2006;295:1647-1657.

## 16 HOW SUPPLIED / STORAGE AND HANDLING

Evamist (NDC 64011-215-41) 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 accurately deliver 56 sprays of 90 mcL after priming. One spray contains 1.53 mg estradiol.

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 25°C (77°F) with excursion permitted to 15° to 30°C (59° to 86°F). Do not freeze.

## 17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (17.3)

### 17.1 Vaginal Bleeding

Inform women of the importance of reporting vaginal bleeding to their healthcare provider as soon as possible.

### 17.2 Common Adverse Reactions with Estrogen

Inform women of the possible side effects of estrogen therapy such as headache, breast pain and tenderness, nausea and vomiting.

### 17.3 FDA-Approved Patient Labeling

#### Evamist

(estradiol transdermal spray)

#### Instructions for use.

##### Read carefully.

Read this PATIENT INFORMATION before you start using Evamist and read the patient information each time you refill your Evamist prescription. There may be new information. This information does not take the place of talking to your healthcare provider about your menopausal symptoms and their treatment.

#### WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT EVAMIST (AN ESTROGEN HORMONE)?

- Estrogens increase the chance of getting cancer of the uterus.  
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 out the cause.
- Do not use estrogens with or without progestins to prevent heart disease, heart attacks, strokes or dementia.  
Using estrogens, with or without progestins, may increase your chance of getting heart attacks, strokes, breast cancer, and blood clots. Using estrogen, with or without progestins, may increase your chance of getting dementia, based on a study of women 65 years of age or older. You and your healthcare provider should talk regularly about whether you still need treatment with Evamist.

#### What is Evamist?

Evamist is a medicine that contains estradiol (an estrogen hormone). When applied to the skin, estradiol is absorbed through the skin into the bloodstream.

#### What is Evamist used for?

Evamist 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, a woman's ovaries are removed during an operation that 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 estrogen treatment. 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
- 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 in the past year
- Currently have or have had blood clots
- Currently have or have had liver problems
- Are allergic to any of the ingredients in Evamist

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

- Think you may be pregnant

#### Tell your healthcare provider:

- If you are breastfeeding

The hormone in Evamist can pass into your breast milk.

- About all your medical problems

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

- About all the medicines you take

This includes prescription and nonprescription medicines, vitamins, and herbal supplements. Some medicines may affect how Evamist works. Evamist may also affect how your other medicines work.

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

You may need to stop taking estrogens.

#### How should I use Evamist?

Evamist is available in a spray applicator that delivers a measured amount of estradiol to the skin with each spray (see Illustration 1).

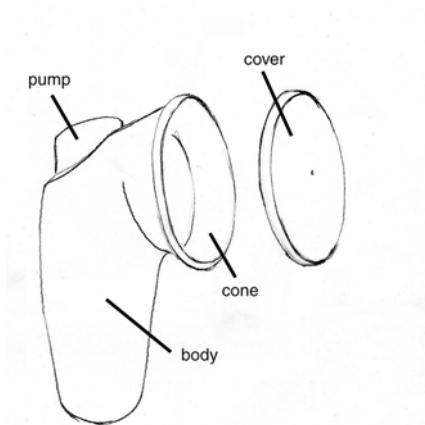


Illustration 1

It is important that you read and follow these directions on how to use Evamist properly.

1. Before using the applicator for the first time, it must be primed. With the cover on, and the applicator upright, fully depress the applicator three times with your thumb or index finger. This is called priming (see Illustration 2). After priming, the applicator is ready to use. The applicator should be primed only once when you first start using a new applicator. **DO NOT PRIME THE APPLICATOR BEFORE EACH DAY'S DOSE.**

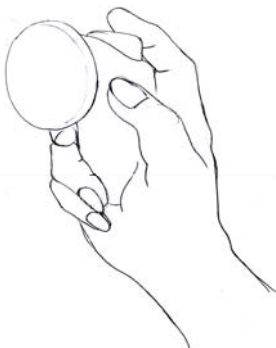


Illustration 2

2. Apply Evamist at the same time each day.
3. Apply your daily dose of Evamist to clean, dry, unbroken skin on the inside of the forearm between the elbow and the wrist (see Illustration 3). Do not apply Evamist to other areas of the skin. To apply the dose, remove the plastic cover, hold the applicator upright and rest the plastic cone flat against the 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. Depress the pump fully once.

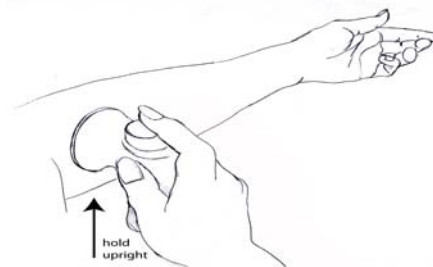


Illustration 3

4. If your healthcare provider tells you to increase the dose to 2 or 3 sprays, you should move the cone before applying the second or third spray to an area of the skin next to but not touching the area of the previous spray (see Illustration 4).

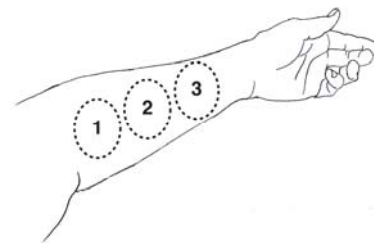


Illustration 4

5. Always place the protective cover back on the cone of the applicator.
6. Do not massage or rub Evamist into the skin. Simply allow the spray to dry for at least 2 minutes before dressing, and at least 30 minutes before washing.
7. Evamist contains alcohol, and alcohol-based liquids are flammable. Avoid fire, flame or smoking when using Evamist until the spray has dried. Do not apply Evamist while standing near a flame.
8. Never apply Evamist directly to the breast or in or around the vagina.

Start at the lowest dose (1 spray) and talk to your healthcare provider about how well that dose is working for you. Treatment with estrogen should be started at the lowest dose possible, and used only for as long as needed to provide relief of moderate to severe hot flashes associated with menopause. You and your healthcare provider should talk regularly (every 3-6 months) about the dose you are taking and whether you still need treatment with Evamist.

The Evamist applicator contains enough product to allow for initial priming of the pump with three sprays plus application for 56 sprays. The product will last approximately 56 days if you use 1 spray each day, 28 days if you use 2 sprays each day and 18 days if you use 3 sprays each day.

Do not use this applicator for more than 56 sprays even though the bottle may not be completely empty.

Evamist can be stored in a clean, dry place at room temperature (15° to 30°C or 59° to 86°F) and does not need refrigeration. Do not freeze. Evamist should not be used after the expiration date. When the applicator has been used for 56 sprays you can discard it in normal household waste.

#### **What should I do if I miss a dose?**

If you miss a dose, do not double the dose on the next day to catch up. If your next dose is less than 12 hours away, it is best just to wait and apply your normal dose the next day. If it is more than 12 hours until the next dose, apply the dose you missed and resume your normal dosing the next day.

**What should I avoid while using Evamist?**

- Do not allow others to make contact with the area of skin where you applied the spray for at least 30 minutes after application.
- Evamist contains alcohol and alcohol-based liquids are flammable. Avoid fire, flame or smoking until the spray has dried.

**What are the possible side effects of estrogens?**

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

Serious but less common side effects include:

- Breast cancer
- Cancer of the uterus
- Stroke
- Heart attack
- Blood clots
- Dementia
- Gallbladder disease
- Ovarian cancer
- High blood pressure
- Liver problems
- High blood sugar
- Enlargement of benign tumors of the uterus (“fibroids”)

Some of the warning signs of these serious side effects include:

- Breast lumps
- Unusual vaginal bleeding
- Dizziness and faintness
- Changes in speech
- Severe headaches
- Chest pain
- Shortness of breath
- Pains in your legs
- Changes in vision
- Vomiting
- Yellowing of the skin, eyes or nail beds

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

Less serious but common side effects include:

- Headache
- Breast pain
- Irregular vaginal bleeding or spotting
- Stomach/abdominal cramps, bloating
- Nausea and vomiting
- Hair loss
- Fluid retention
- Vaginal yeast infection

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

**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 (a different prescribed hormone medication) 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 otherwise. If members of your family have had breast cancer or if you have 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, are overweight, 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.

**General information about the safe and effective use of Evamist.**

Medicines are sometimes prescribed for conditions that are not mentioned 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.

**Keep Evamist out of the reach of children.**

This leaflet provides a summary of 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.

You can get more information by calling the toll free number (877) 567-7676.

**What are the ingredients in Evamist?**

Active ingredient: estradiol (an estrogen hormone)

Inactive ingredients: octisalate (a common active ingredient in some sunscreens used to enhance skin penetration), alcohol (to dissolve the drug)

Manufactured by  
DPT  
San Antonio, TX 78215

For  
Ther-Rx Corporation  
St. Louis, MO 63044

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/s/

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Scott Monroe

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