Choosing a hormone therapy that's right for *her*

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ASCEND THERAPEUTICS

By Anne Moore, DNP, WHNP/ANP-BC, FAANP

Most women will experience symptoms of estrogen decline as they transition through the menopausal years. These can include vasomotor symptoms (VMS) and those related to vulvovaginal atrophy, now known as genitourinary syndrome of menopause (GSM). These VMS and GSM symptoms can have an adverse impact on quality of life (QOL).[1,2] Although some women tolerate these symptoms or can improve them with lifestyle changes or non-pharmacologic measures, other women, depending on symptom severity and QOL impact, might benefit from hormone therapy (HT).

Observational evidence suggests that transdermal estradiol, as compared with oral estrogen, may be associated with lower risks for cardiovascular disease.

Nurse practitioners (NPs) caring for women are familiar with HT options such as the various estrogen and progestogen formulations and the combination estrogen/selective estrogen receptor modulators. Providing patient-specific guidance regarding options is critical in improving satisfaction and compliance. This article provides a short discussion of estrogen products in general, and addresses the attributes of a transdermal gel product that some women find appealing in terms of its ease of use and efficacy in treating both VMS and the symptoms of GSM.

Exogenous estrogen options

Once it is determined that a patient is a candidate for HT and that her VMS, and possibly vaginal dryness as well, are significantly affecting her QOL, patient discussion should be initiated regarding HT options. The objective is to arrive at a mutual decision about the particular type of exogenous estrogen, dosage, and route of delivery that is a best "fit" for the woman. For those women who desire an estrogen product and who have been informed of the risks associated with estrogen use, formulations containing estradiol, conjugated equine estrogens, plant-based estrogens, or esterified estrogens are available. Some women may have a preference regarding an animal-derived estrogen, plant-based estrogen, or synthetic estrogen formulations.

Non-oral estrogen products may have a safety advantage over oral estrogen products.[3] Because oral estrogen products, including oral estradiol, undergo first-pass hepatic metabolism, they may be more likely than non-oral estrogens to lead to adverse metabolic changes such as elevated triglycerides, decreased low-density lipoprotein particle size, and increased production of certain coagulation factors and C-reactive protein.[4] A growing body of observational evidence suggests that transdermal estradiol, as compared with oral estrogen, may be associated with lower risks for cardiovascular disease,[5] cerebrovascular disease,[6] and venous thromboembolism.[7,8]

Transdermal HT options

There are four transdermal options for VMS relief—

patch, emulsion, spray, gel—and one intravaginal option. Other intravaginal estradiol products include creams, a ring, and a tablet. These products are reserved for women whose sole menopause-related complaints involve GSM symptoms.[9] Numerous clinical trials conducted over the past two decades have evaluated the efficacy and safety of the transdermal patch,[10-16] emulsion,[17] spray,[18] and gel[1,2,19] in controlling VMS. One aspect of the non-patch transdermal estradiol products is that they vanish after they are applied and then dry, with no visible signs that HT is being used.

More about one estradiol gel product

Among all of the non-patch transdermal estradiol products, including the gel products, only one, EstroGel® 0.06% (estradiol gel), has an FDA-approved dual indication: relief of moderate to severe VMS and relief of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause.[20] Clinical research showed that use of EstroGel at a dosage of 1.25 g (containing 0.75 mg estradiol), as compared with placebo, was associated with significant reductions in the frequency and severity of moderate to severe hot flashes at weeks 4 and 12.[20] In the same study, vaginal wall cytology results demonstrated a significant increase from baseline in the percent of superficial epithelial cells at week 12 for EstroGel versus no significant change from baseline for placebo. The most commonly reported side effects of EstroGel in clinical studies were breast pain, headache, and flatulence.[20]

A survey of EstroGel users (N = 890) related to product satisfaction showed that 88% were satisfied or extremely satisfied with it and 89% thought it was very easy or somewhat easy to use.[21] Among the 620 respondents who had used a previous therapy for their menopausal symptoms, 89% reported that they preferred EstroGel, 7% had no preference, and 4% preferred the previous product.

One pump of the EstroGel metered-dose dispenser supplies one dose of the gel (1.25 g), which contains 0.75 mg of estradiol. The gel is applied to clean, dry, unbroken skin at the same time each day. The patient applies the gel to one arm from wrist to shoulder; she need not massage or rub in the gel. After applying the gel, which dries in 2-5 minutes and leaves no odor or sticky residue, she should wash her hands with soap and water to reduce the chance of medication spread.

All systemic estrogen users with an intact uterus should consider adding a progestogen to their HT regimen in order to reduce the risk of endometrial cancer.[3] Several synthetic progestogens and oral micronized progesterone are FDA approved for this purpose. Oral progestogen may be added as a separate pill or a provided as a combined estrogen-progestogen pill. Combination estrogen-progestogen transdermal patches are also available. Topical cream or gel preparations of progestogen may not exert sufficient activity to protect the endometrium and are not approved for this purpose.

The North American Menopause Society recommends prescribing estrogen at the lowest effective dose for the shortest time needed.

Regardless of which HT is used, The North American Menopause Society recommends prescribing estrogen at the lowest effective dose for the shortest time needed.[9] NPs can assist each woman in navigating through the array of HT options to facilitate selection of the regimen and/or delivery system that is most appropriate for her unique needs.

Please see EstroGel® 0.06% (estradiol gel) boxed warning and prescribing information immediately following this page.

Anne Moore is the Women's Health Clinical Trainer at the Tennessee Department of Health, Division of Family Health and Wellness, in Nashville, and a member of the Editorial Advisory Board for *Women's Healthcare: A Clinical Journal for NPs*. An honorarium funded by Ascend Therapeutics has been received by Ms. Moore.

Visit www.NPWomensHealthcare.com/?p=4166 for a complete list of references.

ESTROGel® 0.06%
(estradiol gel)

Rx only

Brief Summary (for full Prescribing Information and Patient Information refer to package insert).

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

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 progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken 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

Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia *[see Warnings and Precautions (5.1, 5.3), and Clinical Studies (14.3, 14.4)]***.**

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)]***.**

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and other dosage forms of estrogens.

Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

Estrogen Plus Progestin Therapy

Cardiovascular Disorders and Probable Dementia

Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia *[see Warnings and Precautions (5.1, 5.3), and Clinical Studies (14.3, 14.4)]***.**

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 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)].*

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)]***.**

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and MPA and other combinations and dosage forms of estrogens and progestins.

Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

1 INDICATIONS AND USAGE

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

1.2 Treatment of Moderate to Severe Symptoms of Vulvar and Vaginal Atrophy due to Menopause.

Limitation of Use

When prescribing solely for the treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause, topical vaginal products should be considered.

2 DOSAGE FORMS AND STRENGTHS

EstroGel 0.06% is an estradiol transdermal gel. One pump depression delivers 1.25 g of gel that contains 0.75 mg estradiol.

3 CONTRAINDICATIONS

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

- Undiagnosed abnormal genital bleeding
- Known, suspected, or history of breast cancer
- Known or suspected estrogen-dependent neoplasia
- Active DVT, PE, or history of these conditions
- Active arterial thromboembolic disease (for example, stroke and MI), or a history of these conditions
- Known anaphylactic reaction or angioedema to EstroGel
- Known liver impairment or disease
- Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders
- Known or suspected pregnancy

4 WARNINGS AND PRECAUTIONS

4.1 Cardiovascular Disorders

An increased risk of stroke and DVT has been reported with estrogen-alone therapy. An increased risk of PE, DVT, stroke and MI has been reported with estrogen plus progestin therapy. Should any of these occur or be suspected, estrogen with or without progestin therapy should be discontinued immediately.

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) should be managed appropriately.

Stroke

In the WHI estrogen-alone substudy, a statistically significant increased risk of stroke was reported 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). The increase in risk was demonstrated in year 1 and persisted *[see Clinical Studies (14.3)]*. Should a stroke occur or be suspected, estrogen-alone therapy should be discontinued immediately.

Subgroup analysis 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 the WHI estrogen plus progestin substudy, a statistically significant increased risk of stroke was reported 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) *[see Clinical Studies (14.3)]*. The increase in risk was demonstrated after the first year and persisted.[1] Should a stroke occur or be suspected, estrogen plus progestin therapy should be discontinued immediately.

Coronary Heart Disease

In the WHI estrogen-alone substudy, no overall effect on coronary heart disease (CHD) events (defined as nonfatal MI, silent MI, or CHD death) was reported in women receiving estrogen-alone compared to placebo[2] *[see Clinical Studies (14.3)]*.

Subgroup analyses of women 50 to 59 years of age suggest a statistically non-significant reduction in CHD events (CE [0.625 mg]-alone compared to placebo) in women with less than 10 years since menopause (8 versus 16 per 10,000 women-years).[1]

In the WHI estrogen plus progestin substudy, there was a statistically non-significant increased risk 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 coronary heart disease. 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 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 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 (14.3)]*. Should a VTE occur or be suspected, estrogen-alone therapy should be discontinued immediately.

In the WHI estrogen plus progestin substudy, 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)]*. Should a VTE occur or be suspected, estrogen plus progestin therapy should be discontinued immediately.

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

4.2 Malignant Neoplasms

Endometrial Cancer

An increased risk of endometrial cancer has been reported with the use of unopposed estrogen therapy in women with a uterus. The reported endometrial cancer risk among unopposed estrogen users is about 2 to 12 times greater than in nonusers, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than 1 year. The greatest risk appears 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 progestin therapy is important. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken 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 progestin 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 most important randomized clinical trial providing information about breast cancer in estrogen-alone users is the WHI substudy of daily CE (0.625 mg)-alone. 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) 0.8])*[5] *[see Clinical Studies (14.3)]*.

The most important randomized clinical trial providing information about breast cancer in estrogen plus progestin users is the WHI substudy of daily CE (0.625 mg) plus MPA (2.5 mg). After a mean follow-up of 5.6 years, the estrogen plus progestin substudy reported an increased risk of invasive breast cancer in women who took daily CE plus MPA.

In this substudy, prior use of estrogen-alone or estrogen plus progestin therapy was reported by 26 percent of the women. The relative risk of invasive breast cancer was 1.24, and the absolute risk was 41 versus 33 cases per 10,000 women-years, for CE plus MPA compared with placebo *[see Clinical Studies (14.3)]*. 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 (14.3)]*.

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. However, 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 WHI estrogen plus progestin substudy reported a statistically non-significant increase in 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 percent CI, 0.77-3.24). The absolute risk for CE plus MPA versus placebo was 4 versus 3 cases per 10,000 women-years.[7] In some epidemiologic studies, the use of estrogen plus progestin and estrogen-only products, in particular for 5 or more years, has been associated with an increased risk of ovarian cancer. However, the duration of exposure associated with increased risk is not consistent across all epidemiologic studies, and some report no association.

4.3 Probable Dementia

In the 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 *[see Use in Specific Populations (8.5), and Clinical Studies (14.4)]*.

4.4 Gallbladder Disease

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

4.5 Hypercalcemia

Estrogen administration may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If hypercalcemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

4.6 Visual Abnormalities

Retinal vascular thrombosis has been reported in patients receiving estrogens. Discontinue medication pending examination if there is sudden partial or complete loss of vision or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, estrogens should be permanently discontinued.

4.7 Addition of a Progestin when a Woman has not had a Hysterectomy

Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer.

There are, however, possible risks that may be associated with the use of progestins with estrogens compared to estrogen-alone regimens. These include an increased risk of breast cancer.

4.8 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. .

4.9 Hypertriglyceridemia

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

4.10 Hepatic Impairment and/or Past History of Cholestatic Jaundice

Estrogens may be poorly metabolized in women with impaired liver function. For women with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised, and in the case of recurrence, medication should be discontinued.

4.11 Hypothyroidism

Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Women with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T_4 and T_3 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. These women should have their thyroid function monitored in order to maintain an acceptable range.

4.12 Fluid Retention

Estrogens may cause some degree of fluid retention. Women with conditions that might be influenced by this factor, such as a cardiac or renal dysfunction, warrant careful observation when estrogen-alone is prescribed.

4.13 Hypocalcemia

Estrogen therapy should be used with caution in women with hypoparathyroidism as estrogen-induced hypocalcemia may occur.

4.14 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. For women known to have residual endometriosis post-hysterectomy, the addition of progestin should be considered.

4.15 Hereditary Angioedema

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

4.16 Exacerbation of Other Conditions

Estrogen therapy may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions.

4.17 Alcohol-based Products are Flammable

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

4.18 Moisturizer Lotion Application

Use of moisturizing lotion one hour after application of EstroGel 0.06% significantly increased estradiol absorption *[see Clinical Pharmacology (12.3)]*.

4.19 Laboratory Tests

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

4.20 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) levels leading to increased circulating total thyroid hormone levels, as measured by protein-bound iodine (PBI), T_4 levels (by column or by radioimmunoassay) or T_3 levels by radioimmunoassay. T_3 resin uptake is decreased, reflecting the elevated TBG. Free T_4 and T_3 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 HDL_2 cholesterol subfraction concentrations, reduced low-density lipoprotein (LDL) cholesterol concentration, increased triglyceride levels.

Impaired glucose tolerance.

5 ADVERSE REACTIONS

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

- Cardiovascular Disorders *[see Boxed Warning, and Warnings and Precautions (5.1)]*
- Malignant Neoplasms *[see Boxed Warning, and Warnings and Precautions (5.2)]*

5.1 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 clinical practice.

EstroGel was studied in 2 well-controlled, 12-week clinical trials. Incidence of adverse drug reactions ≥5 percent for 1.25 g EstroGel 0.06% and placebo is given in Table 1.

TABLE 1
Incidence of Adverse Drug Reactions ≥5 Percent Occurrence in the EstroGel Treatment Group for the Intent-to-Treat Safety Population in 2 Well-controlled Clinical Studies (Expressed as Percent of Treatment Group)

Body System/ Adverse Drug Reactions	EstroGel 0.06% 1.25 g /day (n=168)	Placebo (n=73)
BODY AS A WHOLE		
Headache	9.5	2.7
DIGESTIVE SYSTEM		
Flatulence	5.4	4.1
UROGENITAL SYSTEM		
Breast pain	10.7	8.2

In 2 controlled clinical trials, application site reactions were reported by 0.6 percent of patients who received 1.25 g of EstroGel. Other skin reactions, such as pruritus and rash, were also noted.

5.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of EstroGel. 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

Endometrial cancer

Breast

Pain; tenderness; breast cancer

Cardiovascular

Deep vein thrombosis; myocardial ischemia; phlebitis

Gastrointestinal

Nausea; abdominal distension; diarrhea; stomach discomfort

Skin

Alopecia; rash; pruritus; application site: dryness, pain, discoloration, reaction, rash

Eyes

Retinal vein occlusion

Central nervous system

Headache; dizziness; insomnia; hypoesthesia; meningioma; aphasia; bradyphrenia; paresthesia

Miscellaneous

Drug ineffective; hot flush; arthralgia; night sweats; drug effect decreased; pain in extremity; fatigue; weight increased; pain; hypersensitivity; dyspnea; malignant mesenchymoma; angioedema; hepatitis acute; face edema; accidental exposure; myoclonus; gait disturbance; flushing

6 DRUG INTERACTIONS

No drug-drug interaction studies have been conducted for EstroGel.

6.1 Metabolic Interactions

In vitro and *in vivo* studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4, such as St. John's wort (*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 estrogen and may result in side effects.

7 USE IN SPECIFIC POPULATIONS

7.1 Pregnancy

EstroGel should not be used during pregnancy *[see Contraindications (4)]*. There appears to be little or no increased risk of birth defects in children born to women who have used estrogens and progestins as an oral contraceptive inadvertently during early pregnancy.

7.2 Nursing Mothers

EstroGel should not be used during lactation. Estrogen administration to nursing women has been shown to decrease the quantity and quality of the breast milk. Detectable amounts of estrogen have been identified in the milk of women receiving estrogen therapy. Caution should be exercised when EstroGel is administered to a nursing woman.

7.3 Pediatric Use

EstroGel is not indicated in children. Clinical studies have not been conducted in the pediatric population.

7.4 Geriatric Use

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

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 developing 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 (14.4)]*.

7.5 Renal Impairment

The effect of renal impairment on the pharmacokinetics of EstroGel has not been studied.

7.6 Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of EstroGel has not been studied.

8 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 EstroGel together with institution of appropriate symptomatic care.

9 Storage and Handling

Keep out of reach of children.

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

Manufactured for:
ASCEND Therapeutics® US, LLC
Herndon, VA 20170
By DPT Laboratories
San Antonio, TX 78215

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