ESTRADIOL- estradiol film, extended release
Noven Therapeutics, LLC

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ESTRADIOL TRANSDERMAL SYSTEM safely and effectively. See full prescribing information for ESTRADIOL TRANSDERMAL SYSTEM

ESTRADIOL TRANSDERMAL SYSTEM
Initial U.S. Approval: 1975

WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, PROBABLE DEMENTIA, and BREAST CANCER

See full prescribing information for complete boxed warning.

Estrogen-Alone Therapy
- **There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens (5.2)**
- **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)**

Estrogen Plus Progestin Therapy
- **The WHI estrogen plus progestin substudy reported increased risks of DVT, pulmonary embolism (PE), 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 progestogen therapy for the prevention of cardiovascular disease or dementia (5.1, 5.3)**

RECENT MAJOR CHANGES

Warnings and Precautions, Malignant Neoplasms (5.2)	02/2024

INDICATIONS AND USAGE

ESTRADIOL TRANSDERMAL SYSTEM is an estrogen indicated for:
- Treatment of moderate to severe vasomotor symptoms due to menopause (1.1)
- Prevention of postmenopausal osteoporosis (1.2)
  Limitation of Use
  When prescribing solely for the treatment of postmenopausal osteoporosis, first consider the use of non-estrogen medications. Consider estrogen therapy only for women at significant risk of osteoporosis.

DOSAGE AND ADMINISTRATION

Start therapy with ESTRADIOL TRANSDERMAL SYSTEM 0.0375 mg per day applied to the skin twice weekly for the treatment of moderate to severe vasomotor symptoms due to menopause. Dosage adjustment should be guided by the clinical response (2.1)
Start therapy with ESTRADIOL TRANSDERMAL SYSTEM 0.025 mg per day applied to the skin twice weekly for the prevention of postmenopausal osteoporosis. The dose may be adjusted as necessary (2.2)
Place ESTRADIOL TRANSDERMAL SYSTEM on a clean, dry area on the lower abdomen (below the umbilicus) or buttocks. Do not apply ESTRADIOL TRANSDERMAL SYSTEM to the breasts (2.3)

DOSAGE FORMS AND STRENGTHS

Transdermal system: 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day (3)

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 a history of these conditions (4, 5.1)
- Active arterial thromboembolic disease (for example, stroke or MI), or a history of these conditions (4, 5.1)
- Known anaphylactic reaction, angioedema, or hypersensitivity to ESTRADIOL TRANSDERMAL SYSTEM(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 (5.4)
- Discontinue estrogen if severe hypercalcemia, loss of vision, severe hypertriglyceridemia or cholestatic jaundice occurs (5.5, 5.6, 5.9, 5.10)
- Monitor thyroid function in women on thyroid replacement therapy (5.11, 5.18)

ADVERSE REACTIONS

The most common adverse reactions (greater than or equal to 5 percent) with ESTRADIOL TRANSDERMAL SYSTEM are: headache, breast tenderness, back pain, pain in limb, nasopharyngitis, dyspepsia, nausea, sinusitis, and intermenstrual bleeding (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Noven at 1-800-455-8070 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*

DRUG INTERACTIONS

Inducers and/or 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.

Revised: 2/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, PROBABLE DEMENTIA, and BREAST CANCER

Estrogen-Alone Therapy

Endometrial Cancer

There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a 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 or random endometrial sampling when indicated, to rule out malignancy in postmenopausal women with 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 (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens (CE) [0.625 mg]-alone, relative to placebo *[see Warnings and Precautions (5.1), and Clinical Studies (14.3)]*.

The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE (0.625 mg)-alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women *[see Warnings and Precautions (5.3), Use in Specific Populations (8.5), and Clinical Studies (14.4)]*.

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 (14.3, 14.4)]*.
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 route 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.

Estrogen Plus Progestin Therapy

Cardiovascular Disorders and Probable Dementia

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

***Warnings and Precautions (5.1), and Clinical Studies (14.3)]*.**

The WHIMS estrogen plus progestin ancillary study of the WHI, reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CE (0.625 mg) combined with MPA (2.5 mg), relative to placebo. It is unknown whether this finding applies to younger postmenopausal women *[see Warnings and Precautions (5.3), Use in Specific Populations (8.5), and Clinical Studies (14.4)]*.

Do not use estrogen plus progestogen therapy for the prevention of cardiovascular disease or dementia *[see Warnings and Precautions (5.1, 5.3), and Clinical Studies (14.3, 14.4)]*.

Breast Cancer

The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer *[see Warnings and Precautions (5.2), and Clinical Studies (14.3)]*.

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 progestogen 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.

1 INDICATIONS AND USAGE

ESTRADIOL TRANSDERMAL SYSTEM is indicated for:

1.1 Treatment of Moderate to Severe Vasomotor Symptoms Due to Menopause

1.2 Prevention of Postmenopausal Osteoporosis

Limitation of Use
When prescribing solely for the prevention of postmenopausal osteoporosis, first consider the use of non-estrogen medications. Consider estrogen therapy only for women at significant risk of osteoporosis.

2 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, 5.14)]*.

Use of 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. Reevaluate postmenopausal women periodically as clinically appropriate to determine if treatment is still necessary.

2.1 Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause

Start therapy with ESTRADIOL TRANSDERMAL SYSTEM 0.0375 mg per day applied to the skin twice weekly. Make dosage adjustments based on clinical response.

Attempt to taper or discontinue the medication at 3 to 6 month intervals.

2.2 Prevention of Postmenopausal Osteoporosis due to Menopause

2.3 Application Instructions

Place the adhesive side of ESTRADIOL TRANSDERMAL SYSTEM on a clean, dry area on the lower abdomen (below the umbilicus) or buttocks. Do not apply ESTRADIOL TRANSDERMAL SYSTEM to the breasts.

Replace ESTRADIOL TRANSDERMAL SYSTEM twice weekly (every 3-4 days).

Rotate the sites of application, with an interval of at least 1 week allowed between applications to a particular site.

Select an area for application that is not oily, damaged, or irritated. Avoid the waistline, since tight clothing may rub the system off. Apply the system immediately after opening the pouch and removing the protective liner. Press the system firmly in place with the palm of the hand for about 10 seconds, making sure there is good contact with the skin, especially around the edges. In the event that a system falls off, reapply the same system or apply a new system to another location. If a woman has forgotten to apply ESTRADIOL TRANSDERMAL SYSTEM, have her apply a new system as soon as possible. Apply the new system on the original treatment schedule. The interruption of treatment in women taking ESTRADIOL TRANSDERMAL SYSTEM might increase the likelihood of breakthrough bleeding, spotting and recurrence of symptoms.

3 DOSAGE FORMS AND STRENGTHS

Transdermal system: 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day.

4 CONTRAINDICATIONS

ESTRADIOL TRANSDERMAL SYSTEM 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 a 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 or angioedema or hypersensitivity to ESTRADIOL

TRANSDERMAL SYSTEM
- Hepatic impairment or disease
- Protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders

5 WARNINGS AND PRECAUTIONS

5.1 Cardiovascular Disorders

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. Immediately discontinue estrogen with or without progestogen 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 venous thromboembolism (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 per 10,000 women-years, respectively). The increase in risk was demonstrated in year 1 and persisted *[see Clinical Studies (14.3)]*. 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]

In WHI estrogen plus progestin substudy reported a statistically significant increased risk of stroke in women 50 to 79 years of age receiving CE (0.625 mg) plus MPA (2.5 mg) compared to women in the same age group receiving placebo (33 versus 25 strokes per 10,000 women-years, respectively) *[see Clinical Studies (14.3)]*. The increase in risk was demonstrated after the first year and persisted.[1] Immediately discontinue estrogen plus progestogen therapy if a stroke occur 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 CE (0.625 mg) plus MPA (2.5 mg) compared to women in the same age group receiving placebo (33 versus 25 strokes per 10,000 women-years) *[see Clinical Studies, (14.3)]*. The increase in risk was demonstrated after the first year and persisted.[1] Immediately discontinue estrogen plus progestogen 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 nonfatal MI, silent MI, or CHD death) in women receiving estrogen-alone compared to placebo2 *[see Clinical Studies (14.3)]*.

Subgroup analyses of women 50 to 59 years of age, who were less than 10 years since

menopause, suggest a reduction (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 reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (41 versus 34 per 10,000 women years).[1] An increase in relative risk was demonstrated in year 1, and a trend toward decreasing relative risk was reported in years 2 through 5 *[see Clinical Studies (14.3)]*.

In postmenopausal women with documented heart disease (n = 2,763, average 66.7 years of age), in a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study; HERS), treatment with daily CE (0.625 mg) plus MPA (2.5 mg) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE plus MPA did not reduce the overall rate of CHD events in postmenopausal women with established CHD. There were more CHD events in the CE plus MPA-treated group than in the placebo group in year 1, but not during the subsequent years. Two thousand, three hundred and twenty-one (2,321) women from the original HERS trial agreed to participate in an open-label extension of HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE plus MPA group and the placebo group in the 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 2 years3 *[see Clinical Studies (14.3)]*. 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 was reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (35 versus 17 per 10,000 women-years). Statistically significant increases in risk for both DVT (26 versus 13 per 10,000 women-years) and PE (18 versus 8 per 10,000 women-years) were also demonstrated. The increase in VTE risk was demonstrated during the first year and persisted[4]*[see Clinical Studies (14.3)]*. Immediately discontinue estrogen plus progestogen 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.

5.2 Malignant Neoplasms

Endometrial cancer

An increased risk of endometrial cancer has been reported with the use of unopposed estrogen therapy in women with a uterus. The reported endometrial cancer risk among unopposed estrogen users is about 2 to 12 times greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with the use of estrogens for less than 1 year. The greatest risk appears to be associated with prolonged use, with increased risks of 15- to 24-fold for 5 to 10 years or more. This risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

Clinical surveillance of all women using estrogen-alone or estrogen plus progestogen therapy is important. Perform adequate diagnostic measures, including directed or random endometrial sampling when indicated, to rule out malignancy in postmenopausal women with 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 estrogen dose. Adding a progestogen to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

Breast Cancer

The WHI substudy of daily CE (0.625 mg)-alone provided information about breast cancer in estrogen-alone users. In the WHI estrogen-alone substudy, after an average follow-up of 7.1 years, daily CE-alone was not associated with an increased risk of invasive breast cancer (relative risk [RR] 0.80)5 *[see Clinical Studies (14.3)]*.

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. 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.6 Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 versus 36 cases per 10,000 women-years for CE plus MPA compared with placebo. In the same substudy, invasive breast cancers were larger, were more likely to be node positive, and were diagnosed at a more advanced stage in the CE (0.625 mg) plus MPA (2.5 mg) group compared with the placebo group. Metastatic disease was rare, with no apparent difference between the two groups. Other prognostic factors, such as histologic subtype, grade and hormone receptor status did not differ between the groups[6] *[see Clinical Studies (14.3)]*.

Consistent with the WHI clinical trial, 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 abnormal mammograms requiring further evaluation. All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results.

Ovarian Cancer

The CE plus MPA substudy of WHI reporated that estrogen plus progestin increased the risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for CE plus MPA versus placebo was 1.58 (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.[7]

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

5.3 Probable Dementia

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

After an average follow-up of 5.2 years, 28 women in the estrogen-alone group and 19 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE-alone versus placebo was 1.49 (95 percent CI, 0.83-2.66). The absolute risk of probable dementia for CE-alone versus placebo was 37 versus 25 cases per 10,000 women-years[8] *[see Use in Specific Populations (8.5)* and *Clinical Studies (14.4)]*.

In the WHIMS estrogen plus progestin ancillary study of WHI, a population of 4,532 postmenopausal women 65 to 79 years of age was randomized to daily CE (0.625 mg) plus MPA (2.5 mg) or placebo.

After an average follow-up of 4 years, 40 women in the CE plus MPA group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE plus MPA versus placebo was 2.05 (95 percent CI, 1.21-3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 cases per 10,000 women-years[8] *[see Use in Specific Populations (8.5)* and *Clinical Studies (14.4)]*.

When data from the two populations in the WHIMS estrogen-alone and estrogen plus progestin ancillary studies were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95 percent CI, 1.19-2.60). Since both ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women[8] *[see Use in Specific Populations (8.5)* and *Clinical Studies (14.4)]*.

5.4 Gallbladder Disease

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

5.5 Hypercalcemia

Estrogen administration may lead to severe hypercalcemia in women with breast cancer and bone metastases. Discontinue estrogen, including ESTRADIOL TRANSDERMAL SYSTEM, if hypercalcemia occurs, and take appropriate measures to reduce the serum calcium level.

5.6 Visual Abnormalities

Retinal vascular thrombosis has been reported in patients receiving estrogens. Discontinue ESTRADIOL TRANSDERMAL SYSTEM pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. Permanently discontinue estrogens, including ESTRADIOL TRANSDERMAL SYSTEM, if examination reveals papilledema or retinal vascular lesions.

5.7 Addition of a Progestogen When a Woman Has Not Had a Hysterectomy

Studies of the addition of a progestogen for 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer. There are, however, possible risks that may be associated with the use of progestogens with estrogens compared to estrogen-alone regimens. These include an increased risk of breast cancer.

5.8 Elevated Blood Pressure

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

5.9 Exacerbation of Hypertriglyceridemia

In women with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis. Discontinue ESTRADIOL TRANSDERMAL SYSTEM treatment if pancreatitis occurs.

5.10 Hepatic Impairment and/or Past History of Cholestatic Jaundice

Estrogens may be poorly metabolized in women with hepatic impairment. Exercise caution in any woman with a history of cholestatic jaundice associated with past estrogen use or with pregnancy. In the case of recurrence of cholestatic jaundice, discontinue ESTRADIOL TRANSDERMAL SYSTEM.

5.11 Exacerbation of Hypothyroidism

Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Women with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T4 and T3 serum concentrations in the normal range. Women dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. Monitor thyroid function in these women during treatment with ESTRADIOL TRANSDERMAL SYSTEM to maintain their free thyroid hormone levels in an acceptable range.

5.12 Fluid Retention

Estrogens may cause some degree of fluid retention. Monitor any women with a condition(s) that might predispose her to fluid retention, such as cardiac or renal impairment. Discontinue estrogen-alone therapy, including ESTRADIOL TRANSDERMAL SYSTEM, with evidence of medically concerning fluid retention.

5.13 Hypocalcemia

Estrogen-induced hypocalcemia may occur in women with hypoparathyroidism. Consider whether the benefits of estrogen therapy, including ESTRADIOL TRANSDERMAL SYSTEM, outweigh the risks in such women.

5.14 Exacerbation of Endometriosis

A few cases of malignant transformation of residual endometrial implants have been reported in women treated post-hysterectomy with estrogen-alone therapy. Consider the addition of progestogen therapy for women known to have residual endometriosis post-hysterectomy.

5.15 Severe Anaphylactic/Anaphylactoid Reactions and Hereditary Angioedema

A few cases of anaphylactic/anaphylactoid reactions are reported in the postmarketing use of ESTRADIOL TRANSDERMAL SYSTEM. Involvement of skin (hives, pruritus, swollen lips-tongue-face) and either respiratory tract (respiratory compromise) or gastrointestinal tract (abdominal pain, vomiting) are noted.

Angioedema involving eye/eyelid, face, larynx, pharynx, tongue and extremity (hands, legs, ankles, and fingers) with or without urticaria requiring medical intervention are reported in the postmarketing use of ESTRADIOL TRANSDERMAL SYSTEM. Angioedema involving the tongue, glottis, or larynx, may result in airway obstruction. Do not give ESTRADIOL TRANSDERMAL SYSTEM to any woman who develops angioedema during treatment with ESTRADIOL TRANSDERMAL SYSTEM.

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

5.16 Exacerbation of Other Conditions

Estrogen therapy, including ESTRADIOL TRANSDERMAL SYSTEM, may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraines, porphyria, systemic lupus erythematosus, and hepatic hemangiomas. Consider whether the benefits of estrogen therapy outweigh the risks in such women.

5.17 Laboratory Tests

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

5.18 Drug-Laboratory Test Interactions

- Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex; and beta-thromboglobulin; decreased levels of anti-factor Xa and antithrombin III; decreased

antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.
- Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone levels, as measured by protein-bound iodine (PBI), T4 levels (by column or by radioimmunoassay) or T3 levels by radioimmunoassay. T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered. Women on thyroid replacement therapy may require higher doses of thyroid hormone.
- Other binding proteins may be elevated in serum, for example, corticosteroid-binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased total circulating corticosteroids and sex steroids, respectively. Free hormone concentrations, such as testosterone and estradiol, may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).
- Increased plasma high-density lipoprotein (HDL) and HDL2 cholesterol subfraction concentrations, reduced low-density lipoprotein (LDL) cholesterol concentration, increased triglycerides levels.
- Impaired glucose tolerance.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in labeling:
- Cardiovascular Disorders *[see **Boxed Warnings** and Warnings and Precautions (5.1)]*
- Malignant Neoplasms *[see **Boxed Warnings** and Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

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

There were no clinical trials conducted with ESTRADIOL TRANSDERMAL SYSTEM. ESTRADIOL TRANSDERMAL SYSTEM is bioequivalent to Vivelle®. The following adverse reactions are reported with Vivelle therapy:

Table 1: Summary of Most Frequently Reported Adverse Reactions (Vivelle versus Placebo) Regardless of Relationship Reported at a Frequency ≥ 5 Percent

	Vivelle 0.025 mg/ day† (N=47) N (%)	**Vivelle 0.0375 mg/ day† (N=130) N (%)**	**Vivelle 0.05 mg/ day† (N=103) N (%)**	**Vivelle 0.075 mg/ day† (N=46) N (%)**	**Vivelle 0.1 mg/ day† (N=132) N (%)**	**Placebo (N=157) N (%)**
Gastrointestinal disorders						
Constipation	2 (4.3)	5 (3.8)	4 (3.9)	3 (6.5)	2 (1.5)	4 (2.5)
Dyspepsia	4 (8.5)	12 (9.2)	3 (2.9)	2 (4.3)	0	10 (6.4)
Nausea	2 (4.3)	8 (6.2)	4 (3.9)	0	7 (5.3)	5 (3.2)
General disorders and administration site conditions* **						
Influenza-like illness	3 (6.4)	6 (4.6)	8 (7.8)	0	3 (2.3)	10 (6.4)
Pain NOS*	0	8 (6.2)	0	2 (4.3)	7 (5.3)	7 (4.5)

Infections and infestations						
Influenza	4 (8.5)	4 (3.1)	6 (5.8)	0	10 (7.6)	14 (8.9)
Nasopharyngitis	3 (6.4)	16 (12.3)	10 (9.7)	9 (19.6)	11 (8.3)	24 (15.3)
Sinusitis NOS*	4 (8.5)	17 (13.1)	13 (12.6)	3 (6.5)	7 (5.3)	16 (10.2)
Upper respiratory tract infection NOS*	3 (6.4)	8 (6.2)	11 (10.7)	4 (8.7)	6 (4.5)	9 (5.7)
Investigations						
Weight increased	4 (8.5)	5 (3.8)	2 (1.9)	2 (4.3)	0	3 (1.9)
Musculoskeletal and connective tissue disorders						
Arthralgia	0	11 (8.5)	4 (3.9)	2 (4.3)	5 (3.8)	9 (5.7)
Back pain	4 (8.5)	10 (7.7)	9 (8.7)	4 (8.7)	14 (10.6)	10 (6.4)
Neck pain	3 (6.4)	4 (3.1)	4 (3.9)	0	6 (4.5)	2 (1.3)
Pain in limb	0	10 (7.7)	7 (6.8)	2 (4.3)	6 (4.5)	9 (5.7)
Nervous system disorders						
Headache NOS*	7 (14.9)	35 (26.9)	32 (31.1)	23 (50.0)	34 (25.8)	37 (23.6)
Sinus headache	0	12 (9.2)	5 (4.9)	5 (10.9)	2 (1.5)	8 (5.1)
Psychiatric disorders						
Anxiety NEC**	3 (6.4)	5 (3.8)	0	0	2 (1.5)	4 (2.5)
Depression	5 (10.6)	4 (3.1)	7 (6.8)	0	4 (3.0)	6 (3.8)
Insomnia	3 (6.4)	6 (4.6)	4 (3.9)	2 (4.3)	2 (1.5)	9 (5.7)
Reproductive system and breast disorders						
Breast tenderness	8 (17.0)	10 (7.7)	8 (7.8)	3 (6.5)	17 (12.9)	0
Dysmenorrhea	0	0	0	3 (6.5)	0	0
Intermenstrual bleeding	3 (6.4)	9 (6.9)	6 (5.8)	0	14 (10.6)	7 (4.5)
Respiratory, thoracic and mediastinal disorders						
Sinus congestion	0	4 (3.1)	3 (2.9)	3 (6.5)	6 (4.5)	7 (4.5)
Vascular disorders						
Hot flushes NOS*	3 (6.4)	0	3 (2.9)	0	0	6 (3.8)
Hypertension NOS*	2 (4.3)	0	3 (2.9)	0	0	2 (1.3)

†Represents milligrams of estradiol delivered daily by each system
*NOS represents not otherwise specified
**NEC represents not elsewhere classified
***Application site erythema and application site irritation were observed in 3.2% or less of patients across treatment groups.

During the clinical pharmacology studies with ESTRADIOL TRANSDERMAL SYSTEM, 35 percent or less of subjects experienced barely perceptible erythema. No transdermal systems were removed due to irritation. Three subjects (2.2 percent) reported mild discomfort while wearing ESTRADIOL TRANSDERMAL SYSTEM (N=136).

6.2 Postmarketing Experience

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

Breast

Breast enlargement

Cardiovascular

Palpitations, angina unstable

Gastrointestinal

Hemorrhage, diarrhea

Skin

Application site reactions, erythema, rash, hyperhidrosis, pruritis, urticaria

Central Nervous System

Dizziness, paresthesia, migraine, mood swings, emotional disorder, irritability, nervousness

Miscellaneous

Portal vein thrombosis, dyspnea, malaise, fatigue, peripheral edema, muscle spasms, paresthesia oral, swollen tongue, lip swelling, pharyngeal edema

7 DRUG INTERACTIONS

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

ESTRADIOL TRANSDERMAL SYSTEM is not indicated for use in pregnancy. There are no data with the use of ESTRADIOL TRANSDERMAL SYSTEM in pregnant women; however, epidemiologic studies and meta-analyses have not found an increased risk of genital or nongenital birth defects (including cardiac anomalies and limb-reduction defects) following exposure to combined hormonal contraceptives (estrogens and progestins) before conception or during early pregnancy.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

8.2 Lactation

Risk Summary

Estrogens are present in human milk and can reduce milk production in breast-feeding women. This reduction can occur at any time but is less likely to occur once breast-feeding is well established.

The developmental and health benefits of breastfeeding should be considered along with

the mother's clinical need for ESTRADIOL TRANSDERMAL SYSTEM and any potential adverse effects on the breastfed child from ESTRADIOL TRANSDERMAL SYSTEM or from the underlying maternal condition.

8.4 Pediatric Use

ESTRADIOL TRANSDERMAL SYSTEM is not indicated for use in pediatric patients. Clinical studies have not been conducted in the pediatric population.

8.5 Geriatric Use

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

The Women's Health Initiative Studies

In the WHI estrogen-alone substudy (daily CE [0.625 mg]-alone versus placebo), there was a higher relative risk of stroke in women greater than 65 years of age *[see Clinical Studies (14.3)]*.

In the WHI estrogen plus progestin substudy (daily CE [0.625 mg] plus MPA [2.5 mg] versus placebo), there was a higher relative risk of nonfatal stroke and invasive breast cancer in women greater than 65 years of age *[see Clinical Studies (14.3)]*.

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 probable dementia in women receiving estrogen-alone or estrogen plus progestin when compared to placebo *[see Warnings and Precautions (5.3), and Clinical Studies (14.4)]*.

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

10 OVERDOSAGE

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

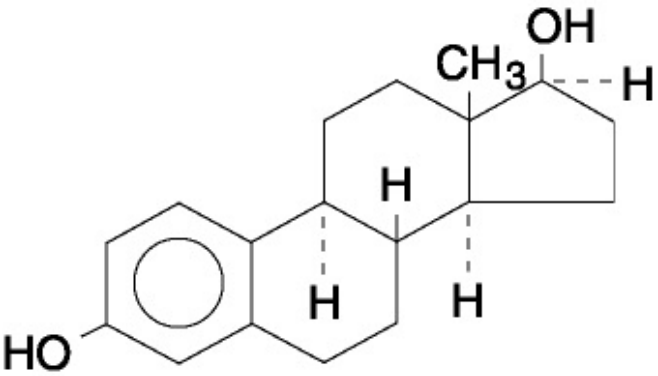
11 DESCRIPTION

ESTRADIOL TRANSDERMAL SYSTEM contains estradiol in a multipolymeric adhesive. The system is designed to release estradiol continuously upon application to intact skin.

Five dosage strengths of ESTRADIOL TRANSDERMAL SYSTEM are available to provide nominal *in vivo* delivery rates of 0.025, 0.0375, 0.05, 0.075, or 0.1 mg of estradiol per day via the skin. Each corresponding system has an active surface area of 1.65, 2.48, 3.30, 4.95, or 6.6 cm^2 and contains 0.41, 0.62, 0.83, 1.24, or 1.65 mg of estradiol USP, respectively. The composition of the systems per unit area is identical.

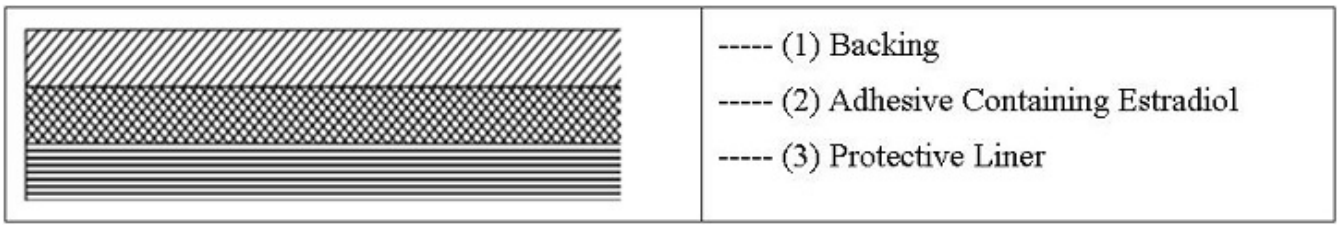
Estradiol USP is a white, crystalline powder, chemically described as estra-1,3,5(10)-triene-3,17β-diol.

The structural formula is



The molecular formula of estradiol is $C_{18}H_{24}O_2$. The molecular weight is 272.39

ESTRADIOL TRANSDERMAL SYSTEM is comprised of three layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are (1) a polyolefin laminate backing (2) an adhesive formulation containing estradiol, acrylic adhesive, silicone adhesive, oleyl alcohol, NF, povidone, USP and dipropylene glycol, and (3) a polyester release liner which is attached to the adhesive surface and must be removed before the system can be used.



The active component of the system is estradiol. The remaining components of the system are pharmacologically inactive.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 mcg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone in the peripheral tissues. Thus, estrone and the sulfate conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.

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

Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH) through a negative feedback

mechanism. Estrogens act to reduce the elevated concentrations of these hormones seen in postmenopausal women.

12.2 Pharmacodynamics

Generally, a serum estrogen concentration does not predict an individual woman's therapeutic response to ESTRADIOL TRANSDERMAL SYSTEM nor her risk for adverse outcomes. Likewise, exposure comparisons across different estrogen products to infer efficacy or safety for the individual woman may not be valid.

12.3 Pharmacokinetics

Absorption

In a single-dose, two way-crossover clinical study conducted in 96 healthy, non-smoking postmenopausal women under fed condition, ESTRADIOL TRANSDERMAL SYSTEM (0.1 mg per day) was bioequivalent to Vivelle (0.1 mg per day) based on estradiol exposure (AUC_{0-84}) and estradiol peak concentration (C_{max}) following a single-dose on the lower abdomen for 84 hours.

Estradiol pharmacokinetics were characterized in a separate open-label, single-center, randomized, single-dose, three-way crossover study conducted in 36 healthy, non-smoking postmenopausal women (aged 40 to 65 years). ESTRADIOL TRANSDERMAL SYSTEM delivering nominal estradiol of approximately 0.025 mg, 0.05 mg, and 0.1 mg per day were applied to the lower abdomen under fed state in a crossover fashion for 84 hours. The mean estradiol pharmacokinetics parameters are summarized in Table 2. AUC and C_{max} are dose proportional from 0.025 mg to 0.1 mg per day.

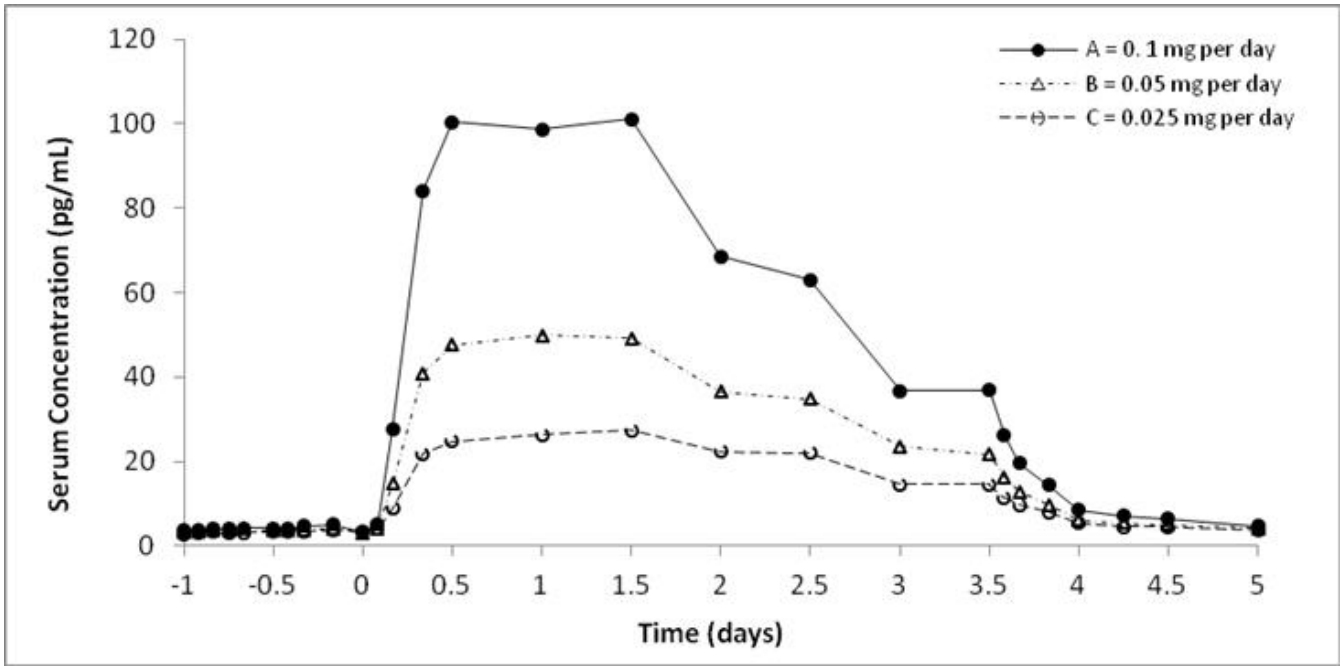
Table 2: Mean (SD) Serum Pharmacokinetic Parameters of Baseline-Uncorrected Estradiol following a Single Dose of ESTRADIOL TRANSDERMAL SYSTEM (N=36)

Parameter	0.1 mg/day	0.05 mg/day	0.025 mg/day
AUC_{84} (pg·hr/mL)	5875 (1857)	3057 (980)	1763 (600)
AUC_{120} (pg·hr/mL)	6252 (1938)	3320 (1038)	1979 (648)
C_{max} (pg/mL)	117 (39.3)	56.6 (17.6)	30.3 (11.1)
T_{max} (hr)[a]	24.0 (8-60)	24.0 (8-60)	36.0 (8-84)

[a]Median (minimum-maximum)

Figure 1 illustrates the mean baseline-uncorrected estradiol serum concentrations of ESTRADIOL TRANSDERMAL SYSTEM at three different strengths.

Figure 1: Mean Baseline-Uncorrected Estradiol Serum Concentration-Time Profiles Following a Single Dose of ESTRADIOL TRANSDERMAL SYSTEM 0.1 mg per day (Treatment A), 0.05 mg per day (Treatment B), and 0.025 mg per day (Treatment C) (N=36)



Distribution

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

Metabolism

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

Excretion

Estradiol, estrone and estriol are excreted in the urine along with glucuronide and sulfate conjugates. The mean half-life values of estradiol calculated from treatment groups in the bioequivalence study and dose-proportionality study after dosing with the ESTRADIOL TRANSDERMAL SYSTEM ranged from 6.2 to 7.9 hours. After removal of the transdermal systems, serum concentrations of estradiol and estrone returned to baseline concentrations within 24 hours.

Adhesion and Adhesive Residue

Based on combined data from bioequivalence and dose proportionality studies consisting of 208 ESTRADIOL TRANSDERMAL SYSTEM observations, approximately 98 percent of the observations had an adhesion score of 0 (i.e., the skin adhesion rate was greater than or equal to 90 percent) over the 84-hour wear period. One woman had a complete detachment during the wear period. Approximately 65 percent of the transdermal systems evaluated in these studies were with ESTRADIOL TRANSDERMAL SYSTEM 0.1 mg per day (6.6 cm^2 active surface area).

After removal of ESTRADIOL TRANSDERMAL SYSTEM, women had either no adhesive residue (score of 0) or light adhesive residue (score of 1). No woman had medium adhesive residue. Of the 208 ESTRADIOL TRANSDERMAL SYSTEM observations, 54 percent had light adhesive residue and 46 percent had no adhesive residue.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term, continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver.

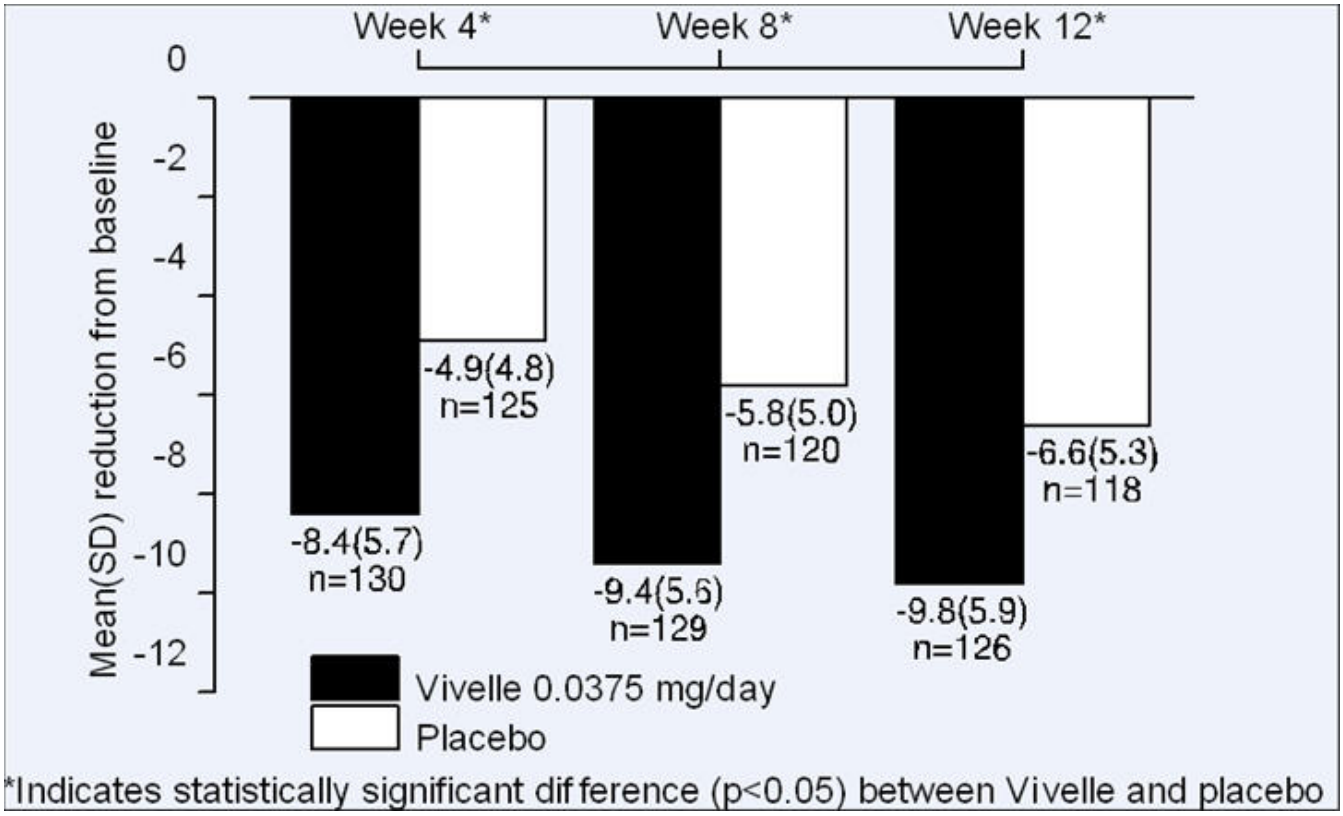
14 CLINICAL STUDIES

14.1 Effects on Vasomotor Symptoms in Postmenopausal Women

There have been no efficacy and safety trials conducted with ESTRADIOL TRANSDERMAL SYSTEM. In a pharmacokinetic study, ESTRADIOL TRANSDERMAL SYSTEM was shown to be bioequivalent to Vivelle.

In two controlled clinical trials with Vivelle, in a total of 356 subjects, the 0.075 and 0.1 mg doses were superior to placebo in relieving vasomotor symptoms at Weeks 4, 8 and 12 of treatment. In these studies, the 0.0375 and 0.05 mg doses did not differ from placebo at Week 4, therefore, a third 12-week placebo-controlled study in 255 subjects was performed with Vivelle to establish the efficacy of the lowest dose of 0.0375 mg. The baseline mean daily number of hot flushes in these 255 subjects was 11.5. Results at Weeks 4, 8, and 12 of treatment are shown in Figure 2.

Figure 2: Mean (SD) change from baseline in mean daily number of hot flushes for Vivelle 0.0375 mg versus Placebo in a 12 week trial.



The 0.0375 mg dose was superior to placebo in reducing both the frequency and severity of vasomotor symptoms at Weeks 4, 8 and 12 of treatment.

14.2 Effects on Bone Mineral Density in Postmenopausal Women

There have been no bone efficacy and safety trials conducted with ESTRADIOL TRANSDERMAL SYSTEM. In a pharmacokinetic study, ESTRADIOL TRANSDERMAL SYSTEM was shown to be bioequivalent to Vivelle.

Efficacy and safety of Vivelle in the prevention of postmenopausal osteoporosis have been studied in a 2-year double-blind, randomized, placebo-controlled, parallel group study. A total of 261 hysterectomized (161) and non-hysterectomized (100), surgically or naturally menopausal women (within 5 years of menopause), with no evidence of osteoporosis (lumbar spine bone mineral density within 2 standard deviations of average peak bone mass, i.e., ≥0.0827 g/cm^2) were enrolled in this study; 194 patients were randomized to one of the four doses of Vivelle (0.1, 0.05, 0.0375, or 0.025 mg/day) and 67 patients to placebo. Over 2 years, study systems were applied to the buttock or the abdomen twice a week. Non-hysterectomized women received oral medroxyprogesterone acetate (2.5 mg/day) throughout the study.

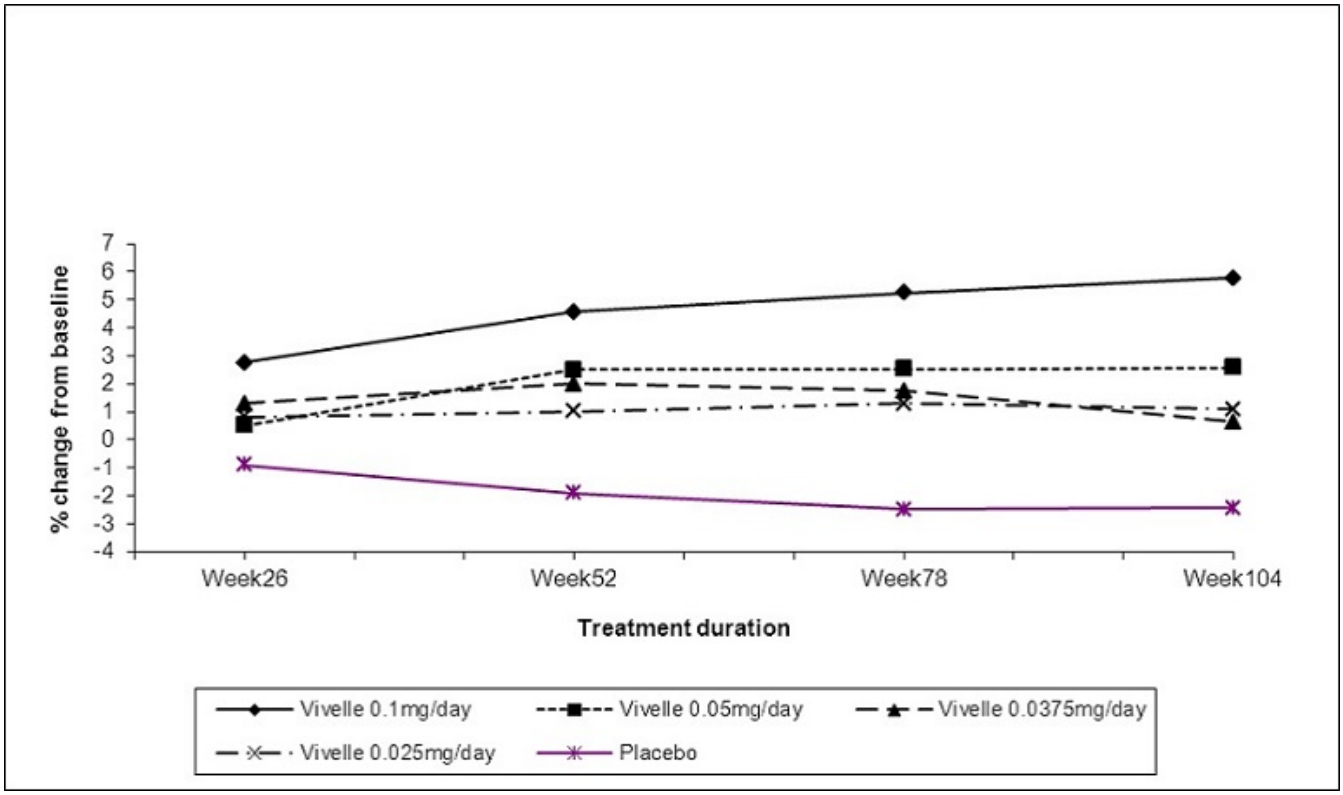
The study population comprised naturally (82 percent) or surgically (18 percent) menopausal, hysterectomized (61 percent) or non-hysterectomized (39 percent) women with a mean age of 52.0 years (range 27 to 62 years); the mean duration of menopause was 31.7 months (range 2 to 72 months). Two hundred thirty-two (89 percent) randomized subjects (173 on active drug, 59 on placebo) contributed data to the analysis of percent change from baseline in bone mineral density (BMD) of the AP lumbar spine, the primary efficacy variable. Patients were given supplemental dietary calcium (100 mg elemental calcium/day) but no supplemental vitamin D. There was an increase in BMD of the AP lumbar spine in all Vivelle dose groups; in contrast to this, a decrease in AP lumbar spine BMD was observed in placebo patients. All Vivelle doses were significantly superior to placebo ($p<0.05$) at all time points with the exception of Vivelle 0.05 mg/day at 6 months. The highest dose of Vivelle was superior to the three

lower doses. There were no statistically significant differences in pairwise comparisons among the three lower doses (See Figure 3).

Figure 3: Bone mineral density – AP Lumbar spine

Least squares means of percentage change from baseline

All randomized women with at least one post-baseline assessment available with last post-baseline observation carried forward

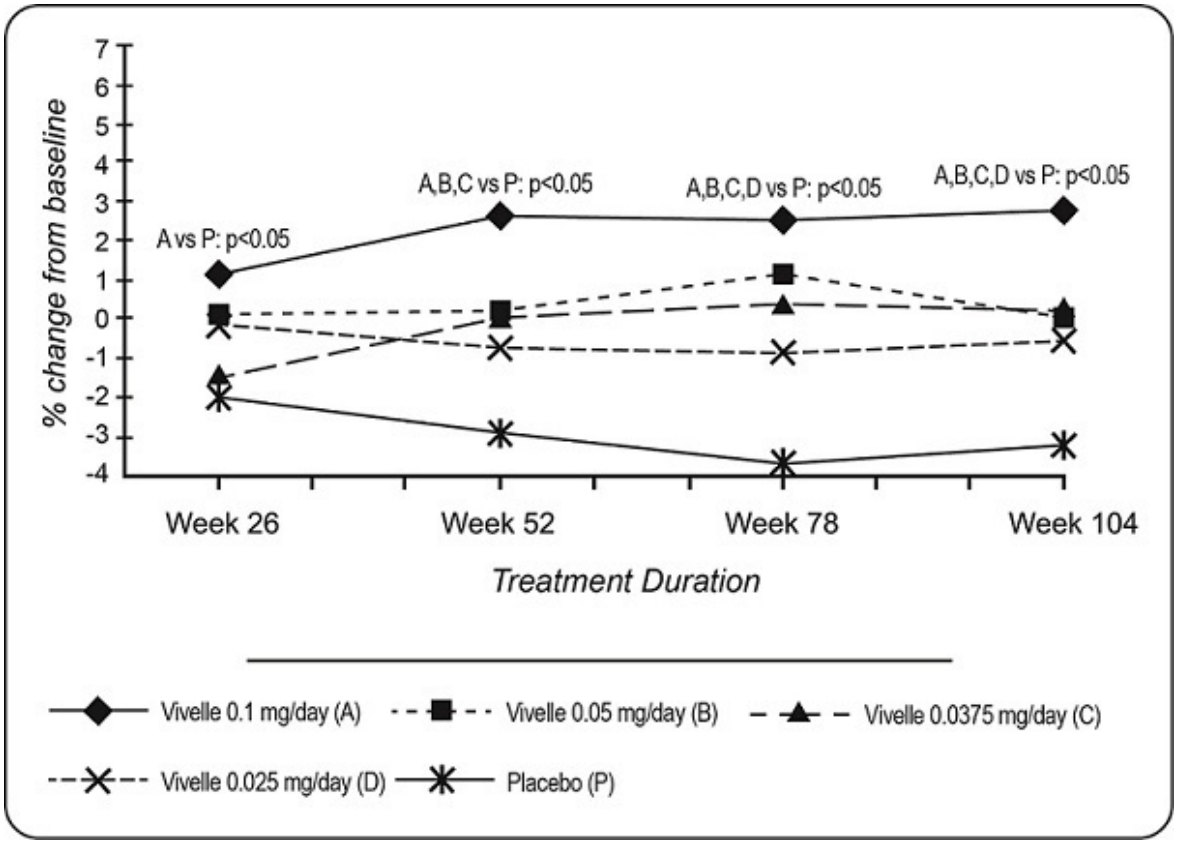


Analysis of percent change from baseline in femoral neck BMD, a secondary efficacy outcome variable, showed qualitatively similar results; all doses of Vivelle were significantly superior to placebo ($p<0.05$) at 24 months. The highest Vivelle dose was superior to placebo at all time points. A mixture of significant and non-significant results were obtained for the lower dose groups at earlier time points. The highest Vivelle dose was superior to the three lower doses, and there were no significant differences among the three lower doses at this skeletal site (see Figure 4).

Figure 4: Bone mineral density - Femoral neck

Least squares means of percentage change from baseline

All randomized women with at least one post-baseline assessment available with last post-baseline observation carried forward



14.3 Women's Health Initiative Studies

The WHI enrolled approximately 27,000 predominantly healthy postmenopausal women in two substudies to assess the risks and benefits of daily oral CE (0.625 mg)-alone or in combination with MPA (2.5 mg) compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of CHD (defined as nonfatal MI, silent MI and CHD death), with invasive breast cancer as the primary adverse outcome. A “global index” included the earliest occurrence of CHD, invasive breast cancer, stroke, PE, endometrial cancer (only in the CE plus MPA substudy), colorectal cancer, hip fracture, or death due to other cause. These substudies did not evaluate the effects of CE-alone or CE plus MPA on menopausal symptoms.

WHI Estrogen-Alone Substudy

The WHI estrogen-alone substudy was stopped early because an increased risk of stroke was observed, and it was deemed that no further information would be obtained regarding the risks and benefits of estrogen-alone in predetermined primary endpoints.

Results of the estrogen-alone substudy, which included 10,739 women (average 63 years of age, range 50 to 79; 75.3 percent White, 15.1 percent Black, 6.1 percent Hispanic, 3.6 percent Other), after an average follow- up of 7.1 years are presented in Table 3.

Table 3: Relative and Absolute Risk Seen in the Estrogen Alone Substudy of WHI[a]

Event	Relative Risk CE vs. Placebo (95% nCI[b])	CE n = 5,310	Placebo n = 5,429
		Absolute Risk per 10,000 Women-Years	

CHD events[c] *Non-fatal MI[c]* *CHD death[c]*	0.95 (0.78–1.16) *0.91 (0.73–1.14)* *1.01 (0.71–1.43)*	54 *40* *16*	57 *43* *16*
All Strokes[c] *Ischemic stroke[c]*	1.33 (1.15–1.68) *1.55 (1.19–2.01)*	45 *38*	33 *25*
Deep vein thrombosis[c,d]	1.47 (1.06–2.06)	23	15
Pulmonary embolism[c]	1.37 (0.90–2.07)	14	10
Invasive breast cancer[c]	0.80 (0.62–1.04)	28	34
Colorectal cancer[e]	1.08 (0.75–1.55)	17	16
Hip fracture[c]	0.65 (0.45–0.94)	12	19
Vertebral fractures[c,d]	0.64 (0.44–0.93)	11	18
Lower arm/wrist fractures[c,d]	0.58 (0.47–0.72)	35	59
Total fractures[c,d]	0.71 (0.64–0.80)	144	197
Death due to other causes[e,f]	1.08 (0.88–1.32)	53	50
Overall mortality[c,d]	1.04 (0.88–1.22)	79	75
Global Index[g]	1.02 (0.92–1.13)	206	201

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

For those outcomes included in the WHI “global index” that reached statistical significance, the absolute excess risk per 10,000 women-years in the group treated with CE-alone was 12 more strokes, while the absolute risk reduction per 10,000 women-years was 7 fewer hip fractures.[9] The absolute excess risk of events included in the “global index” was a non-significant 5 events per 10,000 women-years. There was no difference between the groups in terms of all-cause mortality.

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

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

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

WHI Estrogen Plus Progestin Substudy

The WHI estrogen plus progestin substudy was stopped early. According to the predefined stopping rule, after an average follow-up of 5.6 years of treatment, the

increased risk of invasive breast cancer and cardiovascular events exceeded the specified benefits included in the “global index”. The absolute excess risk of events included in the “global index” was 19 per 10,000 women-years.

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

Results of the CE plus MPA substudy, which included 16,608 women (average 63 years of age, range 50 to 79; 83.9 percent White, 6.8 percent Black, 5.4 percent Hispanic, 3.9 percent Other) are presented in Table 4. These results reflect centrally adjudicated data after an average follow-up of 5.6 years.

Table 4: Relative and Absolute Risk Seen in the Estrogen Plus Progestin Substudy of WHI at an Average of 5.6 Years[a,b]

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

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

14.4 Women's Health Initiative Memory Study

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

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

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

After an average follow-up of 4 years, the relative risk of probable dementia for CE plus MPA versus placebo was 2.05 (95 percent CI, 1.21- 3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 per 10,000 women-years. Probable dementia as defined in this study included AD, VaD and mixed type (having features of both AD and VaD). The most common classification of probable dementia in the treatment group and the placebo group was AD. Since the ancillary study was conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women [see *Warnings and Precautions (5.3)* and *Use in Specific Populations (8.5)]*.

When data from the two populations were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95 percent CI, 1.19-2.60). Differences between groups became apparent in the first year of treatment. It is unknown whether these findings apply to younger postmenopausal women *[see Warnings and Precautions (5.3*) and *Use in Specific Populations (*8.5*)]*.

15 REFERENCES

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7. Anderson GL, et al. Effects of Estrogen Plus Progestin on Gynecologic Cancers and Associated Diagnostic Procedures. *JAMA.* 2003;290:1739-1748.
8. Shumaker SA, et al. Conjugated Equine Estrogens and Incidence of Probable Dementia and Mild Cognitive Impairment in Postmenopausal Women. *JAMA.*2004;291:2947-2958.
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10. Hendrix SL, et al. Effects of Conjugated Equine Estrogen on Stroke in the Women's Health Initiative. Circulation. 2006;113:2425-2434.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

ESTRADIOL TRANSDERMAL SYSTEM, 0.025 mg per day - each 1.65 cm^2 system contains 0.41 mg of estradiol USP for nominal* delivery of 0.025 mg of estradiol per day.

Patient Calendar Pack of 8 Systems……NDC 68968-3425-8

ESTRADIOL TRANSDERMAL SYSTEM, 0.0375 mg per day - each 2.48 cm^2 system contains 0.62 mg of estradiol USP for nominal* delivery of 0.0375 mg of estradiol per day.

Patient Calendar Pack of 8 Systems……NDC 68968-3437-8

ESTRADIOL TRANSDERMAL SYSTEM, 0.05 mg per day - each 3.3 cm^2 system contains 0.83 mg of estradiol USP for nominal* delivery of 0.05 mg of estradiol per day.

Patient Calendar Pack of 8 Systems……NDC 68968-3450-8

ESTRADIOL TRANSDERMAL SYSTEM, 0.075 mg per day - each 4.95 cm^2 system contains 1.24 mg of estradiol USP for nominal* delivery of 0.075 mg of estradiol per day.

Patient Calendar Pack of 8 Systems……NDC 68968-3475-8

ESTRADIOL TRANSDERMAL SYSTEM, 0.1 mg per day - each 6.6 cm^2 system contains 1.65 mg of estradiol USP for nominal* delivery of 0.1 mg of estradiol per day.

Patient Calendar Pack of 8 Systems……NDC 68968-3410-8

*See Description

16.2 Storage and Handling

Store at room temperature 68°F to 77°F (20°C to 25°C); excursions permitted between 15°C and 30°C (59°F and 86°F). [*See USP Controlled Room Temperature*]

Do not store unpouched. Apply immediately upon removal from the protective pouch.

Used transdermal systems still contain active hormone. To discard, fold the sticky side of the transdermal system together, place it in a sturdy child-proof container, and place this container in the trash. Used transdermal systems should not be flushed in the toilet.

17 PATIENT COUNSELING INFORMATION

Advice women to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Vaginal Bleeding
Inform postmenopausal women to report unusual vaginal bleeding to their healthcare providers as soon as possible *[see* Warnings and Precautions *(*5.2*)]*

Possible Serious Adverse Reactions with Estrogen–Alone Therapy
Inform postmenopausal women of 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 less serious but common adverse reactions of estrogen-alone therapy such as headache, breast pain and tenderness, nausea and vomiting.

Patient Information

ESTRADIOL TRANSDERMAL SYSTEM

Read this Patient Information before you start using ESTRADIOL TRANSDERMAL SYSTEM 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 ESTRADIOL TRANSDERMAL SYSTEM (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 ESTRADIOL TRANSDERMAL SYSTEM. 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 of age or older.
- Do not use estrogens with progestins to prevent heart disease, heart attacks, 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 of age or older.
- Only one estrogen-alone product and does 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 studies in the same way, it is not known how the use of ESTRADIOL TRANSDERMAL SYSTEM will affect your chances

of developing these conditions. You and your healthcare provider should talk regularly about whether you still need treatment with ESTRADIOL TRANSDERMAL SYSTEM.

What is ESTRADIOL TRANSDERMAL SYSTEM?

ESTRADIOL TRANSDERMAL SYSTEM is a prescription medicine patch (transdermal system) that contains the estrogen hormone estradiol. When applied to the skin, estradiol is absorbed through the skin into the bloodstream.

What is ESTRADIOL TRANSDERMAL SYSTEM used for?

THE ESTRADIOL TRANSDERMAL SYSTEM is used after menopause to:

- **Reduce moderate to severe hot flashes**
  Estrogens are hormones made by a woman's ovaries. The ovaries normally stop making estrogens when a woman is between 45 and 55 years old. This drop in body estrogen levels causes the "change of life" or menopause (the end of monthly menstrual periods). Sometimes, both ovaries are removed during an operation before natural menopause takes place. The sudden drop in estrogen levels causes "surgical menopause."
  When the estrogen levels begin dropping, some women develop 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 estrogens. In other women, symptoms can be more severe.
- **Help reduce your chances of getting osteoporosis (thin weak bones)**
  Osteoporosis from menopause is a thinning of the bones that makes them weaker and easier to break. If you use ESTRADIOL TRANSDERMAL SYSTEM only to prevent osteoporosis from menopause, talk with your healthcare provider about whether a different treatment or medicine without estrogens might be better for you.

  You and your healthcare provider should talk regularly about whether you should continue treatment with ESTRADIOL TRANSDERMAL SYSTEM.

Who should not use ESTRADIOL TRANSDERMAL SYSTEM? Do not start using ESTRADIOL TRANSDERMAL SYSTEM 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.
- **have been diagnosed with a bleeding disorder**
- **currently have or have had certain cancers**
  Estrogens may increase the chances 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 ESTRADIOL TRANSDERMAL SYSTEM.
- **had a stroke or heart attack**
- **currently have or have had blood clots**
- **currently have or have had liver problems**
- **are allergic to ESTRADIOL TRANSDERMAL SYSTEM or the ingredients in it.**
  See the list of ingredients in ESTRADIOL TRANSDERMAL SYSTEM at the end of this leaflet.

Before you use ESTRADIOL TRANSDERMAL SYSTEM, 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 unusual vaginal bleeding to find out the cause.
- **have any other medical conditions that may become worse while you are using ESTRADIOL TRANSDERMAL SYSTEM**
  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 the face and tongue), 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 ESTRADIOL TRANSDERMAL SYSTEM.
- **are pregnant or think you may be pregnant.**
  ESTRADIOL TRANSDERMAL SYSTEM is not for pregnant women.
- **are breast feeding**
  The hormone in ESTRADIOL TRANSDERMAL SYSTEM 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 ESTRADIOL TRANSDERMAL SYSTEM works. ESTRADIOL TRANSDERMAL SYSTEM 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 ESTRADIOL TRANSDERMAL SYSTEM?

For detailed instructions, see the step-by-step instructions for using ESTRADIOL TRANSDERMAL SYSTEM at the end of this Patient Information

- Use ESTRADIOL TRANSDERMAL SYSTEM exactly as your healthcare provider tells you to use it
- ESTRADIOL TRANSDERMAL SYSTEM is for skin use only
- Change your ESTRADIOL TRANSDERMAL SYSTEM patch 2 times a week or every 3 to 4 days
- Apply your ESTRADIOL TRANSDERMAL SYSTEM patch to a clean, dry area on your lower abdomen or buttocks. This area must be clean, dry, and free of powder, oil or lotion for your patch to stick to your skin
- Apply your ESTRADIOL TRANSDERMAL SYSTEM patch to a different area of your abdomen or your buttocks each time. Do not use the same application site 2 times in the same week.
- Do not apply ESTRADIOL TRANSDERMAL SYSTEM to your breasts
- If you forget to apply a new ESTRADIOL TRANSDERMAL SYSTEM patch, apply a new patch as soon as possible.
- You and your healthcare provider should talk regularly (every 3 to 6 months) about your dose and whether you still need treatment with ESTRADIOL TRANSDERMAL SYSTEM.

How to Change ESTRADIOL TRANSDERMAL SYSTEM

- When changing the patch, peel off the used patch slowly from the skin
- After removal of ESTRADIOL TRANSDERMAL SYSTEM if any adhesive residue remains on your skin, allow the are to dry for 15 minutes. Then, gently rub the area with oil or lotion to remove the adhesive from your skin

- Apply the new patch to a different area of your abdomen or buttocks. This area must be clean, dry, cool and free of powder, oil or lotion.

What are the possible side effects of ESTRADIOL TRANSDERMAL SYSTEM?

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
- high or low blood calcium
- gallbladder disease
- visual abnormalities
- high blood pressure
- high level of fat (triglyceride) in your blood
- liver problems
- changes in your thyroid hormone levels
- fluid retention
- cancer changes of endometriosis
- enlargement of benign tumors of the uterus (“fibroids”)
- worsening of swelling of face and tongue (angioedema) in women with a history of angioedema

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
- swelling of face and tongue with or without red, itchy bumps

Common side effects of ESTRADIOL TRANSDERMAL SYSTEM include:
- headache
- breast pain
- irregular vaginal bleeding or spotting
- stomach or abdominal cramps, bloating
- nausea and vomiting
- hair loss
- fluid retention
- vaginal yeast infection
- redness and/or irritation at patch placement site

These are not all the possible side effects of ESTRADIOL TRANSDERMAL SYSTEM. For more information, ask your healthcare provider or pharmacist. Tell your healthcare provider if you have any side effects that bother you or do not go away. You may report

side effects to Noven at 1-800-455-8070 or to FDA at 1-800-FDA-1088.

What can I do to lower my chances of a serious side effect with ESTRADIOL TRANSDERMAL SYSTEM?

- Talk with your healthcare provider regularly about whether you should continue using ESTRADIOL TRANSDERMAL SYSTEM
- If you have a uterus, talk to your healthcare provider about whether the addition of a progestogen is right for you.
  In general, the addition of a progestogen is generally recommended for a woman 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 ESTRADIOL TRANSDERMAL SYSTEM.
- 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 higher chances of getting heart disease. Ask your healthcare provider for ways to lower your chances of getting heart disease.

How should I store and throw away used ESTRADIOL TRANSDERMAL SYSTEM patches?

- Store ESTRADIOL TRANSDERMAL SYSTEM at room temperature 68°F to 77°F (20°C to 25°C)
- Do not store ESTRADIOL TRANSDERMAL SYSTEM patches outside of their pouches. Apply immediately upon removal from the protective pouch
- Used patches still contain estrogen. To throw away the patch, fold the sticky side of the patch together, place it in a sturdy child-proof container, and place this container in the trash. Used patches should not be flushed in the toilet

KEEP ESTRADIOL TRANSDERMAL SYSTEM and all other medicines out of the reach of children

General information about safe and effective use of ESTRADIOL TRANSDERMAL SYSTEM

Medicines are sometimes prescribed for purposes other than those listed in Patient Information leaflets. Do not use ESTRADIOL TRANSDERMAL SYSTEM for conditions for which it was not prescribed. Do not give ESTRADIOL TRANSDERMAL SYSTEM to other people, even if they have the same symptoms you have. It may harm them.

You can ask your healthcare provider or pharmacist for information about ESTRADIOL TRANSDERMAL SYSTEM that is written for health professionals. You can get more information by calling Grove Pharmaceuticals at 1-844-884-6796.

What are the ingredients in ESTRADIOL TRANSDERMAL SYSTEM?
Active ingredient: estradiol
Inactive ingredients: Polyester film backing, acrylic and silicone adhesives, oleyl alcohol, NF, povidone, USP and dipropylene glycol, a polyester release liner, and a polyester release liner

INSTRUCTIONS FOR USE

ESTRADIOL TRANSDERMAL SYSTEM

Read this PATIENT INFORMATION before you start using ESTRADIOL TRANSDERMAL SYSTEM 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.

You will need the following supplies **(See Figure A)**

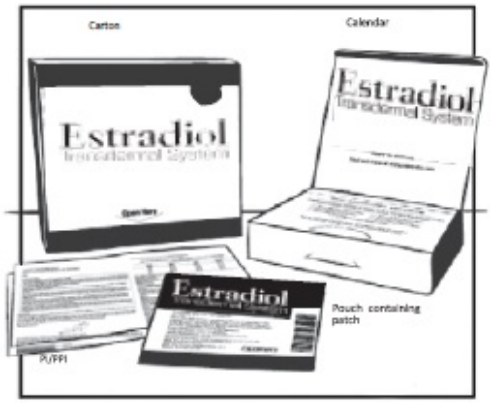

Figure A

Step 1: Pick the days you will change your patch.

- You will need to change your patch 2 times a week or every 3 to 4 days. Use the calendar printed inside your carton to choose the 2 days you will change your patch **(See Figure B).**
- **Remember to change your patch on the same 2 days you marked on your calendar.** If you forget to change your patch on the correct date, apply a new patch as soon as you remember, and continue to follow your original schedule

Figure B

Step 2. Remove the ESTRADIOL TRANSDERMAL SYSTEM patch from the pouch.

- Remove the patch from its protective pouch by tearing at the notch (**do not** use scissors, **See Figure C).**
- Do not remove your patch from the protective pouch until you are ready to apply it

Figure C

Step 3. Remove half of the adhesive liner (See Figure D).

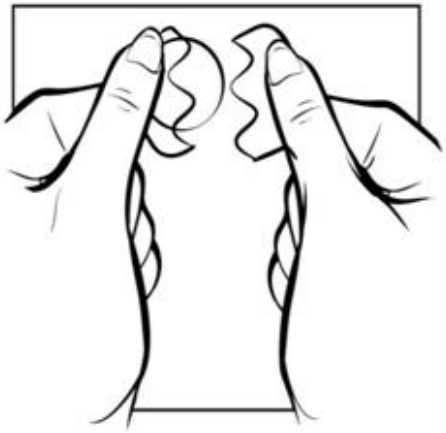

Figure D

Step 4. Placing the patch on your skin.

- Hold the part of the patch that still has the adhesive liner on it
- **Avoid touching the sticky half of the patch with your fingers**
- Apply the exposed sticky half of the patch to 1 of the areas of skin shown below **(See Figures E and F)**

Figure E

Figure F

Note:

- Avoid the waistline, since clothing and belts may cause the patch to be rubbed off

- Do not apply the patch to your breasts
- Only apply the patch to skin that is clean, dry, and free of any powder, oil, or lotion
- You should not apply the patch to injured, burned, or irritated skin, or areas with skin conditions (such as birth marks, tattoos, or that is very hairy)

Step 5: Press the patch firmly onto your skin.

- Remove the remaining half of the adhesive liner and press the entire patch into place with the palm of your hand for 10 seconds
- Rub the edges of the patch with your fingers to make sure that it will stick to your skin **(See Figure G)**

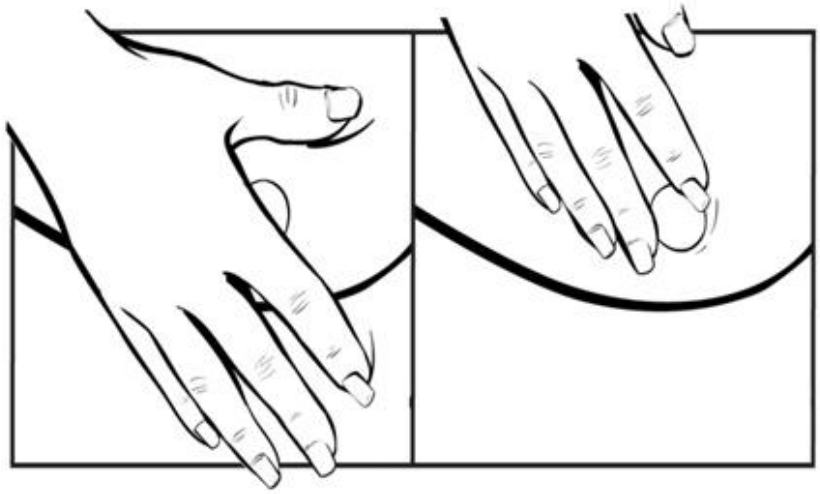

Figure G

Note:

- Showering will not cause your patch to fall off
- If your patch falls off reapply it. If you cannot reapply the patch, apply a new patch to another area **(See Figures D and E)** and continue to follow your original placement schedule
- If you stop using your ESTRADIOL TRANSDERMAL SYSTEM patch or forget to apply a new patch as scheduled, you may have spotting, or bleeding, and recurrence of symptoms

Step 6: Throwing away your used patch.

- When it is time to change your patch, remove the old patch before you apply a new patch
- To throw away the patch, fold the sticky side of the patch together, place it in a sturdy child-proof container, and place this container in the trash. Used patches should not be flushed in the toilet

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

Distributed by:
Grove Pharmaceuticals
Miami, FL 33186

Approved 02/2024

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102631-3

PRINCIPAL DISPLAY PANEL - NDC: 68968-3425-8 - 0.025 mg 8-count Carton Label

NDC 68968-3425-8

0.025 mg/day

Estradiol

Transdermal System

Delivers 0.025 mg/day

Twice-Weekly

Rx Only

Includes 8 Systems

Open Here

Contents: 8 Systems

Rx Only

Each 1.65 cm^2 system contains

0.41 mg of estradiol USP.

Inactive components: acrylic adhesive,

silicone adhesive, oleyl alcohol, dipropylene glycol, povidone,

polyolefin laminate backing, polyester release liner.

For Transdermal Use Only

Important: Package not child-resistant.

Keep out of reach of children.

Apply immediately upon removal from pouch.

Do not store unpouched.

Store at 20°C to 25°C (68°F to 77°F).

[See USP Controlled Room Temperature].

Dosage and Administration: Apply twice-weekly. See package insert.

Estradiol

Transdermal System

Delivers 0.025 mg/day

302410-2

N3 68968-3425-8 8

Grove Pharmaceuticals®

Your Application Schedule

Determine which 2 days of the week you will change

your patch and then mark them on this calendar

Sunday/Wednesday

Monday/Thursday

Tuesday/Friday

Thursday/Sunday

Friday/Monday

Saturday/Tuesday

Wednesday/Saturday

As a handy reminder of your

application schedule, keep this tear out with you.

Pull here for your

Estradiol Transdermal System patches

0.025 mg/day

Dist. by: Grove Pharmaceuticals

Miami, Florida 33186

LOT/EXP

GT|N: 00368968342588

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302410-2

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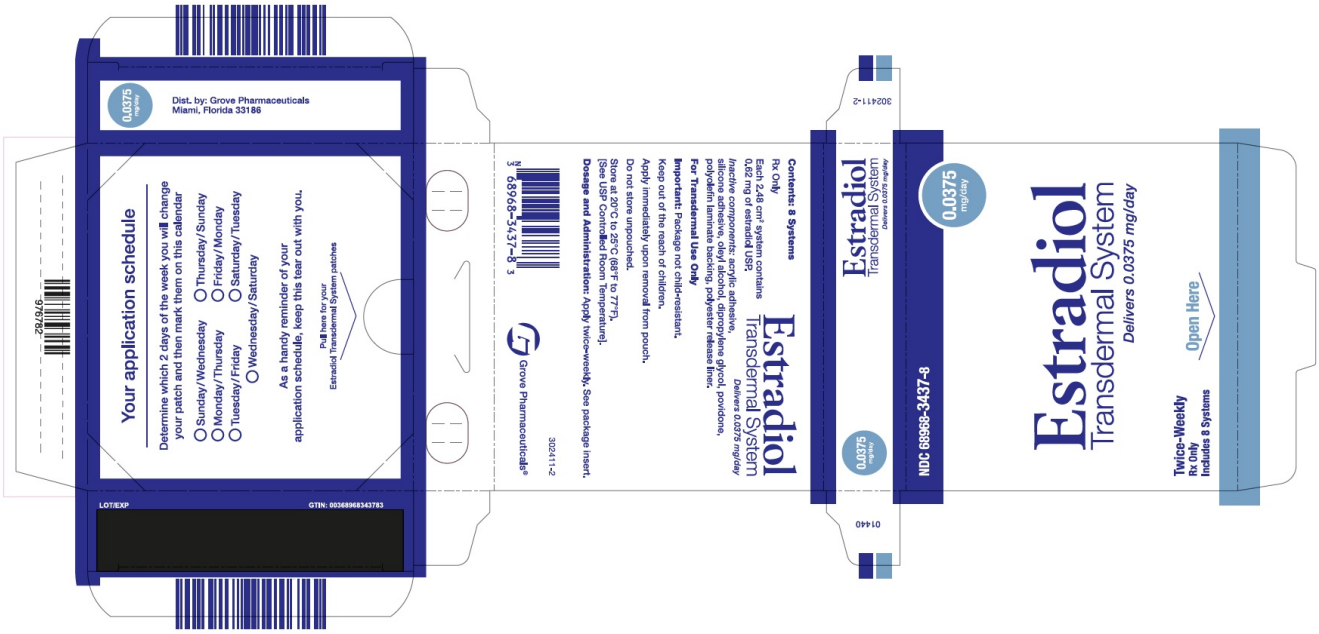
PRINCIPAL DISPLAY PANEL - NDC: 68968-3437-8 - 0.0375 mg 8-count Carton Label



NDC 68968-3437-8

0.0375 mg/day

Estradiol

Transdermal System

Delivers 0.0375 mg/day

Twice-Weekly

Rx Only

Includes 8 Systems

Open Here

Contents: 8 Systems

Rx Only

Each 2.48 cm^2 system contains

0.62 mg of estradiol USP.

Inactive components: acrylic adhesive,

silicone adhesive, oleyl alcohol, dipropylene glycol, povidone,

polyolefin laminate backing, polyester release liner.

For Transdermal Use Only

Important: Package not child-resistant.

Keep out of reach of children.

Apply immediately upon removal from pouch.

Do not store unpouched.

Store at 20°C to 25°C (68°F to 77°F).

[See USP Controlled Room Temperature].

Dosage and Administration: Apply twice-weekly. See package insert.

Estradiol

Transdermal System

Delivers 0.025 mg/day

302411-2

N3 68968-3437-8 8

Grove Pharmaceuticals®

Your Application Schedule

Determine which 2 days of the week you will change

your patch and then mark them on this calendar

Sunday/Wednesday

Monday/Thursday

Tuesday/Friday

Thursday/Sunday

Friday/Monday

Saturday/Tuesday

Wednesday/Saturday

As a handy reminder of your

application schedule, keep this tear out with you.

Pull here for your

Estradiol Transdermal System patches

0.0375 mg/day

Dist. by: Grove Pharmaceuticals

Miami, Florida 33186

LOT/EXP

GT|N: 00368968343783

01440

302411-2

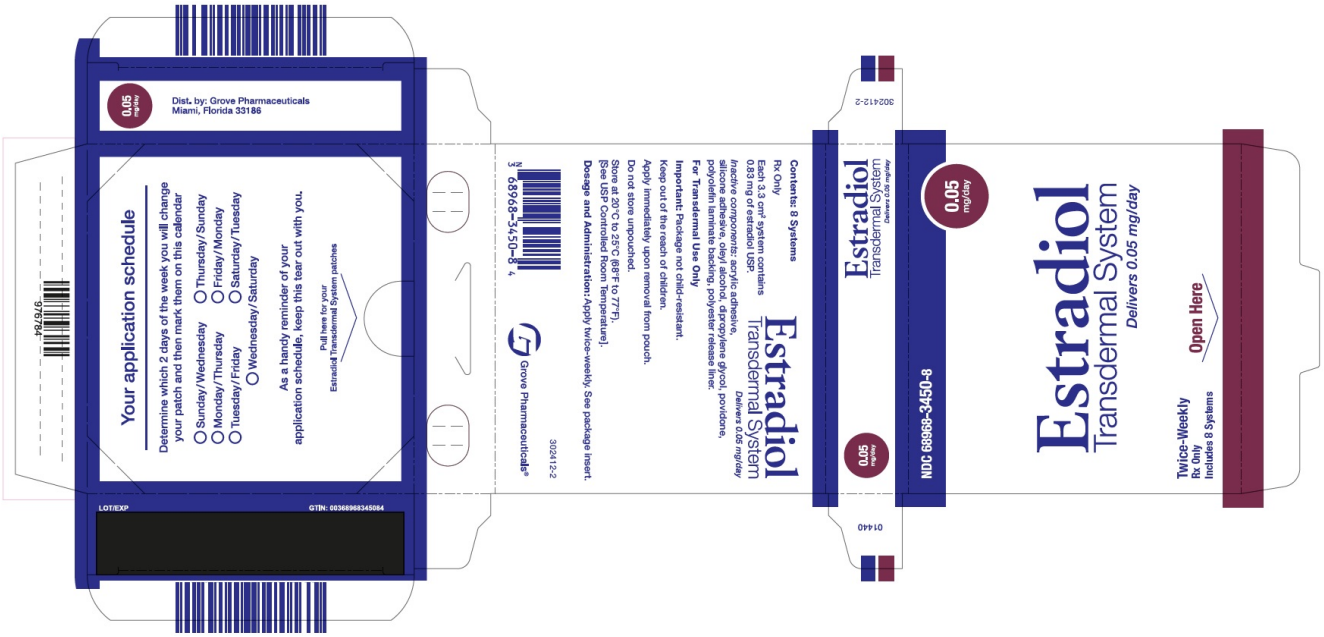
302411-2

302411-2

976782

PRINCIPAL DISPLAY PANEL - NDC: 68968-3450-8 - 0.05 mg 8-count Carton

Label



NDC 68968-3450-8

0.05 mg/day

Estradiol

Transdermal System

Delivers 0.05 mg/day

Twice-Weekly

Rx Only

Includes 8 Systems

Open Here

Contents: 8 Systems

Rx Only

Each 3.3 cm^2 system contains

0.83 mg of estradiol USP.

Inactive components: acrylic adhesive,

silicone adhesive, oleyl alcohol, dipropylene glycol, povidone,

polyolefin laminate backing, polyester release liner.

For Transdermal Use Only

Important: Package not child-resistant.

Keep out of reach of children.

Apply immediately upon removal from pouch.

Do not store unpouched.

Store at 20°C to 25°C (68°F to 77°F).

[See USP Controlled Room Temperature].

Dosage and Administration: Apply twice-weekly. See package insert.

Estradiol

Transdermal System

Delivers 0.05 mg/day

302412-2

N3 68968-3450-8 8

Grove Pharmaceuticals®

Your Application Schedule

Determine which 2 days of the week you will change

your patch and then mark them on this calendar

Sunday/Wednesday

Monday/Thursday

Tuesday/Friday

Thursday/Sunday

Friday/Monday

Saturday/Tuesday

Wednesday/Saturday

As a handy reminder of your

application schedule, keep this tear out with you.

Pull here for your

Estradiol Transdermal System patches

0.05 mg/day

Dist. by: Grove Pharmaceuticals

Miami, Florida 33186

LOT/EXP

GT|N: 00368968345084

01440

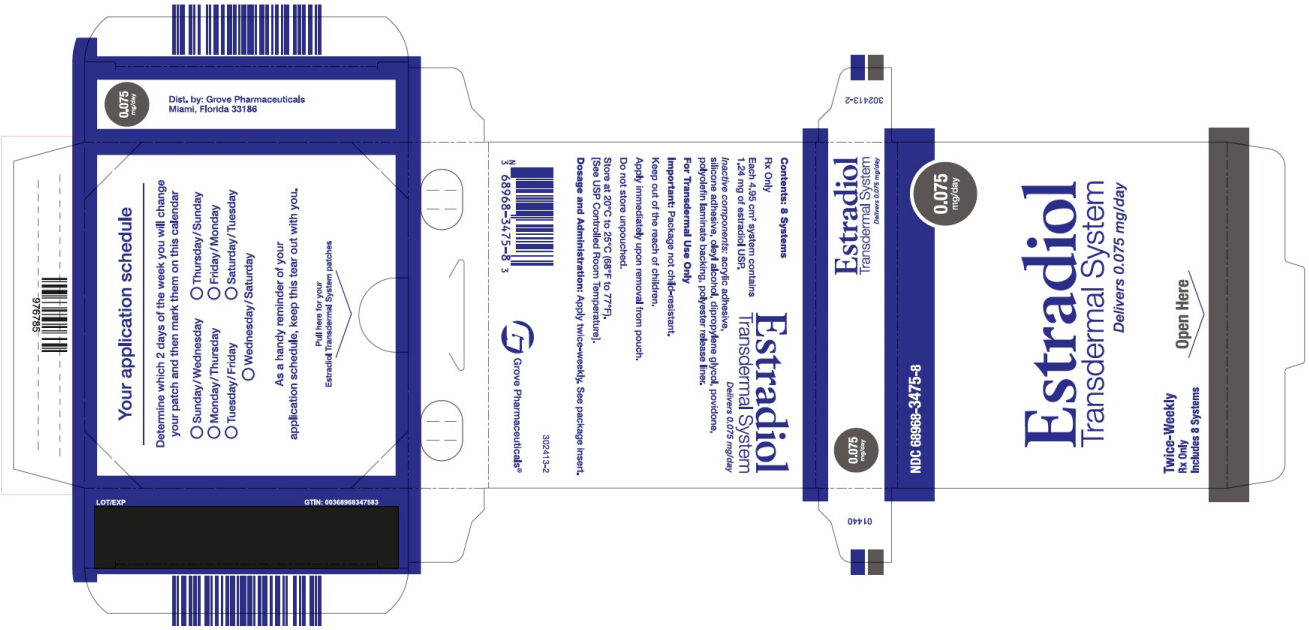
302412-2

302412-2

302412-2

976784

PRINCIPAL DISPLAY PANEL - NDC: 68968-3475-8 - 0.075 mg 8-count Carton Label



NDC 68968-3475-8

0.075 mg/day

Estradiol

Transdermal System

Delivers 0.075 mg/day

Twice-Weekly

Rx Only

Includes 8 Systems

Open Here

Contents: 8 Systems

Rx Only

Each 4.95 cm^2 system contains

1.24 mg of estradiol USP.

Inactive components: acrylic adhesive,

silicone adhesive, oleyl alcohol, dipropylene glycol, povidone,

polyolefin laminate backing, polyester release liner.

For Transdermal Use Only

Important: Package not child-resistant.

Keep out of reach of children.

Apply immediately upon removal from pouch.

Do not store unpouched.

Store at 20°C to 25°C (68°F to 77°F).

[See USP Controlled Room Temperature].

Dosage and Administration: Apply twice-weekly. See package insert.
Estradiol

Transdermal System

Delivers 0.075 mg/day

302413-2

N3 68968-3475-8 8

Grove Pharmaceuticals®

Your Application Schedule

Determine which 2 days of the week you will change

your patch and then mark them on this calendar

Sunday/Wednesday

Monday/Thursday

Tuesday/Friday

Thursday/Sunday

Friday/Monday

Saturday/Tuesday

Wednesday/Saturday

As a handy reminder of your

application schedule, keep this tear out with you.

Pull here for your

Estradiol Transdermal System patches

0.075 mg/day

Dist. by: Grove Pharmaceuticals

Miami, Florida 33186

LOT/EXP

GT|N: 00368968347583

01440

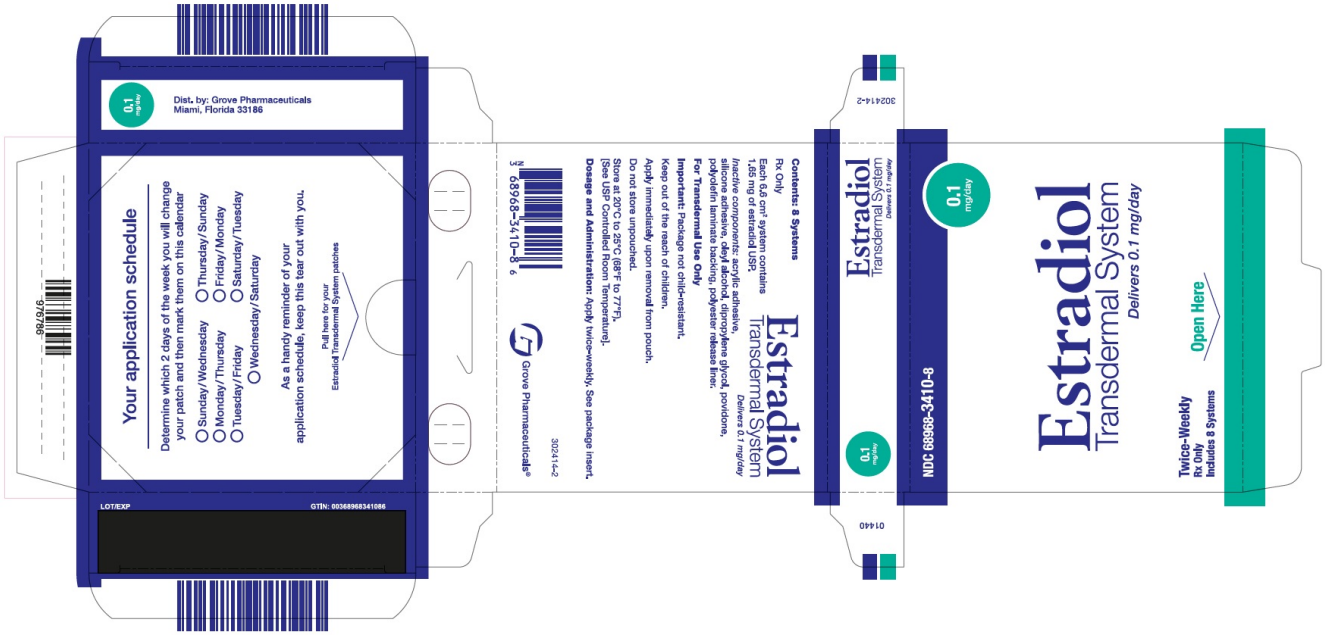
302413-2

302413-2

302413-2

976785

PRINCIPAL DISPLAY PANEL - NDC: 68968-3410-8 - 0.1 mg 8-count Carton Label



NDC 68968-3410-8

0.1 mg/day

Estradiol

Transdermal System

Delivers 0.1 mg/day

Twice-Weekly

Rx Only

Includes 8 Systems

Open Here

Contents: 8 Systems

Rx Only

Each 6.6 cm^2 system contains

1.65 mg of estradiol USP.

Inactive components: acrylic adhesive,

silicone adhesive, oleyl alcohol, dipropylene glycol, povidone,

polyolefin laminate backing, polyester release liner.

For Transdermal Use Only

Important: Package not child-resistant.

Keep out of reach of children.

Apply immediately upon removal from pouch.

Do not store unpouched.

Store at 20°C to 25°C (68°F to 77°F).

[See USP Controlled Room Temperature].

Dosage and Administration: Apply twice-weekly. See package insert.
Estradiol

Transdermal System

Delivers 0.05 mg/day

302414-2

N3 68968-3410-8 8

Grove Pharmaceuticals®

Your Application Schedule

Determine which 2 days of the week you will change

your patch and then mark them on this calendar

Sunday/Wednesday

Monday/Thursday

Tuesday/Friday

Thursday/Sunday

Friday/Monday

Saturday/Tuesday

Wednesday/Saturday

As a handy reminder of your

application schedule, keep this tear out with you.

Pull here for your

Estradiol Transdermal System patches

0.1 mg/day

Dist. by: Grove Pharmaceuticals

Miami, Florida 33186

LOT/EXP

GT|N: 00368968341086

01440

302414-2

302414-2

302414-2

976786

ESTRADIOL

estradiol film, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:68968-3425

Route of Administration	TRANSDERMAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ESTRADIOL (UNII: 4TI98Z838E) (ESTRADIOL - UNII:4TI98Z838E)	ESTRADIOL	0.025 mg in 1 d

Inactive Ingredients

Ingredient Name	Strength
DIPROPYLENE GLYCOL (UNII: E107L85C40)	
OLEYL ALCOHOL (UNII: 172F2WN8DV)	
POVIDONE K30 (UNII: U725QWY32X)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68968-3425-8	8 in 1 CARTON	01/01/2018	
1		1 d in 1 POUCH; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA authorized generic	NDA203752	01/01/2018	

ESTRADIOL

estradiol film, extended release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:68968-3437
Route of Administration	TRANSDERMAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ESTRADIOL (UNII: 4TI98Z838E) (ESTRADIOL - UNII:4TI98Z838E)	ESTRADIOL	0.0375 mg in 1 d

Inactive Ingredients

Ingredient Name	Strength
DIPROPYLENE GLYCOL (UNII: E107L85C40)	
OLEYL ALCOHOL (UNII: 172F2WN8DV)	
POVIDONE K30 (UNII: U725QWY32X)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68968-3437-8	8 in 1 CARTON	01/01/2018	
1		1 d in 1 POUCH; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA authorized generic	NDA203752	01/01/2018	

ESTRADIOL

estradiol film, extended release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:68968-3450
Route of Administration	TRANSDERMAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ESTRADIOL (UNII: 4TI98Z838E) (ESTRADIOL - UNII:4TI98Z838E)	ESTRADIOL	0.050 mg in 1 d

Inactive Ingredients

Ingredient Name	Strength
DIPROPYLENE GLYCOL (UNII: E107L85C40)	
OLEYL ALCOHOL (UNII: 172F2WN8DV)	
POVIDONE K30 (UNII: U725QWY32X)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68968-3450-8	8 in 1 CARTON	01/01/2018	
1		1 d in 1 POUCH; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA authorized generic	NDA203752	01/01/2018	

ESTRADIOL

estradiol film, extended release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:68968-3475
Route of Administration	TRANSDERMAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ESTRADIOL (UNII: 4TI98Z838E) (ESTRADIOL - UNII:4TI98Z838E)	ESTRADIOL	0.075 mg in 1 d

Inactive Ingredients

Ingredient Name	Strength
DIPROPYLENE GLYCOL (UNII: E107L85C40)	
OLEYL ALCOHOL (UNII: 172F2WN8DV)	
POVIDONE K30 (UNII: U725QWY32X)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68968-3475-8	8 in 1 CARTON	01/01/2018	
1		1 d in 1 POUCH; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA authorized generic	NDA203752	01/01/2018	

ESTRADIOL

estradiol film, extended release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:68968-3410
Route of Administration	TRANSDERMAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ESTRADIOL (UNII: 4TI98Z838E) (ESTRADIOL - UNII:4TI98Z838E)	ESTRADIOL	0.10 mg in 1 d

Inactive Ingredients

Ingredient Name	Strength
DIPROPYLENE GLYCOL (UNII: E107L85C40)	
OLEYL ALCOHOL (UNII: 172F2WN8DV)	
POVIDONE K30 (UNII: U725QWY32X)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68968-3410-8	8 in 1 CARTON	01/01/2018	
1		1 d in 1 POUCH; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA authorized generic	NDA203752	01/01/2018	

Labeler - Noven Therapeutics, LLC (166888268)

Revised: 2/2024 Noven Therapeutics, LLC