EVAMIST (estradiol transdermal spray)

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 based upon clinical response (2.1).

Contraindications

- 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 deficiencies, or other known thrombophilic disorders (4)
- Known or suspected pregnancy (4, 8.1)

Warnings and Precautions

- Estrogens increase the risk of gastrointestinal disease (5.6)
- Discontinue estrogen if severe hypercalcaemia, loss of vision, severe hypertensive or cerebrovascular disease occurs (5.4, 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 (5.10 percent): headache, breast tenderness and nipple pain, nausea, back pain, and nasopharyngitis (6.1).

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)

Patient Counseling Information

-SEE PATIENT COUNSELING INFORMATION AND FDA-APPROVED PATIENT LABELING Revised: 08/2017

Full Prescribing Information

1 Indications and Usage

1.1 Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause

2 Dosage and Administration

2.1 Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause

3 Dosage Forms and Strengths

4 Contraindications

5 Warnings and Precautions

5.1 Cardiovascular Disorders

5.2 Malignant Neoplasms

5.3 Probable Dementia

5.4 Unintentional Secondary Exposure to Estrogen

5.5 Gallbladder Disease

5.6 Hypercalcemia

5.7 Visual Acne

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

5.9 Elevated Blood Pressure

5.10 Hypertriglyceridemia

5.11 Hepatitis and/or Past History of Cholestatic Jaundice

5.12 Hypothyroidism

5.13 Fluid Retention

5.14 Hypercalcemia

5.15 Exacerbation of Endometriosis

5.16 Hemorrhoidal Angina

5.17 Exacerbation of Other Conditions

5.18 Alcohol-Based Products are Flammable

5.19 Application of Sunscreen

5.20 Laboratory Tests

5.21 Drug and Laboratory Test Interactions

6 Adverse Reactions

6.1 Clinical Trials Experience

6.2 Postmarketing Experience

7 Drug Interactions

8 Use in Specific Populations

8.1 Pregnancy

8.2 Nursing Mothers

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10 How Supplied/Storage and Handling

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12 Clinical Pharmacology

13 Nonclinical Toxicology

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15 Nonclinical Studies

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17 Patient Counseling Information

17.1 Vaginal Bleeding

17.2 Unintentional Secondary Exposure to Estrogen

17.3 Possible Serious Adverse Reactions with Estrogen-Alone Therapy

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

18 Adverse Drug Reactions

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Full Prescribing Information

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

Eight years of treatment with 17 beta-estradiol as 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 WHI estrogen plus progestin ancillary study of the WHI reported an increased risk of developing probable or possible dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CE (0.625 mg) combined with medroxyprogesterone acetate (MPA) [2.5 mg], relative to placebo [see Warnings and Precautions (6.5, 8.3), and Clinical Studies (14.3, 14.5)].

The WHI estrogen plus progestin study reported increased risks of DVT, pulmonary embolism (PE), stroke, DVT, PE, or history of these conditions (4, 5.1) 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 WHI estrogen plus progestin study reported increased risks of probable dementia in postmenopausal women 65 years of age or older (5.3).

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).

The WHI estrogen plus progestin substudy demonstrated an increased risk of invasive breast cancer (5.2).

The WHI estrogen plus progestin substudy also demonstrated an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CE (0.625 mg) combined with MPA (2.5 mg), relative to placebo. It is unclear whether this finding applies to younger postmenopausal women [see Warnings and Precautions (6.3), Use in Specific Populations (8.5), and Clinical Studies (14.4)]

The WHI estrogen plus progestin study also demonstrated an increased risk of invasive breast cancer (see Warnings and Precautions (6.3), and Clinical Studies (14.3)).

In the absence of comparable data, the 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.

Exogenous Progestin Therapy

Cardiovascular Disorders and Probable Dementia

5.17 Exacerbation of Other Conditions

5.18 Alcohol-Based Products are Flammable

5.19 Application of Sunscreen

5.20 Laboratory Tests

5.21 Drug and Laboratory Test Interactions

6 Adverse Reactions

6.1 Clinical Trials Experience

6.2 Postmarketing Experience

7 Drug Interactions

8 Use in Specific Populations

8.1 Pregnancy

8.2 Nursing Mothers

8.3 Pediatric Use

8.4 Dogs and Cats

9 References

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16 Preclinical Studies

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17.2 Unintentional Secondary Exposure to Estrogen

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.

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 50 ml, which contains 1.53 mg estradiol (3).

Contraindications

- Undiagnosed abnormal genital bleeding

- 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 deficiencies, or other known thrombophilic disorders (4)

- Known or suspected pregnancy (4, 8.1)

Warnings and Precautions

- Estrogens increase the risk of gastrointestinal disease (5.6)

- Discontinue estrogen if severe hypercalcaemia, loss of vision, severe hypertensive or cerebrovascular disease occurs (5.4, 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 (5.10 percent): headache, breast tenderness and nipple pain, nausea, back pain, and nasopharyngitis (6.1).

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)

- General 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, 5.5)

See 17 for Patient Counseling Information and FDA-Approved patient labeling Revised: 08/2017.
2.1 Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause

Estrogen 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 on the cover. The cover should be held upright and vertical for spraying.

One, or two sprays are applied each morning, non-overlapping areas on the inner aspect of the upper arm, starting near the elbow. Sprays should be allowed to dry for approximately 2 minutes before coming into contact with the skin. The site should not be washed for at least one hour. Alternatively, estrogen therapy may be initiated in women with known severe adverse vasomotor symptoms due to menopause, if a new hormone replacement therapy approach is considered.

Strict adherence to the following precautions is advised in order to minimize the potential for secondary exposure to estradiol from breast-fed infants. Women should cover the application area with clothing if another person may come into contact with the area with any risk of skin surface contact. In addition, women may minimize the potential for secondary exposure to estradiol by applying Evamist to other skin surfaces that are not likely to come into contact with another person’s skin surface. Women should avoid application to the inner surface of the forearm, starting near the elbow. Sprays should be allowed to dry for at least one hour. Application of Evamist to other skin surfaces has not been adequately studied.

5.2 Malignant Neoplasms

Endometrial Cancer

An increased risk of endometrial cancer has been reported with the use of unopposed estrogen therapy, most commonly in postmenopausal women. The reported endometrial cancer risk associated with unopposed estrogen use is about 2 to 12 times greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with treatment with combined oral contraceptives for less than 5 years and premenopausal women. In the WHI estrogen-alone substudy, an increased risk of endometrial cancer was noted with prolonged use, with an increased risk of 15- to 24-fold for 5 to 10 years or more. This risk has been attributed to the use of continuous estrogen therapy for at least 6 to 15 years after estrogen therapy was stopped. Clinical surveillance of all women using estrogen-alone or estrogen plus progesterin therapy is important, and may include diagnostic procedures and/or management of abnormal uterine bleeding. There is evidence that both the estrogen and the progestin component are needed 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 therapy was outlined in Patient Counseling Information [see Patient Counseling Information (17.2)] and in the Patient Information Leaflet at the end of the prescribing information.

5.3 Probable Dementia

In the WHIMS estrogen-alone ancillary study, the WHIMS population of 2,947 hysterectomized women who were less than 70 years old (mean age 63 years) was randomized to receive estrogen alone or placebo (see Clinical Studies (14.3)). After an average follow-up of 5.2 years, 28 women in the estrogen group and 19 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia in CE-alone versus placebo was 1.49 (95% CI, 1.03-2.15). The absolute risk for probable dementia with low dose CE was 1.3% (95% CI, 0.2-5.8%).

When data from the two populations in the WHIMS estrogen-alone and estrogen plus progesterone ancillary studies were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.84 (95% CI, 1.11-3.02) with the absolute risk for probable dementia for CE plus MPA versus placebo was 2.05 (95% CI, 1.21-3.48).

When data from the two populations in the WHIMS estrogen-alone and estrogen plus progesterone ancillary studies were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.84 (95% CI, 1.11-3.02) with the absolute risk for probable dementia for CE plus MPA versus placebo was 2.05 (95% CI, 1.21-3.48).

5.4 Unintentional Sexual Exposure to Estradiol

Postmarketing reports of breast budding and breast masses in prepubertal females and girls who were exposed to skin surface contact with estradiol elixir during postmenopausal exposure to Estradiol have been reported. In most cases, the condition resolved with removal of Estradiol exposure.

Unexpected changes in breast tissue or other signs of abnormal sexual development in prepubertal children as well as the possibility of unintentional sexual exposure to Estriol 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 Estriol, the physician should counsel the patient and the child about avoiding further exposure. If necessary, the physician 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 estradiol has been reported.

6. ADVERSE REACTIONS

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

• Cardiovascular Disorders
• Malignant Neoplasms

6.1 Hematologic 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 postmenopausal use of estrogen or with pregnancy, caution should be exercised, and in the case of recurrence, medication should be discontinued.

6.4 Hypertension

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 T3 and T4 serum concentrations in the normal range. Women dependent on thyroid hormones should be closely monitored in order to assess whether increasing doses of their thyroid hormone replacement therapy. Women with thyroid hormone functions may be maintained in their free thyroid hormone levels in an acceptable range.

6.5 Fluid Retention

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

6.6 Hypercalcemia

Estrogen therapy should be used with caution in women with hypercalcemia induced by estrogen-induced hypercalcemia may occur.

6.7 Excoriation of Endometrium

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

6.8 Hereditary Angiodyplasia

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

6.11 Alcohol-Related Products are Flammable

Fire, flame or smoke until the spray has dried.

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

• Cardiovascular Disorders
• Malignant Neoplasms

6.12 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.

7.2 Drug and Laboratory Test Interactions

Accelerated prolactinemia, partial thromboplastin time, and platelet aggregation time; increased prolactin level, increased factors II, VII, VIII, IX, X, XI, fibrinogen, von Willebrand factor, and beta-thromboglobulin; increased levels of fibrinopeptide A, decreased antithrombin III, increased levels of fibrinogen, increased plasminogen activator and antiplasmin activity. Decreased levels of T4 may occur. Increased TSH may occur. Increased circulating total thyroid hormone levels, as measured by protein-bound iodine (PBI), T3, T3 level (or by radioimmunoassay) or T3 levels by radioimmunoassay. T3 uptake is decreased, reflecting the elevated T3. Free T3 and free T4 levels are usually increased. Women on thyroid hormone replacement therapy may require higher doses of thyroid hormone.

Other binding proteins may be elevated in serum, e.g., corticosteroid binding globulin (CBG), coreceptor binding globulin (CRB), alpha- or beta-thromboglobulin, cesthaloprotein, corticosteroids and extrabody, respectively. Free hormone concentrations, such as testosterone and estradiol, may be decreased. Other plasma proteins may be increased in women with hypercalcemia, e.g., alpha-1-antitrypsin, ceruloplasmin.

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

Impaired glucose tolerance.
In the WHI estrogen plus progesteron substudy (daily CE [0.625 mg] plus MPA [2.5 mg] versus placebo), there was a higher relative risk of nodal status 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 progesteron when compared to placebo (see Warnings and Precautions [5.5], 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 (see Warnings and Precautions [5.5], 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.

11 DESCRIPTION

Evamist (estradiol transdermal spray) is designed to deliver estradiol to the bloodstream following topical application to the skin of a rapidly drying solution from a metered-dose pump. Estradiol is a homogenous solution of 1.7% estradiol USP (active ingredient) in alcohol USP and ethylcellulose suspension to provide an adhesive backing.

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.

There have been insufficient 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.
For those outcomes included in the WHI “global index” that reached statistical significance after 5 years of follow-up, the absolute risk reduction for 10,000 women-years was 9.2 per 10,000 women-years. For those outcomes included in the WHI “global index” that reached statistical significance after 8 years of follow-up, the absolute risk reduction for 10,000 women-years was 1.2 per 10,000 women-years.

Table 5. Relative and Absolute Risk Seen in the Estrogen Plus Progesterone Substudy of WHI at an Average of 5.6 Yearsa,b

<table>
<thead>
<tr>
<th>Event</th>
<th>Relative Risk CE/MPA vs. Placebo (95% CI)</th>
<th>CE/MPA (n=9,856)</th>
<th>Placebo (n=10,102)</th>
<th>Absolute Risk per 10,000 Women-Years</th>
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<tbody>
<tr>
<td>CHD eventsa</td>
<td>1.23 (0.95-1.58)</td>
<td>41</td>
<td>34</td>
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<td>CHD deatha</td>
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<tr>
<td>Lower arm fracturesf</td>
<td>0.71 (0.50-1.00)</td>
<td>44</td>
<td>62</td>
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<td>Total fracturesf</td>
<td>0.76 (0.69-0.83)</td>
<td>152</td>
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<tr>
<td>Cataractsg</td>
<td>0.93 (0.82-1.06)</td>
<td>100</td>
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<td>Global indexg</td>
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*Adapted from numerous WHI publications. WHI publications can be accessed at www.nhlbi.nih.gov/whi. 
**Results are based on centrally adjudicated data. 
†Not included in “global index.”

14.3 Women’s Health Initiative Memory Study

The WHI estrogen-alone ancillary study of the WHI enrolled 2,347 postmenopausal hypertensive women 65 years of age or older, and 2,347 postmenopausal women who were 65 years of age or older with a prevalent stroke or subclinical stroke as defined by a score of 2 in 5 years or 10 years of follow-up. The absolute risk reduction for 10,000 women-years was 9.2 per 10,000 women-years. For those outcomes included in the WHI “global index” that reached statistical significance after 5 years of follow-up, the absolute risk reduction for 10,000 women-years was 9.2 per 10,000 women-years.

Timing of the initiation of estrogen plus progestin therapy relative to the start of menopause may affect the overall benefit-risk profile. The WHI estrogen-alone substudy observed that at age 20 to 50 years, 20 to 50 years, and 20 to 50 years of age, the absolute risk reduction for 10,000 women-years was 9.2 per 10,000 women-years.

Table 6. Relative and Absolute Risk Seen in the Estrogen Plus Progesterone Substudy of WHI at an Average of 5.6 Yearsa,b

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†Not included in “global index.”

14.3 Women’s Health Initiative Memory Study

The WHI estrogen-alone ancillary study of the WHI enrolled 2,347 postmenopausal hypertensive women 65 years of age or older, and 2,347 postmenopausal women who were 65 years of age or older with a prevalent stroke or subclinical stroke as defined by a score of 2 in 5 years or 10 years of follow-up. The absolute risk reduction for 10,000 women-years was 9.2 per 10,000 women-years. For those outcomes included in the WHI “global index” that reached statistical significance after 5 years of follow-up, the absolute risk reduction for 10,000 women-years was 9.2 per 10,000 women-years.
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 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 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.
- **have a stroke or heart attack**
- **currently have or have had blood clots**
- **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, angiodema (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.

- **You and 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. Do not allow others, 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, the 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 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”)

**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 Perigo 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, 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.

**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)
(estraadiol 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).

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 A

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

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.

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