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

IMVEXXY® (estradiol vaginal inserts)
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 (5.3)**
- **The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) (5.2)**
- **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 (5.4)**
- **Do not use estrogen-alone therapy for the prevention of cardiovascular disease or dementia (5.2, 5.4)**

Estrogen Plus Progestin Therapy

- **The WHI estrogen plus progestin substudy reported increased risks of stroke, DVT, pulmonary embolism (PE) and myocardial infarction (MI) (5.2)**
- **The WHI estrogen plus progestin substudy reported increased risks of invasive breast cancer (5.3)**
- **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 (5.4)**
- **Do not use estrogen plus progestogen therapy for the prevention of cardiovascular disease or dementia (5.2, 5.4)**

RECENT MAJOR CHANGES

Boxed Warning 11/2021

INDICATIONS AND USAGE

IMVEXXY is an estrogen indicated for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause. (1)

DOSAGE AND ADMINISTRATION

Administer IMVEXXY intravaginally: 1 vaginal insert daily for 2 weeks, followed by 1 insert twice weekly (for example, Monday and Thursday). (2.1)

DOSAGE FORMS AND STRENGTHS

Vaginal inserts: 4 mcg or 10 mcg estradiol. (3)

CONTRAINDICATIONS

- Undiagnosed abnormal genital bleeding (4, 5.3)
- Breast cancer or a history of breast cancer (4, 5.3)
- Estrogen-dependent neoplasia (4, 5.3)
- Active DVT, PE, or history of these conditions (4, 5.2)
- Active arterial thromboembolic disease (for example, stroke and MI), or a history of these conditions (4, 5.2)
- Known anaphylactic reaction, or angioedema, or hypersensitivity to IMVEXXY (4)
- Hepatic impairment or disease (4, 5.11)
- Protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders (4)

WARNINGS AND PRECAUTIONS

- Estrogens increase the risk of gallbladder disease (5.5)
- Discontinue estrogen if severe hypercalcemia, loss of vision, severe hypertriglyceridemia or cholestatic jaundice occurs (5.6, 5.7, 5.10, 5.11)
- Monitor thyroid function in women on thyroid replacement hormone therapy (5.12, 5.19)

ADVERSE REACTIONS

The most common adverse reaction with IMVEXXY (incidence ≥ 3% and greater than placebo) is headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Mayne Pharma at 1-844-825-8500 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Inducers and inhibitors of CYP3A4 may affect estrogen drug metabolism and decrease or increase the estrogen plasma concentration. (7)

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

Revised: 01/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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 (5.3)]*.

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 (5.2), and Clinical Studies (14.2)]*.

The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age and older during 5.2 years of treatment with daily CE (0.625 mg)-alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women *[see Warnings and Precautions (5.4), Use in Specific Populations (8.5), and Clinical Studies (14.3)]*.

Do not use estrogen-alone therapy for the prevention of cardiovascular disease or dementia *[see Warnings and Precautions (5.2, 5.4), and Clinical Studies (14.2, 14.3)]*.

Only daily oral 0.625 mg CE was studied in the estrogen-alone substudy of the WHI. Therefore, the relevance of the WHI findings regarding adverse cardiovascular events and dementia to lower CE doses, other routes of administration, or other estrogen-alone products is not known. Without such data, it is not possible to definitively exclude these risks or determine the extent of these risks for other products. Discuss with your patient the benefits and risks of estrogen-alone therapy, taking into account her individual risk profile.

Prescribe estrogens with or without progestogens at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

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 (5.2), and Clinical Studies (14.2)]*.

The WHIMS estrogen plus progestin ancillary study of the WHI, reported an increased risk of developing probable dementia in postmenopausal women 65 years of age and 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 (5.4), Use in Specific Populations (8.5), and Clinical Studies (14.3)]*.

Do not use estrogen plus progestogen therapy for the prevention of cardiovascular disease or dementia *[see Warnings and Precautions (5.2, 5.4), and Clinical Studies (14.2, 14.3)]*.

Breast Cancer

The WHI estrogen plus progestin substudy demonstrated an increased risk of invasive breast cancer *[see Warnings and Precautions (5.3), and Clinical Studies (14.2)]*.

Only daily oral 0.625 mg CE and 2.5 mg MPA were studied in the estrogen plus progestin substudy of the WHI. Therefore, the relevance of the WHI findings regarding adverse cardiovascular events, dementia and breast cancer to lower CE plus other MPA doses, other routes of administration, or other estrogen plus progestogen products is not known. Without such data, it is not possible to definitively exclude these risks or determine the extent of these risks for other products. Discuss with your patient the benefits and risks of estrogen plus 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

1.1 Treatment of Moderate to Severe Dyspareunia, a Symptom of Vulvar and Vaginal Atrophy, Due to Menopause

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 to use a progestogen in addition to her estrogen therapy. In some cases, however, hysterectomized women with a history of endometriosis may need a progestogen *[see Warnings and Precautions (5.3, 5.15)]*.

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

2.1 Treatment of Moderate to Severe Dyspareunia, a Symptom of Vulvar and Vaginal Atrophy, Due to Menopause

Generally, start therapy with the IMVEXXY 4 mcg dosage strength administered intravaginally; insert with the smaller end up for a depth of about two inches into the vaginal canal. Administer 1 insert daily at approximately the same time for 2 weeks, followed by 1 insert twice weekly, every three to four days (for example, Monday and Thursday). Make dosage adjustment based on the clinical response.

3 DOSAGE FORMS AND STRENGTHS

IMVEXXY are small, light pink, tear-shaped, vaginal inserts for manual placement into the vagina. IMVEXXY inserts contain 4 mcg or 10 mcg of estradiol. Each insert is imprinted in white ink on one side with "04" or "10" corresponding to the insert's dosage strength.

4 CONTRAINDICATIONS

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

- Undiagnosed abnormal genital bleeding *[see Warning and Precautions (5.3)]*.
- Breast cancer or a history of breast cancer *[see Warnings and Precautions (5.3)]*.
- Estrogen-dependent neoplasia *[see Warnings and Precautions (5.3)]*.
- Active DVT, PE, or history of these conditions *[see Warnings and Precautions (5.2)]*.
- Active arterial thromboembolic disease (for example, stroke or MI), or a history of these conditions *[see Warnings and Precautions (5.2)]*.
- Known anaphylactic reaction, angioedema, or hypersensitivity to IMVEXXY.
- Hepatic impairment or disease.
- Protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders.

5 WARNINGS AND PRECAUTIONS

5.1 Risks from Systemic Absorption

IMVEXXY is intended only for vaginal administration. Systemic absorption may occur with the use of IMVEXXY *[see Pharmacokinetics (12.3)]*. The warnings, precautions, and adverse reactions associated with the use of systemic estrogen-alone therapy should be taken into account.

5.2 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 (14.2)]*. Immediately discontinue estrogen-alone therapy if a stroke occurs or is suspected.

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

The WHI estrogen plus progestin substudy reported a statistically significant increased risk of stroke in women 50 to 79 years of age receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women in the same age group receiving placebo (33 versus 25 per 10,000 women-years, respectively) *[see Clinical Studies (14.2)]*. The increase in risk was demonstrated after the first year and persisted.[1] Immediately discontinue estrogen with or without 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 placebo[2] *[see Clinical Studies (14.2)]*.

Subgroup analysis of women 50 to 59 years of age, who were less than 10 years since menopause, suggests 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 in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (41 versus 34 per 10,000 women-years).[1] An increase in relative risk was demonstrated in year 1, and a trend toward decreasing relative risk was reported in years 2 through 5 *[see Clinical Studies (14.2)]*.

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

Venous Thromboembolism

In the WHI estrogen-alone substudy, the risk of VTE (DVT and PE) was increased for women receiving daily CE (0.625 mg)-alone compared to placebo (30 versus 22 per 10,000 women-years), although only the increased risk of DVT reached statistical significance (23 versus 15 per 10,000 women-years). The increase in VTE risk was demonstrated during the first 2 years[3] *[see Clinical Studies (14.2)]*. Immediately discontinue estrogen-alone therapy if a VTE occurs or is suspected.

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

5.3 Malignant Neoplasm

Endometrial Cancer

An increased risk of endometrial cancer has been reported with the use of unopposed estrogen therapy in a woman with a uterus. The reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-fold 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 use of estrogens for less than 1 year. The greatest risk appears associated with prolonged use, with an increased risk of 15- to 24-fold for 5 to 10 years or more, and this risk has been shown to persist for at least 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.

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 in postmenopausal women 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 (14.2)]*.

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% 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. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 versus 36 cases per 10,000 women-years for CE plus MPA compared with placebo. In the same substudy, invasive breast cancers were larger, were more likely to be node positive, and were diagnosed at a more advanced stage in the CE (0.625 mg) plus MPA (2.5 mg) group compared with the placebo group. Metastatic disease was rare, with no apparent difference between the two groups. Other prognostic factors, such as histologic subtype, grade and hormone receptor status did not differ between the groups[6] *[see Clinical Studies (14.2)]*.

Consistent with the WHI clinical trial, observational studies have also reported an increased risk of breast cancer for estrogen plus progestin therapy, and a smaller increased risk for estrogen-alone therapy, after several years of use. The risk increased with duration of use, and appeared to return to baseline over about 5 years after stopping treatment (only the observational studies have substantial data on risk after stopping). Observational studies also suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen plus progestin therapy as compared to estrogen-alone therapy. 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 therapy 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 reported that estrogen plus progestin increased the risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE plus MPA versus placebo was 1.58 (95% confidence interval [CI], 0.77 to 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% 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 to 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.

5.4 Probable Dementia

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

After an average follow-up of 5.2 years, 28 women in the estrogen-alone group and 19 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE-alone versus placebo was 1.49 (95% CI, 0.83 to 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 (14.3)]*.

In the WHIMS estrogen plus progestin ancillary study, a population of 4,532 postmenopausal women 65 to 79 years of age was randomized to daily CE (0.625 mg) plus MPA (2.5 mg) or placebo. After an average follow-up of 4 years, 40 women in the CE plus MPA group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE plus MPA versus placebo was 2.05 (95% CI, 1.21 to 3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 cases per 10,000 women-years[8] *[see Use in Specific Populations (8.5), and Clinical Studies (14.3)]*.

When data from the two populations in the WHIMS estrogen-alone and estrogen plus progestin ancillary studies were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95% CI, 1.19 to 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 (14.3)]*.

5.5 Gallbladder Disease

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

5.6 Hypercalcemia

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

5.7 Visual Abnormalities

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

5.8 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.

5.9 Elevated Blood Pressure

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

5.10 Exacerbation of Hypertriglyceridemia

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

5.11 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 IMVEXXY.

5.12 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 IMVEXXY to maintain their free thyroid hormone levels in an acceptable range.

5.13 Fluid Retention

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

5.14 Hypocalcemia

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

5.15 Exacerbation of Endometriosis

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

5.16 Hereditary Angioedema

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

5.17 Exacerbation of Other Conditions

Estrogen therapy, including IMVEXXY, may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic hemangiomas. Consider whether the benefits of estrogen therapy outweigh the risks in women with these conditions.

5.18 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 symptoms of vulvar and vaginal atrophy due to menopause.

5.19 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 antifactor 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) levels leading to increased circulating total thyroid hormone 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 concentrations, increased triglyceride levels.
- Impaired glucose tolerance.

6 ADVERSE REACTIONS

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

- Cardiovascular Disorders *[see Boxed Warning, Warnings and Precautions (5.2)]*.
- Malignant Neoplasms *[see Boxed Warning, Warnings and Precautions (5.3)]*.

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.

The safety of IMVEXXY 4 mcg and 10 mcg was assessed in a single, double-blind, parallel-group, placebo-controlled trial (N = 382). The duration of treatment in this trial was 12 weeks (dosing occurred every day for 14 days and then twice weekly thereafter for maintenance).

Adverse reactions with an incidence of ≥ 3% in any IMVEXXY group and numerically greater than those reported in the placebo group are listed in Table 1.

Table 1: Treatment-Emergent Adverse Reactions Reported at a Frequency of ≥3% and Numerically More Common in Women Receiving IMVEXXY

Preferred Term	IMVEXXY 4 mcg (N = 191)	IMVEXXY 10 mcg (N = 191)	Placebo (N = 192)
Nervous system disorders, n (%)			
Headache	7 (3.7)	5 (2.6)	6 (3.1)

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of IMVEXXY 4 and 10 mcg. 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.

Genitourinary system

Vaginal discharge.

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 side effects.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

IMVEXXY is not indicated for use in pregnancy. There are no data with the use of IMVEXXY 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 females. 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 IMVEXXY and any potential adverse effects on the breastfed child from IMVEXXY or from the underlying maternal condition.

8.4 Pediatric Use

IMVEXXY 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 IMVEXXY to determine whether those over 65 years of age differ from younger subjects in their response to IMVEXXY.

The Women's Health Initiative Studies

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

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

The Women's Health Initiative Memory Study

In the WHIMS ancillary studies of postmenopausal women 65 to 79 years of age, there was an increased risk of developing probable dementia in women receiving estrogen-alone or estrogen plus progestin when compared to placebo *[see Warnings and Precautions (5.4), and Clinical Studies (14.3)]*.

Since both ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women[8] *[see Warnings and Precautions (5.4), and Clinical Studies (14.3)]*.

10 OVERDOSAGE

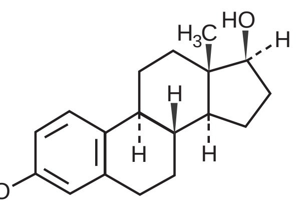
Overdosage of estrogen may cause nausea, vomiting, breast tenderness, abdominal pain, drowsiness and fatigue, and withdrawal bleeding may occur in women. Treatment of overdose consists of discontinuation of IMVEXXY therapy with institution of appropriate symptomatic care.

11 DESCRIPTION

IMVEXXY (estradiol vaginal inserts) are small, light pink, tear-shaped, vaginal inserts for manual placement into the vagina. Inserts contain 4 mcg or 10 mcg of estradiol, an estrogen. Each insert is imprinted in white ink on one side with "04" or "10" corresponding to the insert's dosage strength. IMVEXXY vaginal inserts are used intravaginally. When the insert comes in contact with the vaginal mucosa, estradiol is released into the vagina.

Estradiol is chemically described as estra-1,3,5 (10)-triene-3,17β-diol. The chemical formula is $C_{18}H_{24}O_2$ with a molecular weight of 272.38.

The structural formula is:



IMVEXXY (estradiol vaginal inserts) contain the following inactive ingredients: ammonium hydroxide, ethanol, ethyl acetate, ethylene glycol palmitostearate, FD&C Red #40, gelatin, glycerin, isopropyl alcohol, lecithin, medium chain triglycerides, polyethylene glycol, polyethylene glycol stearates, polyvinyl acetate phthalate, propylene glycol, purified water, sorbitol-sorbitan solution, and titanium dioxide. FDA approved acceptance criteria for assay, organic impurities, and dissolution tolerances differ from the USP test.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

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

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

Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH), and FSH, through a negative feedback mechanism. Estrogens act to reduce the elevated levels 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 IMVEXXY 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

Estrogen drug products are well absorbed through the skin, mucous membranes, and the gastrointestinal tract. The vaginal delivery of estrogens circumvents first-pass metabolism.

In a multicenter, double-blind placebo-controlled study of 574 postmenopausal women randomized to placebo, or 4 and 10 mcg of IMVEXXY, a subset of 54 women participated in a pharmacokinetics substudy. Women received 1 vaginal insert daily for the first 2 weeks, followed by 1 insert twice weekly for the following 10 weeks.

Mean (±SD) serum estradiol and estrone following 14 days of once daily administration of IMVEXXY are shown in Figure 1. Administration of the 4 mcg and 10 mcg IMVEXXY vaginal inserts and placebo once daily for 14 days resulted in a mean estradiol $C_{avg\,(0\text{-}24)}$ of 3.6, 4.6, and 4.3 pg/mL, respectively, Table 2.

Figure 1: Mean (±SD) Serum Concentration of Estradiol and Estrone on Day 14 Following Daily Administration of IMVEXXY 4 mcg, IMVEXXY 10 mcg, and Placebo

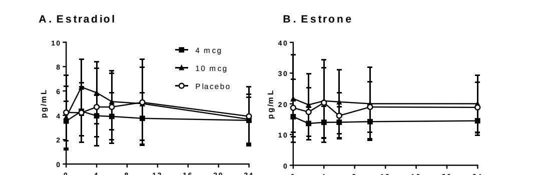


Table 2: Arithmetic Mean (SD) of Estradiol and Estrone Pharmacokinetic Parameters Following 14 Daily Doses – Unadjusted for Baseline

	Estradiol		Estrone	
	C_{max} (pg/mL)	$C_{avg\,(0\text{-}24)}$ (pg/mL)	C_{max} (pg/mL)	$C_{avg\,(0\text{-}24)}$ (pg/mL)
4 mcg	4.8 (2.3)	3.6 (1.8)	16.0 (5.5)	13.6 (4.8)
10 mcg	7.3 (2.4)	4.6 (2.3)	23.9 (13.5)	19.3 (10.2)
Placebo	5.5 (3.4)	4.3 (2.8)	22.8 (10.9)	17.8 (7.5)

At Day 84, estradiol concentrations compared to Baseline concentrations were: 4.3 vs 3.9 pg/mL for 4 mcg; 4.8 vs 5.0 pg/mL for 10 mcg; and 4.4 vs 4.5 pg/mL for placebo.

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 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 the 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.

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 Moderate to Severe Dyspareunia in Postmenopausal Women

The effectiveness and safety of IMVEXXY on moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy due to menopause were examined in one placebo-controlled clinical trial.

This 12-week, randomized, double-blind, placebo-controlled, parallel-group trial enrolled 574 generally healthy postmenopausal women between 40 to 75 years of age (mean 59 years of age) who at baseline assessment had ≤ 5% superficial cells on a vaginal smear, a vaginal pH > 5.0, and also identified, at baseline, moderate to severe dyspareunia as the most bothersome symptom to her. Greater than 90% of women also reported moderate to severe vaginal dryness at baseline. Treatment groups included 4 mcg IMVEXXY (N = 191), 10 mcg IMVEXXY (N = 191), and placebo (N = 192). All women were assessed for improvement in the mean change from Baseline to Week 12 for the co-primary efficacy variables of: most bothersome moderate to severe symptom of dyspareunia, percentage of vaginal superficial and percentage of vaginal parabasal cells on a vaginal smear, and vaginal pH.

IMVEXXY 4 mcg and 10 mcg inserts were statistically superior to placebo in reducing the severity of moderate to severe dyspareunia at Week 12 (see Table 3). A statistically significant increase in the percentage of superficial cells and a corresponding statistically significant decrease in the percentage of parabasal cells on a vaginal smear was also demonstrated for IMVEXXY 4 and 10 mcg inserts ($p < 0.0001$). The mean reduction in vaginal pH between Baseline and Week 12 was also statistically significant for IMVEXXY 4 and 10 mcg inserts ($p < 0.0001$).

Table 3: Efficacy of Dyspareunia Associated with Postmenopausal Vulvar and Vaginal Atrophy (Least Square Mean Change from Baseline to Week 12 in Severity of Woman's Self-Identified Most Bothersome Moderate to Severe Symptom of Vulvar and Vaginal Atrophy)

Most Bothersome Moderate to Severe Symptom at Baseline	IMVEXXY 4 mcg (N = 151)	IMVEXXY 10 mcg (N = 154)	Placebo (N = 163)
Dyspareunia			
Baseline Mean (SD)	2.7 (0.48)	2.6 (0.48)	2.7 (0.46)
LS Mean Change from Baseline (SE)	-1.52 (0.071)	-1.69 (0.071)	-1.28 (0.070)
p-value vs placebo	0.0149	<0.0001	------

The modified intent-to-treat population (MITT) included only women in the ITT population who at baseline met the inclusion criteria of ≤ 5% superficial cells on a vaginal smear, a vaginal pH > 5.0, and who identified moderate or severe dyspareunia as her most bothersome vaginal symptom.
Definitions: SD – standard deviation; SE – standard error; LS – least square

14.2 Women's Health Initiative Studies

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

IMVEXXY®
(estradiol vaginal inserts)
129585

IMVEXXY®
(estradiol vaginal inserts)
129585

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% White, 15.1% Black, 6.1% Hispanic, 3.6% Other) after an average follow-up of 7.1 years, are presented in Table 4.

Table 4: Relative and Absolute Risk Seen in the Estrogen-Alone Substudy of WHI[a]

Event	Relative Risk CE vs Placebo (95% nCI[b])	CE N = 5,310	Placebo N = 5,429
		Absolute Risk per 10,000 Women-Years	
CHD events[c]	0.95 (0.78-1.16)	54	57
Non-fatal MI[c]	*0.91 (0.73-1.14)*	*40*	*43*
CHD death[c]	*1.01 (0.71-1.43)*	*16*	*16*
All Strokes[c]	1.33 (1.05-1.68)	45	33
Ischemic stroke[c]	*1.55 (1.19-2.01)*	*38*	*25*
Deep vein thrombosis[c,d]	1.47 (1.06-2.06)	23	15
Pulmonary embolism[c]	1.37 (0.90-2.07)	14	10
Invasive breast cancer[c]	0.80 (0.62-1.04)	28	34
Colorectal cancer[c]	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, pulmonary embolism, 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 with 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 difference 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 50-59 years of age a non-significant trend toward reduced risk for CHD *[hazard ratio (HR) 0.63 (95% CI, 0.36 to 1.09)]* and overall mortality *[HR 0.71 (95% CI, 0.46 to 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 reductions 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% White, 6.8% Black, 5.4% Hispanic, 3.9% Other) are presented in Table 5. These results reflect centrally adjudicated data after an average follow-up of 5.6 years.

Table 5: Relative and Absolute Risk Seen in the Estrogen 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[e]	0.81 (0.48-1.36)	6	7
Cervical cancer[e]	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,g]	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 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, PE, colorectal cancer, hip fracture, or death due to other causes.

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

14.3 Women's Health Initiative Memory Study

The WHIMS estrogen-alone ancillary study of WHI enrolled 2,947 predominately healthy hysterectomized postmenopausal women 65 to 79 years of age and older (45% were 65 to 69 years of age; 36% were 70 to 74 years of age; 19% 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% CI, 0.83 to 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 types (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 (5.4), and Use in Specific Populations (8.5)]*.

The WHIMS estrogen plus progestin ancillary study of WHI enrolled 4,532 predominantly healthy postmenopausal women 65 years of age and older (47% were 65 to 69 years of age; 35% were 70 to 74 years; 18% 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% CI, 1.21 to 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 types (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 (5.4), 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% CI, 1.19 to 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 (5.4), and Use in Specific Populations (8.5)]*.

15 REFERENCES

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4. Cushman M, et al. Estrogen Plus Progestin and Risk of Venous Thrombosis. JAMA. 2004; 292:1573-1580.
5. Stefanick ML, et al. Effects of Conjugated Equine Estrogens on Breast Cancer and Mammography Screening in Postmenopausal Women with Hysterectomy. JAMA. 2006; 295:1647-1657.
6. Chlebowski RT, et al. Influence of Estrogen Plus Progestin on Breast Cancer and Mammography in Healthy Postmenopausal Women. JAMA. 2003; 289:3243-3253.
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9. Jackson RD, et al. Effects of Conjugated Equine Estrogen on Risk of Fractures and BMD in Postmenopausal Women with Hysterectomy: Results from the Women's Health Initiative Randomized Trial. J Bone Miner Res. 2006; 21:817-828.
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

IMVEXXY (estradiol vaginal inserts) are small, light pink, tear-shaped inserts for manual placement into the vagina. Inserts contain 4 mcg or 10 mcg of estradiol. Each insert is imprinted in white ink on one side with "04" or "10" corresponding to the insert's dosage strengths.

IMVEXXY (estradiol vaginal inserts), 4 mcg and 10 mcg, are provided in opaque push-through blisters and are packaged in cartons containing either 18 inserts for the starter pack or 8 inserts for the maintenance pack.

IMVEXXY 4 mcg	8 inserts	NDC 68308-747-08
IMVEXXY 4 mcg	18 inserts	NDC 68308-747-18
IMVEXXY 10 mcg	8 inserts	NDC 68308-748-08
IMVEXXY 10 mcg	18 inserts	NDC 68308-748-18

Keep out of reach of children. Packages are not child-resistant.

16.2 Storage and Handling

Store at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F). [See USP Controlled Room Temperature.]

17 PATIENT COUNSELING INFORMATION

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

Vaginal Bleeding

Inform postmenopausal women of the importance of reporting vaginal bleeding to their healthcare provider as soon as possible *[see Warnings and Precautions (5.3)]*.

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 (5.2, 5.3, 5.4)]*.

Possible Common Adverse Reactions with Estrogen-Alone Therapy

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

PATIENT INFORMATION
IMVEXXY® (im vex' ee)
(estradiol vaginal inserts)

Read this Patient Information before you start using IMVEXXY 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 IMVEXXY (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 IMVEXXY. 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 of 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 and older.
- Do not use estrogens with progestogens 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 and older.
- Only one estrogen-alone product and dose have been shown to increase your chances of getting strokes, blood clots, and dementia. Only one estrogen with progestogen product and dose have been shown to increase your chances of getting heart attacks, strokes, breast cancer, blood clots, and dementia. Because other products and doses have not been studied in the same way, it is not known how the use of IMVEXXY will affect your chances of having these conditions.
- You and your healthcare provider should talk regularly about whether you still need treatment with IMVEXXY.

What is IMVEXXY?

IMVEXXY is a prescription medicine that contains an estrogen hormone in a vaginal insert.

What is IMVEXXY used for?

IMVEXXY is used after menopause to treat moderate to severe painful intercourse, a symptom of changes in and around your vagina, due to menopause.

Who should not use IMVEXXY?

Do not start taking IMVEXXY 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 (womb). If you have or have had cancer, talk with your healthcare provider about whether you should use IMVEXXY.
- **currently have or have had blood clots.**
- **had a stroke or heart attack.**
- **currently have or have had liver problems.**
- **are allergic to IMVEXXY or any of its ingredients.** See the list of ingredients in IMVEXXY at the end of this leaflet.

Before you use IMVEXXY, 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 or spotting to find out the cause.
- **have any other medical conditions that may become worse while you are using IMVEXXY.** Your healthcare provider may need to check you more carefully if you have certain medical conditions, such as asthma (wheezing), epilepsy (seizures), diabetes, migraine, endometriosis, lupus, angioedema (swelling of 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.** You may need to stop using IMVEXXY.
- **are pregnant or think you may be pregnant.** Imvexxy is not for pregnant women.
- **are breast feeding.** The hormone in IMVEXXY 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 IMVEXXY works.

IMVEXXY may also affect how other medicines work. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get new medicine.

How should I use IMVEXXY?

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

- Use IMVEXXY exactly as your healthcare provider tells you to use it.
- IMVEXXY is a vaginal insert that you place in your vagina.
- IMVEXXY is only for use in the vagina. **Do not** take IMVEXXY by mouth (orally).
- Estrogens should be used at the lowest dose possible for your treatment and for only as long as needed.
- Put 1 IMVEXXY insert inside your vagina, 1 time a day at about the same time for the first two weeks.
- Then put 1 IMVEXXY insert into your vagina two times a week, every three to four days (for example, Monday and Thursday), for as long as you use IMVEXXY.
- You and your healthcare provider should talk regularly (for example, every 3 to 6 months) about the dose you are using and whether you still need treatment with IMVEXXY.

What are the possible side effects of IMVEXXY?

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

Serious, but less common side effects could include:

- heart attack
- breast cancer
- dementia
- gallbladder disease
- high levels of fat (triglyceride) in your blood
- enlargement of benign tumors of the uterus ("fibroids")
- stroke
- cancer of the lining of the uterus (womb)
- high or low blood calcium
- visual abnormalities
- liver problems
- worsening of swelling of face and tongue (angioedema) in women with a history of angioedema
- blood clots
- cancer of the ovary
- high blood pressure
- changes in your thyroid hormone levels

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

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

Common side effects of IMVEXXY include:

- headache
- breast tenderness or pain
- nausea and vomiting

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

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. You may also report side effects to Mayne Pharma at 1-844-825-8500.

PATIENT INFORMATION
IMVEXXY® (im vex' ee)
(estradiol vaginal inserts)

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

- Talk with your healthcare provider regularly about whether you should continue using IMVEXXY.
- If you have a uterus (womb), talk with your healthcare provider about whether the addition of a progestogen is right for you. In general, the addition of a progestogen is recommended for a woman with a uterus to reduce the chance of getting cancer of the uterus.
- See your healthcare provider right away if you get vaginal bleeding while using IMVEXXY.
- 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 had breast lumps or an abnormal mammogram, you may need to have breast exams more often.
- If you have high blood pressure, high cholesterol (fat in the blood), diabetes, are overweight, or if you use tobacco, you may have a higher chance of getting heart disease. Ask your healthcare provider for ways to lower your chances of getting heart disease

General information about the safe and effective use of IMVEXXY.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use IMVEXXY for a condition for which it was not prescribed. Do not give IMVEXXY to other people, even if they have the same symptoms you have. It may harm them. You can ask your pharmacist or healthcare provider for information about IMVEXXY that is written for health professionals.

What are the ingredients in IMVEXXY?

Active ingredient: IMVEXXY (estradiol vaginal inserts) are small, light pink, tear-shaped inserts that contain estradiol.

Inactive ingredients: Each insert also contains ammonium hydroxide, ethanol, ethyl acetate, ethylene glycol palmitostearate, FD&C Red #40, gelatin, glycerin, isopropyl alcohol, lecithin, medium chain triglycerides, polyethylene glycol, polyethylene glycol stearates, polyvinyl acetate phthalate, propylene glycol, purified water, sorbitol-sorbitan solution, and titanium dioxide. IMVEXXY is supplied in blister cartons of 18 or 8 vaginal inserts.

IMVEXXY® (im vex' ee) (estradiol vaginal inserts)

Instructions For Use
IMVEXXY® (im vex' ee)
(estradiol vaginal inserts)

Read this Instructions for Use before you start using IMVEXXY 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.

How should I use IMVEXXY?

- IMVEXXY is an insert only for use in the vagina. Do not take by mouth.
- Put 1 IMVEXXY insert inside your vagina, 1 time a day at about the same time for the first two weeks, then put 1 IMVEXXY insert into your vagina two times a week, every three to four days (for example, Monday and Thursday), for as long as you use IMVEXXY.
- Write down the days you will put in your IMVEXXY insert.
- Wash and dry your hands before handling the IMVEXXY insert.

Step 1: Push 1 IMVEXXY insert through the foil of the blister package.

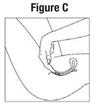
Figure A

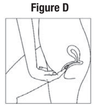
Step 2: Hold the IMVEXXY insert with the larger end between your fingers.

Figure B

Step 3: Select the best position for vaginal insertion that is most comfortable for you to put in the IMVEXXY insert. See Figure C for suggested insertion in the lying down position or Figure D for suggested insertion in the standing position. With the smaller end up, put the insert about two inches into your vagina using your finger.

Figure C **or** **Figure D**





If you have any questions, please ask your healthcare provider or pharmacist.

How should I store IMVEXXY?

- Store IMVEXXY at room temperature between 68°F to 77°F (20°C to 25°C).
- IMVEXXY packaging is not child-resistant.

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

For information, call Mayne Pharma at 1-844-825-8500

Distributed by: **Mayne Pharma** Raleigh, NC 27609

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

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