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Evamist®
(estradiol transdermal spray)

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Please see Important Safety Information including Boxed Warning, in full Prescribing Information

TERMS AND CONDITIONS

Patient Instructions: In order to redeem this offer you must have a valid prescription for Evamist® (estradiol transdermal spray) and you may not be enrolled in a state or federally funded prescription benefit program, including, but not limited to, Medicare, Medicaid, Veterans Affairs (VA), Department of Defense (DOD), or TRICARE. Follow the dosage instructions given by the doctor. This offer may not be redeemed for cash. By using this offer, you are certifying that you meet the eligibility criteria and will comply with the terms and conditions described in the Restrictions section. Patients with questions about the offer should call **1-844-415-0672**.

Pharmacist: When you apply this offer, you are certifying that you have not submitted a claim for reimbursement under any federal, state, or other governmental programs for this prescription and will not seek reimbursement from health insurance or any third party for any part of the benefit the patient receives through this program. Participation in this program must comply with all applicable laws and regulations as a pharmacy provider. By participating in this program, you are certifying that you will comply with the terms and conditions described in the Restrictions section below.

Pharmacist instructions for a patient with an Eligible Third Party Payer: Submit the claim to the primary Third Party Payer first, then submit the balance due to Change Healthcare as a Secondary Payer COB [coordination of benefits] with patient responsibility amount and a valid Other Coverage Code, (e.g. 8). The patient is responsible for the first \$25 and the card pays up to the next \$70 on each applicator. The patient is responsible for any remaining balance. Reimbursement will be received from Change Healthcare.

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Restrictions: This offer is valid in the United States. Offer not valid for prescriptions reimbursed under Medicaid, a Medicare drug benefit plan, VA, Tricare or other federal or state health programs (such as medical assistance programs). If the patient is eligible for drug benefits under any such program or is Medicare eligible and enrolled in employer-sponsored group waiver health plans or government-subsidized prescription drug benefit programs for retirees, the patient cannot use this offer. By using this offer, the patient and pharmacist certify that they will comply with any terms or requirements imposed on patients or providers by the health insurance to notify the health insurance plan of the existence and/or value of this offer. Offer not valid for patients under 18 years of age. It is illegal to (or offer to) sell, purchase, or trade this offer. This offer is not transferable and is limited to one offer per person. Not valid if reproduced. Void where prohibited by law. This is not insurance. Program managed by ConnectiveRx, LLC, on behalf Padagis US LLC. The parties reserve the right to rescind, revoke or amend this offer without notice at any time.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all of 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, PROBABLE DEMENTIA, BREAST CANCER, AND UNINTENTIONAL SECONDARY EXPOSURE TO ESTROGEN

See full prescribing information for complete boxed warning.

Estragen-Alone Therapy

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

Estragen Plus Progestin Therapy

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

Unintentional Secondary Exposure

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

RECENT MAJOR CHANGES
Boxed Warning 8/2023
Warnings and Precautions, Malignant Neoplasms (5.2) 12/2023

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

FULL PRESCRIBING INFORMATION: CONTENTS*
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WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, PROBABLE DEMENTIA, BREAST CANCER, AND UNINTENTIONAL SECONDARY EXPOSURE TO ESTROGEN
Estragen-Alone Therapy

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

Cardiovascular Disorders and Probable Dementia
The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (60 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens (CE) (0.625 mg)-alone, relative to placebo [see Warnings and Precautions (5.1), and Clinical Studies (14.2)].

The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age and older during 5.2 years of treatment with daily CE (0.625 mg)-alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women [see Warnings and Precautions (5.3), Use in Specific Populations (8.5), and Clinical Studies (14.3)].

Do not use estrogen-alone therapy for the prevention of cardiovascular disease or dementia [see Warnings and Precautions (5.1, 5.3), and Clinical Studies (14.2, 14.3)]. Only daily oral 0.625 mg CE was studied in the estrogen-alone substudy of the WHI. Therefore, the relevance of the WHI findings regarding adverse cardiovascular events and dementia to lower CE doses, other routes of administration, or other estrogen-alone products is not known. Without such data, it is not possible to definitively exclude these risks or determine the extent of these risks for other products. Discuss with your patient the benefits and risks of estrogen-alone therapy, taking into account her individual risk profile. Prescribe estrogens with or without progestogens at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

DOSAGE AND ADMINISTRATION

- Start therapy with one spray of Evamist once daily each morning to forearm (2.1)
- Dosage adjustment to two or three sprays of Evamist should be guided by the clinical response (2.1)
- Spray: One spray consists of 90 mcL which contains 1.53 mg estradiol (3)

DOSAGE FORMS AND STRENGTHS

- Undiagnosed abnormal genital bleeding (4, 5.2)
- Breast cancer or a history of breast cancer (4, 5.2)
- 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, angioedema, or hypersensitivity to Evamist (4)
- Hepatic impairment or disease (4, 5.10)
- Protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders (4)

CONTRAINDICATIONS

- Undiagnosed abnormal genital bleeding (4, 5.2)
- Breast cancer or a history of breast cancer (4, 5.2)
- 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, angioedema, or hypersensitivity to Evamist (4)
- Hepatic impairment or disease (4, 5.10)
- Protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders (4)

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

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

The most common adverse reactions (≥ 5 percent) with Evamist are: headache, breast tenderness and nipple pain, nausea, back pain, and nasopharyngitis. (6.1)

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

DRUG INTERACTIONS

- Inducers and inhibitors of CYP3A4 may affect estrogen drug metabolism and decrease or increase the estrogen plasma concentration. (7.1)

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

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Estrogen Plus Progestin Therapy

Cardiovascular Disorders and Probable Dementia
The WHI estrogen plus progestin substudy reported increased risks of pulmonary embolism (PE), DVT, stroke and myocardial infarction (MI) in postmenopausal women (60 to 79 years of age) during 5.6 years of treatment with daily oral CE (0.625 mg) combined with medroxyprogesterone acetate (MPA) (2.5 mg), relative to placebo [see Warnings and Precautions (5.1), and Clinical Studies (14.2)].

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

Do not use estrogen plus progestin therapy for the prevention of cardiovascular disease or dementia [see Warning and Precautions (5.1, 5.3), and Clinical Studies (14.2)]. Only daily oral 0.625 mg CE and 2.5 mg MPA were studied in the estrogen plus progestin substudy of the WHI. Therefore, the relevance of the WHI findings regarding adverse cardiovascular events, dementia and breast cancer to lower CE plus other MPA doses, other routes of administration, or other estrogen plus progestogen products is not known. Without such data, it is not possible to definitively exclude these risks or determine the extent of these risks for other products. Discuss with your patient the benefits and risks of estrogen plus progestin therapy, taking into account her individual risk profile. Prescribe estrogens with or without progestogens at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

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

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

Generally, when estrogen is prescribed for a postmenopausal woman with a uterus, consider addition of a progestogen to reduce the risk of endometrial cancer. Generally, a woman without a uterus does not need a progestogen in addition to her estrogen therapy. In some cases, however, hysterectomized women who have a history of endometriosis may need a progestogen [see Warnings and Precautions (5.2, 5.15)].

Use estrogen-alone, or in combination with a progestogen, at the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman. Re-evaluate postmenopausal women periodically as clinically appropriate to determine whether treatment is still necessary.

Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause

Evamist therapy with one spray of Evamist per day. Make dosage adjustment based on the clinical response. Prime the Evamist container by spraying 5 sprays with the cover on before applying the first dose from a new applicator. Hold the container upright and vertical for spraying.

Apply one, two or three sprays each morning to adjacent, non-overlapping areas on the inner surface of the forearm, starting near the elbow. Allow the spray to dry for approximately 2 minutes before covering the area with clothing. Do not wash the application site for at least one hour. Application of Evamist to other skin surfaces has not been adequately studied. Evamist should not be applied to skin surfaces other than the forearm.

Strict adherence to the following precautions is advised in order to minimize the potential for adverse exposure to estradiol from Evamist-treated skin. Cover the Evamist application site with clothing if another person may come into contact with that area of skin after the spray dries. Additional precautions to minimize unintentional secondary exposure are outlined in Patient Counseling Information [see Patient Counseling Information] and in the Patient Information Leaflet at the end of the prescribing information.

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

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

- Undiagnosed abnormal genital bleeding [see Warnings and Precautions (5.2)].
- Breast cancer or a history of breast cancer [see Warnings and Precautions (5.2)].
- Estrogen-dependent neoplasia [see Warnings and Precautions (5.2)].
- Active DVT, PE, or history of these conditions [see Warnings and Precautions (5.1)].
- Active arterial thromboembolic disease (for example, stroke or MI), or a history of these conditions [see Warnings and Precautions (5.1)].
- Known anaphylactic reaction, angioedema, or hypersensitivity to Evamist.
- Hepatic impairment or disease.
- Protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders.

WARNINGS AND PRECAUTIONS

Increased risks of stroke and DVT are reported with estrogen-alone therapy. Increased risks of PE, DVT, stroke, and MI are reported with estrogen plus progestin therapy. Should any of these occur or be suspected, estrogen with or without progestin therapy should be discontinued. Immediately discontinue estrogen with or without progestin therapy if any of these occur or are suspected.

Manage appropriately any risk factors for arterial vascular disease (for example, hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or versus thromboembolic (VTE) (for example, personal history or family history of VTE, obesity, and systemic lupus erythematosus).

Stroke
The WHI estrogen-alone substudy reported a statistically significant increased risk of stroke in women 50 to 79 years of age receiving daily CE (0.625 mg)-alone compared to women in the same age group receiving placebo (45 versus 33 strokes per 10,000 women-years, respectively).

The increase in risk was demonstrated in year 1 and persisted [see Clinical Studies (14.2)].

Immediately discontinue estrogen-alone therapy if a stroke occurs or is suspected.

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

The WHI estrogen plus progestin substudy reported a statistically significant increased risk of stroke in women 50 to 79 years of age receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women in the same age group receiving placebo (53 versus 25 strokes per 10,000 women-years, respectively).

Immediately discontinue estrogen plus progestin therapy if a stroke occurs or is suspected.

Coronary Heart Disease
The WHI estrogen-alone substudy reported no overall effect on coronary heart disease (CHD) events (defined as non-fatal MI, silent MI, or CHD death) in women receiving estrogen-alone compared to placebo [see Clinical Studies (14.2)].

Subgroup analyses of women 50 to 59 years of age, who were less than 10 years since menopause, suggest a reduced (not statistically significant) of CHD events in those women receiving daily CE (0.625 mg)-alone compared to placebo (8 versus 16 per 10,000 women-years).¹

The WHI estrogen plus progestin substudy reported an increased risk (not statistically significant) of CHD events in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (41 versus 34 per 10,000 women-years).¹ An increase in relative risk was demonstrated in year 1, and a trend toward decreasing relative risk was reported in years 2 through 5 [see Clinical Studies (14.2)].

In postmenopausal women with documented heart disease (n = 2,763), average 66.7 years of age, in a controlled clinical trial of secondary prevention of cardiovascular disease Heart and Estrogen/Progestin Replacement Study (HERS), treatment with daily CE (0.625 mg) plus MPA (2.5 mg) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE plus MPA did not reduce the overall rate of CHD events in postmenopausal women with established CHD. There were more CHD events in the CE plus MPA-treated group than in the placebo group in year 1, but not during the subsequent years. Two thousand, three hundred and twenty-one (2,321) women from the original HERS trial agreed to participate in an open label extension of the original HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE plus MPA group and the placebo group in HERS, HERS II, and overall.

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

Immediately discontinue estrogen-alone therapy if a VTE occurs or is suspected.

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

Immediately discontinue estrogen plus progestin therapy if a VTE occurs or is suspected.

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

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 dose of 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 and this risk has been shown to persist for at least 15 to years after estrogen therapy is discontinued.

Clinical surveillance of all women using estrogen-alone or estrogen plus progestin therapy is important. Perform adequate diagnostic measures, including directed or random endometrial sampling when indicated, to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal genital bleeding with unknown etiology. There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent dosages. Adding a progestogen to postmenopausal estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

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

Only daily oral 0.625 mg CE and 2.5 mg MPA were studied in the estrogen plus progestin substudy of the WHI. Therefore, the relevance of the WHI findings regarding adverse cardiovascular events, dementia and breast cancer to lower CE plus other MPA doses, other routes of administration, or other estrogen plus progestogen products is not known. Without such data, it is not possible to definitively exclude these risks or determine the extent of these risks for other products. Discuss with your patient the benefits and risks of estrogen plus progestin therapy, taking into account her individual risk profile. Prescribe estrogens with or without progestogens at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

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

After a mean follow-up of 5.6 years, the WHI substudy of daily CE (0.625 mg) plus MPA (2.5 mg) reported an increased risk of invasive breast cancer in women who took daily CE plus MPA compared to placebo. In this substudy, prior use of estrogen-alone or estrogen plus progestin therapy was reported by 26 percent of the women. The relative risk of invasive breast cancer was 1.24 and the absolute risk was 41 versus 33 cases per 10,000 women-years for CE plus MPA compared with placebo [see Clinical Studies (14.2)]. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 versus 25 cases per 10,000 women-years, for CE plus MPA compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.04, and the absolute risk was 40 versus 36 cases per 10,000 women-years for CE plus MPA compared with placebo. In the same substudy, invasive breast cancers were larger, were more likely to be node positive, and were diagnosed at a more advanced stage in the CE (0.625 mg) plus MPA (2.5 mg) group compared with the placebo group. Metastatic disease was rare, with no apparent difference between the two groups. Other prognostic factors, such as histologic subtype, grade and hormone receptor status did not differ between the groups [see Clinical Studies (14.2)].

Consistent with the WHI clinical trials, observational studies have also reported an increased risk of breast cancer with estrogen plus progestin therapy, and a smaller increase in the risk for breast cancer with estrogen-alone therapy, after several years of use. One large meta-analysis of prospective cohort studies reported increased risks that were dependent upon duration of use and could last up to >10 years after discontinuation of estrogen plus progestin therapy and estrogen-alone therapy. Extension of the WHI trials also demonstrated increased breast cancer risk associated with estrogen plus progestin therapy. Observational studies also suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen plus progestin therapy as compared to estrogen-alone therapy. These studies have not generally found significant variation in the risk of breast cancer among different estrogen plus progestin combinations, doses, or routes of administration.

The use of estrogen-alone and estrogen plus progestin has been reported to result in an increase in circulating triglyceride levels. In the WHI estrogen-alone substudy, the relative risk for ovarian cancer for CE plus MPA versus placebo was 1.59 (95 percent CI, 0.77-3.24) but it was not statistically significant. The absolute risk for CE plus MPA versus placebo was 4 versus 3 cases per 10,000 women-years.²

A meta-analysis of 17 prospective and 35 retrospective epidemiologic studies found that women who used hormonal therapy for menopausal symptoms had an increased risk for ovarian cancer. The primary analysis, using case-control comparisons, included 12 110 cancer cases from the 17 prospective studies. The relative risks associated with current use of hormonal therapy was 1.41 (95% CI, 1.32 to 1.50; there was no difference in the risk estimates by duration of the exposure (less than 5 years [median of 3 years] vs. greater than 5 years [median of 10 years] of use before the cancer diagnosis). The relative risk associated with combined current and recent use (discontinued use within 5 years before cancer diagnosis) was 1.37 (95% CI 1.27-1.48), and the elevated risk was significant for both estrogen-alone and estrogen plus progestin products. The exact duration of hormone therapy use associated with an increased risk of ovarian cancer, however, is unknown.

Probable Dementia

In the WHI Memory Study (WHIMS) estrogen-alone ancillary study, a population of 2,947 hysterectomized women 65 to 79 years of age was randomized to daily CE (0.625 mg)-alone or placebo. After an average follow-up of 5.2 years, 28 women in the estrogen-alone group and 19 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE-alone versus placebo was 1.83-49.95 percent CI, 0.83-2.68. The increase in risk was demonstrated in year 1 and persisted [see Clinical Studies (14.3)].

Subgroup analyses of women 65 to 69 years of age suggest no increased risk of dementia for those women receiving CE (0.625 mg)-alone versus those receiving placebo (18 versus 21 per 10,000 women-years).¹

The WHIMS estrogen plus progestin ancillary study, a population of 4,532 postmenopausal women 65 to 79 years of age was randomized to daily CE (0.625 mg) plus MPA (2.5 mg) or placebo. After an average follow-up of 4 years, 40 women in the CE plus MPA group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE plus MPA versus placebo was 2.05 (95 percent CI, 1.21-3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 cases per 10,000 women-years [see Use in Specific Populations (8.5) and Clinical Studies (14.3)].

Subgroup analyses of women 65 to 69 years of age suggest no increased risk of dementia for those women receiving CE (0.625 mg) plus MPA (2.5 mg) versus placebo (18 versus 21 per 10,000 women-years).¹

The WHI estrogen plus progestin substudy reported an increased risk (not statistically significant) of CHD events in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (41 versus 34 per 10,000 women-years).¹ An increase in relative risk was demonstrated in year 1, and a trend toward decreasing relative risk was reported in years 2 through 5 [see Clinical Studies (14.2)].

In postmenopausal women with documented heart disease (n = 2,763), average 66.7 years of age, in a controlled clinical trial of secondary prevention of cardiovascular disease Heart and Estrogen/Progestin Replacement Study (HERS), treatment with daily CE (0.625 mg) plus MPA (2.5 mg) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE plus MPA did not reduce the overall rate of CHD events in postmenopausal women with established CHD. There were more CHD events in the CE plus MPA-treated group than in the placebo group in year 1, but not during the subsequent years. Two thousand, three hundred and twenty-one (2,321) women from the original HERS trial agreed to participate in an open label extension of the original HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE plus MPA group and the placebo group in HERS, HERS II, and overall.

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

Immediately discontinue estrogen-alone therapy if a VTE occurs or is suspected.

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

Immediately discontinue estrogen plus progestin therapy if a VTE occurs or is suspected.

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

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 dose of 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 and this risk has been shown to persist for at least 15 to years after estrogen therapy is discontinued.

Clinical surveillance of all women using estrogen-alone or estrogen plus progestin therapy is important. Perform adequate diagnostic measures, including directed or random endometrial sampling when indicated, to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal genital bleeding with unknown etiology. There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent dosages. Adding a progestogen to postmenopausal estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

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

Only daily oral 0.625 mg CE and 2.5 mg MPA were studied in the estrogen plus progestin substudy of the WHI. Therefore, the relevance of the WHI findings regarding adverse cardiovascular events, dementia and breast cancer to lower CE plus other MPA doses, other routes of administration, or other estrogen plus progestogen products is not known. Without such data, it is not possible to definitively exclude these risks or determine the extent of these risks for other products. Discuss with your patient the benefits and risks of estrogen plus progestin therapy, taking into account her individual risk profile. Prescribe estrogens with or without progestogens at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

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

Hereditary Angioedema

Exogenous estrogens may exacerbate symptoms of angioedema in women with hereditary angioedema. Consider whether the benefits of estrogen therapy, including Evamist, outweigh the risks in such women.

Table 5. Relative and Absolute Risk Seen in the Estrogen Alone Substudy of WHI*

Event	Relative Risk CE vs. Placebo (95% nCI) [†]	CE (n = 5,310)	Placebo (n = 5,429)
		Absolute Risk per 10,000 Women-Years	
CHD events [‡]	0.95 (0.78-1.16)	54	57
Non-fatal MI [‡]	0.91 (0.73-1.14)	40	43
CHD death [‡]	1.01 (0.71-1.43)	16	16
All strokes [‡]	1.33 (1.05-1.69)	45	33
Ischemic stroke [‡]	1.53 (1.19-2.01)	38	25
Deep vein thrombosis [‡]	1.47 (1.06-2.06)	23	15
Pulmonary embolism [‡]	1.37 (0.90-2.07)	14	10
Invasive breast cancer [‡]	0.80 (0.62-1.04)	28	34
Colorectal cancer [‡]	1.08 (0.75-1.55)	17	16
Hip fracture [‡]	0.65 (0.45-0.94)	12	19
Vertebral fractures [‡]	0.64 (0.44-0.93)	11	18
Lower arm/wrist fractures [‡]	0.58 (0.47-0.72)	35	59
Total fractures [‡]	0.71 (0.64-0.80)	144	197
Death due to other causes [‡]	1.08 (0.88-1.32)	53	50
Overall mortality [‡]	1.04 (0.88-1.22)	79	75
Global index [‡]	1.02 (0.92-1.13)	206	201

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

For those outcomes included in the WHI "global index" that reached statistical significance, the absolute excess risk per 10,000 women-years in the group treated with CE-alone was 12 more strokes, while the absolute risk reduction per 10,000 women-years was 7 fewer hip fractures.¶ The absolute excess risk of events included in the "global index" was a non-significant 5 events per 10,000 women-years. There was no difference between the groups in terms of all-cause mortality.
No overall difference for primary CHD events (nonfatal MI, silent MI and CHD death) and invasive breast cancer incidence in women receiving CE-alone compared to placebo was reported in final centrally adjudicated results from the estrogen-alone substudy, after an average follow-up of 7.1 years.
Centrally adjudicated results for stroke events from the estrogen-alone substudy, after an average follow-up of 7.1 years, reported no significant differences in distribution of stroke subtypes or severity, including fatal strokes, in women receiving CE-alone compared to placebo. Estrogen-alone increased the risk for ischemic stroke, and this excess risk was present in all subgroups of women examined.¶
Timing of the initiation of estrogen-alone therapy relative to the start of menopause may affect the overall risk benefit profile. The WHI estrogen-alone substudy stratified by age showed in women 50 to 59 years of age a non-significant trend toward reduced risk for CHD [hazard ratio (HR) 0.63 (95 percent CI, 0.36-1.09)] and overall mortality [HR 0.71 (95 percent CI, 0.46-1.11)].
WHI Estrogen Plus Progestin Substudy
The WHI estrogen plus progestin substudy was stopped early. According to the predefined stopping rule, after an average follow-up of 5.6 years of treatment, the increased risk of invasive breast cancer and cardiovascular events exceeded the specified benefits included in the "global index". The absolute excess risk of events included in the "global index" was 19 per 10,000 women-years.
For those outcomes included in the WHI "global index" that reached statistical significance after 5.6 years of follow-up, the absolute excess risks per 10,000 women-years in the group treated with CE plus MPA were 7 more CHD events, 8 more strokes, 10 more PEs, and 6 more invasive breast cancers, while the absolute risk reduction per 10,000 women-years were 6 fewer colorectal cancers and 5 fewer hip fractures.
Results of the CE plus MPA substudy which included 16,608 women (average 63 years of age; range 50 to 79 years of age: 83.9 percent White, 6.5 percent Black, 5.4 percent Hispanic, 3.9 percent Other) are presented in Table 6. These results reflect centrally adjudicated data after an average follow-up of 5.6 years.

Table 6. Relative and Absolute Risk Seen in the Estrogen Plus Progestin

Event	Relative Risk CE/MPA vs. Placebo (95% nCI) [†]	CE/MPA (n = 8,506)	Placebo (n = 8,102)
		Absolute Risk per 10,000 Women-Years	
CHD events	1.23 (0.99-1.53)	41	34
Non-fatal MI	1.28 (1.00-1.63)	31	25
CHD death [‡]	1.10 (0.70-1.75)	8	8
All strokes	1.31 (1.03-1.69)	33	25
Ischemic stroke	1.44 (1.09-1.90)	26	18
Deep vein thrombosis [‡]	1.95 (1.43-2.67)	26	13
Pulmonary embolism	2.13 (1.45-3.11)	18	8
Invasive breast cancer [‡]	1.24 (1.01-1.54)	41	33
Colorectal cancer	0.61 (0.42-0.87)	10	16
Endometrial cancer [‡]	0.81 (0.48-1.36)	6	7
Cervical cancer [‡]	1.44 (0.47-4.42)	2	1
Hip fracture	0.67 (0.47-0.96)	11	16
Vertebral fractures [‡]	0.65 (0.46-0.92)	11	17
Lower arm/wrist fractures [‡]	0.71 (0.59-0.85)	44	62
Total fractures [‡]	0.76 (0.69-0.83)	152	199
Overall Mortality [‡]	1.00 (0.83-1.19)	52	52
Global Index [‡]	1.13 (1.02-1.25)	184	165

*Adapted from numerous WHI publications. WHI publications can be viewed at www.nhlbi.nih.gov/whi.
†Results are based on centrally adjudicated data.
‡Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.
§Not included in "global index".
¶Includes metastatic and non-metastatic breast cancer, with the exception of in situ breast cancer.
||All deaths, except from breast or colorectal cancer, definite or probable CHD, PE or cerebrovascular disease.
||A subset of the events was combined in a "global index", defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, PE, endometrial cancer, colorectal cancer, hip fracture, or death due to other causes.
Timing of the initiation of estrogen plus progestin therapy relative to the start of menopause may affect the overall risk benefit profile. The WHI estrogen plus progestin substudy stratified by age showed in women 50 to 59 years of age a non-significant trend toward reduced risk for overall mortality [HR 0.69 (95 percent CI, 0.44-1.07)].

14.3 Women's Health Initiative Memory Study
The WHIMS estrogen-alone ancillary study of the WHI, enrolled 2,947 predominantly healthy hysterectomized postmenopausal women 65 to 79 years of age 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 CE (0.625 mg) on the incidence of probable dementia (primary outcome) compared to placebo.
After an average follow-up of 5.2 years, the relative risk of probable dementia for CE-alone versus placebo was 1.49 (95 percent CI, 0.83-2.66). The absolute risk of probable dementia for CE-alone versus placebo was 37 versus 25 cases per 10,000 women-years. Probable dementia as defined in this study included Alzheimer's disease (AD), vascular dementia (VaD) and mixed type (having features of both AD and VaD). The most common classification of probable dementia in the treatment group and the placebo group was AD. Since the ancillary study was conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women [see Warnings and Precautions (5.3) and Use in Specific Populations (8.5)].

The WHIMS estrogen plus progestin ancillary study of WHI enrolled 4,532 predominantly healthy postmenopausal women 65 years of age and older (47 percent were 65 to 69 years of age, 35 percent were 70 to 74 years of age, and 18 percent were 75 years of age and older) to evaluate the effects of daily CE (0.625 mg) plus MPA (2.5 mg) on the incidence of probable dementia (primary outcome) compared to placebo.
After an average follow-up of 4 years, the relative risk of probable dementia for CE plus MPA versus placebo was 2.05 (95 percent CI, 1.12-3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 per 10,000 women-years. Probable dementia as defined in this study included AD, VaD and mixed type (having features of both AD and VaD). The most common classification of probable dementia in the treatment group and the placebo group was AD. Since the ancillary study was conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women [see Warnings and Precautions (5.3) and Use in Specific Populations (8.5)].

When data from the two populations were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95 percent CI, 1.19-2.69). Differences between groups became apparent in the first year of treatment. It is unknown whether these findings apply to younger postmenopausal women [see Warnings and Precautions (5.3) and Use in Specific Populations (8.5)].

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16 HOW SUPPLIED/STORAGE AND HANDLING
16.1 How Supplied
Evamist (NDC 0574-2067-27) is supplied as a homogeneous solution of estradiol USP, octisalate USP and alcohol USP. The liquid formulation of Evamist is packaged in a glass vial fitted with a metered-dose pump. The unit is encased in a plastic housing with a conical bell opening that controls the distance, angle, and area of application of the metered-dose spray. Each metered-dose pump contains 8.1 mL and is designed to deliver 56 sprays of 90 µL after priming. One spray contains 1.53 mg estradiol.
16.2 Storage and Handling
Keep out of reach of children.
Alcohol and alcohol-based liquids are flammable. Avoid fire, flame or smoking until the spray has dried.
Store at room temperature 20°C to 25°C (68°F to 77°F); excursion permitted between 15°C to 30°C (59°F to 86°F). Do not freeze.

17 PATIENT COUNSELING INFORMATION
Advise women to read the FDA-approved patient labeling (Patient Information and Instructions for Use)
Vaginal Bleeding
Inform postmenopausal women to report any vaginal bleeding to their healthcare provider as soon as possible [see Warnings and Precautions (5.2)].
Unintentional Secondary Exposure to Evamist
Provide the following information about secondary exposure to Evamist:
• Apply Evamist as directed and keep children from contacting exposed application site(s). If direct contact with the application site occurs, the contact area should be washed thoroughly with soap and water. Women should cover the Evamist application site, after the 2 minute drying period, with clothing if another person may come in contact with that area of skin. [See FDA-Approved Patient Information Leaflet at the end of the prescribing information.]
• Look for signs of unexpected sexual development, such as breast mass or increased breast size in prepubertal children.
• If signs of unintentional secondary exposure are noticed:
◦ Have children evaluated by a healthcare provider.
◦ Discontinue Evamist until the cause(s) is identified for any unexpected sexual development in children under their care.
◦ Women should contact their healthcare provider and discuss the appropriate use and handling of Evamist when around children.
◦ If conditions for safe use cannot be met, Evamist should be discontinued and alternative treatments for menopausal signs and symptoms should be considered.
• Pets may also be unintentionally exposed to Evamist if above precautions are not followed.
Possible Serious Adverse Reactions with Estrogen-Alone Therapy
Inform postmenopausal women of the possible serious adverse reactions of estrogen-alone therapy including Cardiovascular Disorders, Malignant Neoplasms, and Probable Dementia [see Warnings and Precautions (5.1, 5.2, 5.3)].
Possible Common Adverse Reactions with Estrogen-Alone Therapy
Inform postmenopausal women of possible less serious but common adverse reactions of estrogen-alone therapy such as headache, breast pain and tenderness, nausea and vomiting.



Manufactured by Padagis®
Yeruham, Israel
www.padagis.com
Rev 04-24
9E400 RC PH3

Patient Information

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

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

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

- Using estrogen-alone may increase your chance of getting cancer of the uterus (womb).
- Report any unusual vaginal bleeding right away while you are using EVAMIST. Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out 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 and older.
- Do not use estrogens with progestogens to prevent heart disease, heart attack, strokes, or dementia.
- Using estrogens with progestogens may increase your chances of getting heart attacks, strokes, breast cancer, or blood clots.
- Using estrogens with progestogens 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).
- Only one estrogen-alone product and dose have been shown to increase your chances of getting strokes, blood clots, and dementia. Only one estrogen with progestogen product and dose have been shown to increase your chances of getting heart attacks, strokes, breast cancer, blood clots, and dementia. Because other products and doses have not been studied in the same way, it is not known how the use of EVAMIST will affect your chances of these conditions. 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 of life. This drop in body estrogen levels causes the "change of life" or menopause (the end of monthly menstrual periods). Sometimes, both ovaries are removed during an operation before natural menopause takes place. The sudden drop in estrogen levels causes "surgical menopause."
When the estrogen levels begin dropping, some women get very uncomfortable symptoms, such as feelings of warmth in the face, neck, and chest, or sudden intense 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;
- have been diagnosed with a bleeding disorder.
- currently have or have had certain cancers.

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.

- had a stroke or heart attack.
 - currently have or have had blood clots.
 - currently have or have had liver problems.
 - are allergic to EVAMIST or any of its ingredients.
- See the list of ingredients in EVAMIST at the end of this leaflet

Before you use EVAMIST, tell your healthcare provider about all of your medical conditions, including 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 that may become worse while you are using EVAMIST.
Your healthcare provider may need to check you more carefully if you have certain conditions, such as asthma (wheezing), epilepsy (seizures), diabetes, migraine, endometriosis, lupus, angioedema (swelling of face or 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 pregnant or think you may be pregnant.
EVAMIST is not for pregnant women.
- are breastfeeding.
The hormone in EVAMIST can pass into your breast milk.

Tell your healthcare provider about all the medicines you take including prescription and over-the-counter medicines, vitamins and herbal supplements. Some medicines may affect how EVAMIST works. Some other medicines and food products may increase or decrease the concentration of the hormone in EVAMIST in the blood. EVAMIST may affect how your other medicines work, and other medicines may affect how EVAMIST works. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I use EVAMIST?

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

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

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

- have the child checked right away by their healthcare provider.
- stop using EVAMIST and call your healthcare provider right away.
- talk to your healthcare provider about the correct use of EVAMIST when around children.

- Talk to your healthcare provider about other treatments for your menopause symptoms if accidental exposure to EVAMIST cannot be avoided.
- You and your healthcare provider should talk regularly (for example, every 3 to 6 months) about the dose you are taking and whether you still need treatment with EVAMIST.

What should I avoid while using EVAMIST?

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

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
- breast cancer
- cancer of the lining of the uterus (womb)
- cancer of the ovary
- dementia
- gallbladder disease
- high or low calcium levels
- changes in vision
- high blood pressure
- high levels of fat in your blood (triglycerides)
- liver problems
- changes in thyroid hormone levels
- swelling or fluid retention
- cancer changes of endometriosis
- enlargement of benign tumors of the uterus ("fibroids")
- worsening swelling of face or tongue (angioedema) in women who have a history of angioedema
- changes in laboratory test results such as bleeding time and high blood sugar levels

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

- new breast lumps
 - unusual vaginal bleeding
 - changes in vision or speech
 - sudden new severe headaches
 - severe pains in your chest or legs with or without shortness of breath, weakness and fatigue
- Common side effects of EVAMIST include:**
- headache
 - breast pain
 - irregular vaginal bleeding or spotting
 - stomach or abdominal cramps, bloating
 - nausea and vomiting
 - hair loss
 - fluid retention
 - vaginal yeast infection

Tell your healthcare provider if you have any side effects that bother you or do not go away. These are not all the possible side effects of EVAMIST. Call your doctor for medical advice about side effects. You may also report side effects to Padagis® 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 progestogen is right for you.
- In general, the addition of a progestogen is recommended for women with a uterus to reduce the chance of getting cancer of the uterus (womb).
- 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 purposes other than those listed in Patient Information leaflets. Do not use EVAMIST for a condition 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. You can ask your pharmacist or healthcare provider for information about EVAMIST that is written for health professionals.

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

What are the ingredients in EVAMIST?

Active ingredient: estradiol
Inactive ingredients: octisalate, alcohol
Manufactured by Padagis® Yeruham, Israel
www.padagis.com
Rev 04-24 9E400 RC PH3

Instructions for Use

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

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

The parts of your EVAMIST applicator

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

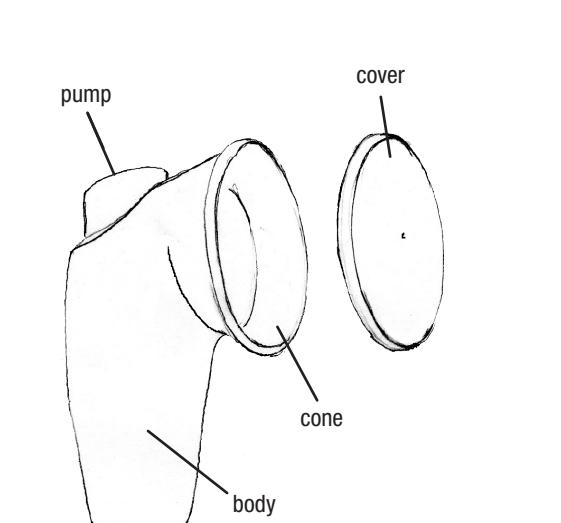


Figure A

Step 1. Priming your EVAMIST

- Before you use your EVAMIST applicator for the first time, the applicator must be primed.
- Hold the EVAMIST applicator upright. Keep the cover on. Fully press down the pump button 5 times with your thumb or index finger (see Figure B). After priming, the EVAMIST applicator is ready to use.
- The EVAMIST applicator should be primed only 1 time when you first start using a new applicator. Do not prime the EVAMIST applicator before your dose each day.

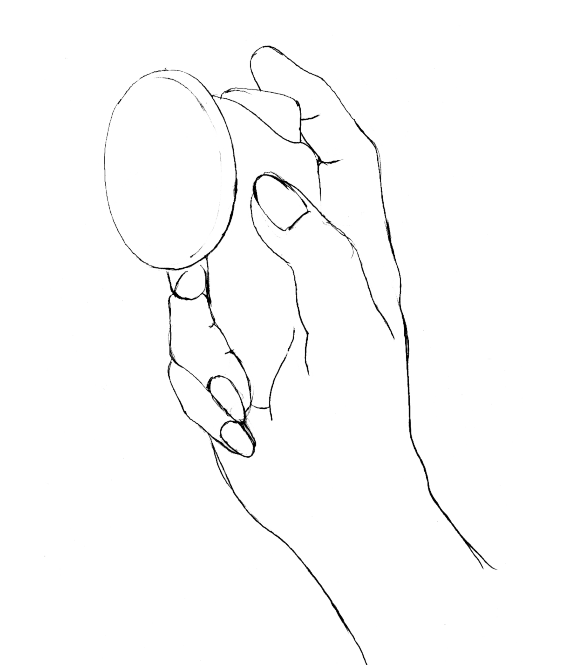


Figure B

Step 2. Using your EVAMIST

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

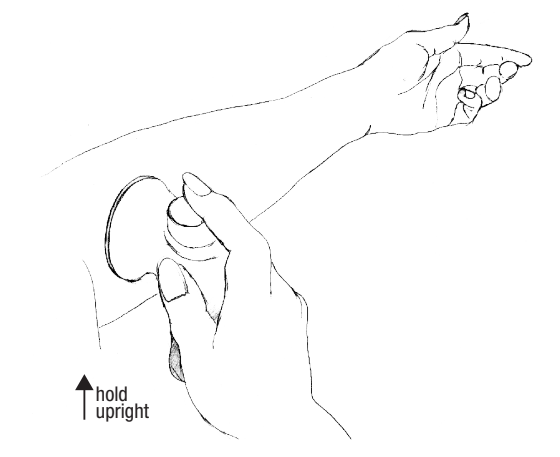


Figure C

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

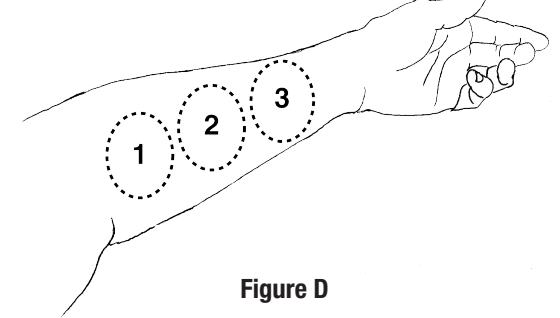


Figure D

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

Step 3. After you use EVAMIST

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

Step 4. Throwing away used EVAMIST applicators

- Your EVAMIST applicator contains enough medicine to allow for initial priming of the pump with 5 sprays and application of 56 sprays.
- Do not use your EVAMIST applicator for more than 56 application sprays even though the bottle may not be completely empty. You may not get the correct dose.
- Always replace the cover over the cone of your EVAMIST applicator before you throw it away to prevent accidental exposure to other people or pets.

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



Manufactured by Padagis®
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Rev 04-24 9E400 RC PH3