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A SUPPLEMENT TO

NOVEMBER 2007

Transdermal Estrogen Therapy: Evidence and Update

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What Does the ESTHER Study Add to the Evidence?

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Up until July 2002, based on the accumulated evidence, estrogen therapy was gaining in importance for treating the most common symptoms of estrogen decline in menopausal women: vasomotor symptoms, urogenital atrophy, and bone loss. The use of oral hormone therapy in postmenopausal women has been profoundly reduced as a result of the Women's Health Initiative (WHI) studies of the effects of oral estrogen therapy (conjugated equine estrogen 0.625 mg/d) and oral estrogen/progestin therapy (conjugated equine estrogen 0.625 mg/d and medroxyprogesterone acetate 2.5 mg/d). As an antidote to the potential risks of oral therapy, the transdermal route of administration is gaining significant attention, and may be of benefit to many patients taking hormone therapy.

Issues in Hormone Therapy: WHI and Updates

The WHI studies were conducted in women aged 50 years or older without menopausal symptoms, most of whom were 10 years or more beyond menopause. In brief, the estrogen-alone study found that compared with placebo, oral estrogen was associated with no dif-

ference in risk for heart attack, increased risk of stroke, increased risk of blood clots, an uncertain effect on breast cancer, no difference in risk for colorectal cancer, reduced risk of fracture, and, in a substudy in women aged ≥ 65 years, no protection against mild cognitive impairment and an increased risk of dementia.¹⁻³ The estrogen-progestin study found that hormone therapy was associated with increased risks of heart attack, stroke, blood clots, and breast cancer, reduced risk of colorectal cancer, fewer fractures, and, in a substudy in women aged ≥ 65 years, no protection against mild cognitive impairment and an increased risk of dementia.

Updates to the WHI have tended to confirm the notion that the main study findings cannot always be straightforwardly generalized to the entire population of postmenopausal women. Some analyses have shown possible heart benefits in women aged 50 to 59 or in those starting hormone therapy <10 years after menopause.^{3,4} In the estrogen-alone study, coronary artery calcium (CAC) scores, which are predictive of coronary events, were lower with estrogen treatment versus placebo in women aged 50 to 59 years.^{3,5} A combined analysis of the two WHI studies has shown that³:

- Risk of heart attack may not be increased in women starting hormone therapy <10 years after menopause, but there is increasing risk in those 10 or more years beyond menopause
- Risk of stroke is increased regardless of when therapy is started or years from menopause
- Risk of death from any cause appeared to be reduced in women who started therapy at age 50 to 59 years.

The WHI notes: "This new, combined analysis from the WHI hormone trials does not change the current recommendation that hormone therapy should not be

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used for prevention of heart attacks. If hormones do not increase risk of heart attack at younger ages—and even if they reduce risk in these age groups—there is no certainty that any benefit will persist with long-term use into older ages.”³

Updated Recommendations

What to make of all this information? The FDA states that hormone therapy should not be used to protect against heart disease and that the dosage and duration of therapy should be the minimum required to achieve treatment goals. With regard to coronary heart disease risk, a 2007 North American Menopause Society (NAMS) position statement⁶ on estrogen and progestogen use in peri- and postmenopausal women notes that:

- The potential effects of hormone therapy in primary prevention remain unclear in perimenopausal and early postmenopausal women initiating treatment early after reaching menopause and continuing it for a number of years
- Data do not support its use in secondary prevention
- Pending additional data, systemic therapy is not recommended as a single or primary indication for coronary protection in women of any age.

As to what hormone therapy should be used for, the NAMS statement indicates that “treatment of moderate to severe vasomotor symptoms (ie, hot flashes and night sweats) remains the primary indication” for systemic hormone therapy. With regard to other menopause-related disorders, the statement indicates that local vaginal therapy is generally recommended when hormone therapy is used solely for moderate to severe symptoms of vulvar and vaginal atrophy, and that systemic therapy can be considered an option, along with other government-approved products, in preventing osteoporosis in women who require drug therapy for osteoporosis risk reduction (including those at high 5- to 10-year risk of fracture).

Low-Dose and Transdermal Options

The NAMS statement also indicates that lower-than-standard doses of hormone therapy should be considered. Low-dose systemic therapy includes lower doses of oral esterified or conjugated estrogens or 17 β -estradiol and transdermal 17 β -estradiol gels, lotion, or patches, and transvaginal systemic vaginal rings. Numerous studies have shown that low-dose hormone therapy is efficacious in relieving vasomotor and vulvovaginal symptoms and maintaining bone mineral density, and low-dose treatment is better tolerated than standard-dose treatment. Indeed, the superiority of

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transdermal estradiol replacement compared to oral formulations on the basis of the main intermediate coronary heart disease markers has been clearly established by randomized comparative trials (Table 1).⁷ Furthermore, laboratory findings (not from comparative studies) show transdermal superiority on additional clinical measures (Table 2).^{8,9} The American Association of Clinical Endocrinologists has also included a recommendation for transdermal administration of estrogen in their latest medical guidelines for clinical practice for the management of

menopause, with a specific preference for clinical situations such as in women with hypertension and/or hypertriglyceridemia, or increased risk of cholelithiasis.¹⁰

Advantages of transdermal gels, lotions, and patches or transvaginal systemic vaginal rings include avoidance of hepatic first-pass metabolism of oral agents (associated with increased hepatic production of procoagulant factors) and avoidance of the wide daily variation (peaks and troughs) in blood levels of the hormone after oral dosing. Indeed, the recently reported update of the Estrogen and Thromboembolism Risk (ESTHER) study¹¹ indicates that transdermal estrogen is associated with a dramatically reduced risk of venous thromboembolism (VTE) compared with oral treatment, with the study findings echoing the WHI finding of increased risk of clotting with oral hormone therapy.

The ESTHER Study: Risk of Venous Thromboembolism With Oral and Transdermal Treatment

The ESTHER study was a French multicenter case-control study of VTE among postmenopausal women aged 45 to 70 years.¹¹ The population included 208 consecutive hospital cases and 63 consecutive outpatient cases with a first documented episode of idiopathic VTE. To be included, women hospitalized with VTE had to have no prior history of VTE, no contraindications to hormone therapy (eg, breast cancer, endometrial cancer, cardiovascular disease), and no predisposing factors for VTE, including surgical intervention within the past month, trauma with immobilization or illness necessitating bed rest for >8 days, known cancer, or any systemic inflammatory disease. Women diagnosed with VTE as outpatients could not have been referred to clinical centers for estrogen advice or known thrombophilia. Each woman with VTE was matched with 1 to 3 controls without VTE on the basis of study center, age, admission date,

Table 1.* Comparison of oral and transdermal estradiol formulations on main intermediate risk markers for coronary heart disease⁷

Factor	Oral	Transdermal
Triglycerides	↑	↓
LDL particle size	↓	↑
Frag 1 + 2 prothrombin	↑	↔
Von Willebrand F	↑	↔
C-reactive protein	↑	↔ or ↓

*Clinical significance not known.

LDL = low density lipoprotein, F = factor.

and area of residence. The 426 hospital controls had to have been admitted to the hospital for a diagnosis unrelated to estrogen use; the 184 community controls could not have been referred to their treatment centers for estrogen advice or known thrombophilia.

Women with VTE had significantly greater body mass index and greater age at menopause (1 year difference) and were significantly more likely to have a family history of VTE and a personal history of varicose veins. There were no differences between the two groups in terms of current smoking, surgical or natural menopause, hysterectomy, or proportions of women who were past users of estrogen therapy or who never used estrogen therapy.

Cases and controls differed with regard to hormone therapy use. Table 3 shows the risks for VTE for users versus nonusers of hormone therapy by estrogen route and type of progestogen after adjustment for other risk factors. The risk for VTE was no greater in current users of transdermal estrogen than in nonusers; the odds ratio (OR) of 0.9 and 95% confidence interval (CI) of 0.4 to 2.1 indicate a nonsignificantly smaller risk in users. By comparison, the risk of VTE in users of oral estrogen was 4 times greater than in nonusers (OR 4.2, 95% CI 1.5 to 11.6). The study also reviewed the impact of progestogens when added to the estrogens. With regard to progestogens, the study found no significant association between the risk of VTE and the use of micronized progesterone or pregnane derived forms of progestogens; however, users of norpregnane derivatives had a 4-fold greater risk of VTE compared with nonusers.

These findings strongly suggest that route of estrogen administration is important in risk for VTE and needs to be considered in evaluating the risk-benefit profile for hormone treatment in individual patients.¹² As noted above, oral estrogen administration, but not transdermal estrogen, is associated with increased coagulant effects, including elevated prothrombin fragment 1+2 and factor

VII levels, and elevated levels of C-reactive protein, a marker of systemic inflammation.¹³ However, the precise mechanisms underlying the greater risk of VTE associated with oral estrogen, and with norpregnane derivatives, remain to be elucidated. This same reduction in thrombosis risk with transdermal estrogen delivery was found in women carriers of prothrombotic mutations (i.e. factor V Leiden, prothrombin G20210A mutation),¹⁴ and in overweight and obese patients.¹⁵ In each instance the risk of thrombosis with the transdermal route of estrogen administration was not higher than seen in the group of “non-users” of estrogen.

It is also unclear whether transdermal estrogen administration might be associated with reduced risk of other cardiovascular events. In this regard, however, it should be remembered that transdermal estrogen therapy was associated with a nonsignificant increase in risk of cardiovascular events in a small study in women who already had ischemic heart disease.¹⁶

In the absence of clinical trials directly comparing effects of oral and transdermal estrogen on cardiovascular events, the Kronos Early Estrogen Prevention Study (KEEPS) may provide some idea of differences in effect on surrogate markers of cardiovascular disease. In this ongoing trial, recently menopausal women are receiving oral conjugate equine estrogen (0.45 mg/d) plus micronized progesterone (200 mg/d) or transdermal estradiol (50 µg/d) plus micronized progesterone (200 mg/d) and are being evaluated for changes in carotid intima-media thickness, CAC score, and thrombotic, inflammatory, and other biomarkers.

Practical Implications

Given the potential safety benefits, transdermal delivery should be considered for all menopausal patients

Table 2. Oral and transdermal estrogens: Laboratory findings^{8,9}

Factor	Oral Estrogen	Transdermal E ₂
HDL [†]	↑ ↑	↑
LDL [†]	↓ ↓ ↓	↓
Triglycerides [†]	↑	↓/↔
Carbohydrate metabolism [†]	Impaired glucose tolerance test	↔
Clotting factors [†]	↑ Clotting factors ↓ Antithrombin III	↔ ↔
Systolic BP [†]	↑	↓
SHBG [†]	↑	↔

*Not from comparative clinical studies. †Clinical significance not known. HDL = high density lipoprotein, LDL = low density lipoprotein, BP = blood pressure, SHBG = sex hormone-binding globulin, E₂ = estradiol.

Table 3. Risk of VTE for users versus nonusers of hormone therapy by estrogen route and type of progestogen

	Cases (n=259)	Controls (n=603)	Odds ratio (95% confidence interval) for VTE for users versus nonusers*
Nonuse**	146	384	1
Oral estrogen use	45	39	4.2 (1.5-11.6)
Transdermal estrogen use	67	180	0.9 (0.4-2.1)
No progestogens	14	40	---
Micronized progesterone	19	63	0.7 (0.3-1.9)
Pregnane derivatives***	39	79	0.9 (0.4-2.3)
Norpregnane derivatives	40****	37****	3.9 (1.5-10.0)

Analysis excludes users of oral estrogen combined with nortestosterone derivatives (12 cases, 7 controls); for this subgroup, OR (95% confidence interval) for VTE for users versus nonusers was 6.7 (2.1-21.9).

*Adjusted for obesity status, familial history of VTE, history of varicose veins, education, age at menopause, hysterectomy, and cigarette smoking.

**Since recentness of treatment did not affect risk of VTE, past users and never users were pooled as nonusers.

*** Pregnane derivatives used included dydrogesterone, medrogestone, chlormadinone acetate, cyproterone acetate, and medroxyprogesterone acetate.

****22 cases and 19 controls received nomegestrol acetate and 18 cases and 18 controls received promegestone.

Adapted with permission from Canonico et al.¹¹

for whom estrogen is prescribed. In particular, as noted earlier, the American Association of Clinical Endocrinologists has included a recommendation for transdermal hormone administration in their latest clinical guidelines, with an emphasis on the benefits of transdermal preparations for women with hypertension and/or hypertriglyceridemia, or increased risk of cholelithiasis. Specifics on the clinical considerations and benefits of transdermal hormone delivery are provided in the next article. □

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Transdermal Estrogen: Clinical Characteristics

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Estrogen therapy for postmenopausal women can be delivered orally, vaginally (both local and systemic effects), by injection, or by the percutaneous or transdermal (gel, patch) routes. Estrogen products in these categories are shown in Table 1. Although oral therapy has long been the standard form of estrogen therapy in the United States, findings in the Women's Health Initiative (WHI) trials and other studies, such as the Estrogen and Thromboembolism Risk (ESTHER) study,^{1,2} have raised safety concerns with oral therapy, as reviewed in the foregoing article, and have refocused attention on the potential advantages associated with other forms of estrogen treatment. It bears noting that transdermal therapy accounts for approximately 70% of estrogen therapy use in France and Italy.³

Transdermal Estrogen Delivery: Avoidance of First-Pass Metabolism and Improved Pharmacokinetics

Transdermal treatment was developed in part to avoid the need to provide large oral doses of hormone and to overcome the effect of first-pass hepatic and gastrointestinal metabolism. Since first-pass hepatic clearance removes a significant proportion of drug from the circulation, large oral doses of estrogen must be given to ensure that adequate systemic levels of estradiol are reached to achieve and maintain therapeutic response. With oral 17 β -estradiol tablet dosing, levels of estradiol several-fold greater than those in the circulation, accumulate in liver sinusoids, with these supraphysiologic levels stimulating synthesis of a variety of hepatic proteins, including those involved in hemostasis, in a manner not observed in premenopausal women. Oral estrogen is also metabolized to estrone in the gastrointestinal tract and then to either estrone or estradiol in the liver. During the menstrual cycle in premenstrual women, the estradiol:estrone ratio in the circulation approximates 1, whereas estrone predominates in the postmenopausal state; a number of studies have shown that oral estrogen administration leads to high circulating levels of estrone. By comparison, transdermal administration of estradiol results in reduced induction of liver enzymes and more-physiologic levels of estradiol and estrogen metabolites, with an estradiol:estrone ratio more similar to that found in premenopausal women.⁴⁻⁶ Although clinical significance of the avoidance of the

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Table 1. Estrogen therapy options

Oral	Patches	Dermal	Vaginal
Cenestin	Alora	Divigel	Estrace
Enjuvia	Climara	Elestrin	Estring
Estrace	Esclim	EstroGel	Femring
Estratab	Estraderm	Estrasorb	Premarin
Femtrace	Menostar		Vagifem
Ortho-Est	Vivelle		
Menest	Vivelle-Dot		
Premarin			

first pass metabolism has not been determined, avoidance of the first-pass effect is associated with avoidance of the effects on coagulation factors observed with oral treatment. This mechanism may explain reduced risk for clotting disorders (eg, venous thromboembolism) with transdermal administration; in particular, oral estrogen significantly increases levels of acute-phase proteins (eg, C-reactive protein and serum amyloid A), procoagulant factors (eg, prothrombin fragments 1+2), and several key enzymes involved in plaque disruption, whereas transdermal estrogen does not have these effects.⁶⁻⁷ It is important to note that estrogens increase the risk of endometrial cancer and estrogens with or without progestins should not be used for the prevention of cardiovascular disease. In addition, the estrogen-alone substudy of the WHI reported increased risks of stroke and deep vein thrombosis in postmenopausal women during 6.8 and 7.1 years, respectively, of treatment with 0.625 mg per day oral conjugated estrogens (CE). The Women's Health Initiative memory Study, a substudy of WHI, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during treatment with 0.625 mg CE alone (5.2 years) or combined with 2.5 mg medroxyprogesterone acetate (4 years).

Dosing with oral 17 β -estradiol also results in marked variability of circulating levels of estradiol throughout the day, with peaks occurring shortly after administration and nadirs occurring prior to the subsequent dose (Figure 1).⁵ Transdermal administration of estradiol, in contrast, mimics the follicular phase of estradiol during the menstrual cycle. With application of the estradiol to the skin, estradiol is transported across intact skin into the circulation by passive diffusion. The rate of diffusion

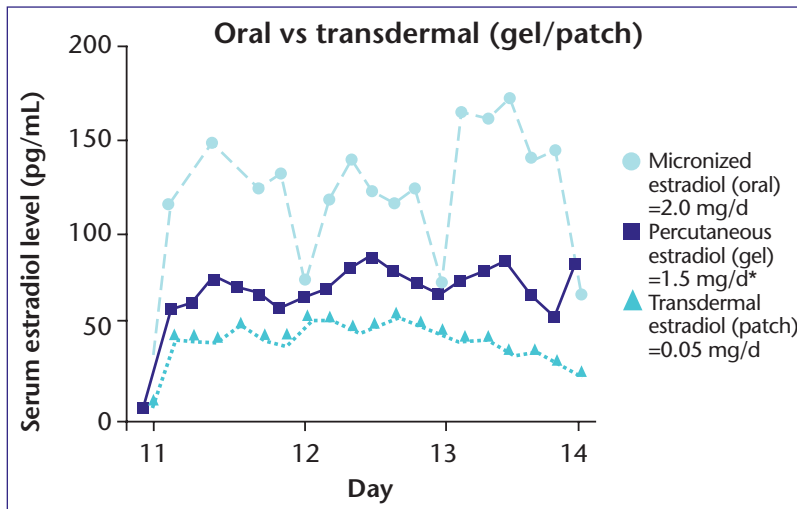


FIGURE 1. Serum estradiol concentrations at steady state in a crossover study in 13 subjects receiving oral micronized estradiol 2.0 mg/d, estradiol gel 1.5 mg/d, or estradiol patch 0.05 mg/d, with a 14-day washout between treatment periods. The comparison of steady state levels has not been studied in well-controlled comparative studies.

*The dose of estradiol gel was twice that is currently approved for use in the United States. Adapted with permission from Scott.⁵

across the stratum corneum is the rate limiting factor of entry into the circulation, with the reservoir effect of this structure allowing continuous release of estradiol into the circulation. Figure 1 shows a comparison of steady-state levels of estradiol with oral dosing and transdermal administration via gel and patch⁵ (data obtained from a crossover study and not from well-controlled comparative studies); serum levels are more evenly maintained with transdermal administration compared with oral administration, with the use of the gel also avoiding the dip in estradiol levels at the end of the patch treatment cycle.

Percutaneous Estradiol Gel Delivery

Estradiol gel 0.06%, marketed as EstroGel, was the first product to employ a gel vehicle for estrogen, and currently is approved for use in more than 70 countries. It has been used in Europe since 1975, is the leading estrogen-replacement product in Europe, the leading transdermal estrogen product in Canada, and has a long history of clinical use, backed by more than 65 journal publications reporting on over 40 different clinical studies. However, the long history of use does not mitigate the risks associated with EstroGel or other estrogen hormone replacement products. EstroGel 0.06% was approved for use in the United States in 2004.⁸ The product is a clear, colorless absorptive hydroalcoholic gel containing 0.06% estradiol supplied in a nonaerosol, metered-dose pump. In clinical studies, the most commonly reported adverse events for EstroGel were

headache, infection, breast pain, vaginitis, abdominal pain, pain, and rash. The active ingredient is a synthetic 17β-estradiol (derived from a plant source) that is bioidentical to the estradiol produced in the body.

It should be noted that ‘bioidentical hormone’ (also referred to as bioequivalent) is strictly defined as a hormone that is chemically identical to the hormone produced in the body. This definition should not be confused with the use of ‘bioidentical’ to refer to hormone preparations compounded for an individual as an alternative to pharmaceutical dose forms of estrogens or progestogens—eg, hormonal substances prepared in individualized dose forms (including gels, suppositories, sublingual tablets, and oral tablets) that are not commercially available. As noted in the 2007 North American Menopause Society (NAMS) position statement,⁹ caution is warranted in the use of these latter products in the absence of regulatory oversight in terms of quality, purity, and batch consistency of ingredients. Other organizations have also issued cautionary statements regarding this issue, including the American College of Obstetricians and Gynecologists, the American Society for Reproductive Medicine, the American Association of Clinical Endocrinologists, and The Endocrine Society.

EstroGel Data

The approved dosage of EstroGel 0.06% available in the United States is the 1.25-g dose, which contains 0.75 mg estradiol per dose and which delivers 0.035 mg of estradiol per day to the circulation. Figure 2 shows mean levels of estradiol on day 14 in postmenopausal women receiving estradiol gel 0.06%, 1.25 g for 14 days.⁶ The time-averaged serum estradiol concentration on day 14 was 28.3 pg/mL.

The safety and efficacy of EstroGel 0.06% in treatment of menopausal vasomotor symptoms were established for United States regulatory purposes in two pivotal trials, consisting of a placebo-controlled trial and a comparative trial with an estradiol patch. In the placebo-controlled trial,¹⁰ 75 women received the EstroGel 1.25-g dose and 73 received a placebo gel for 12 weeks, with the study gels applied once daily to the skin of the arm from the shoulder to the wrist. Patients had a mean age of approximately 51 years and it had been 10 to 11 years since their last menses; the only significant difference between groups was greater body weight in the women randomized to EstroGel. Over 12 weeks, women receiving Estro-

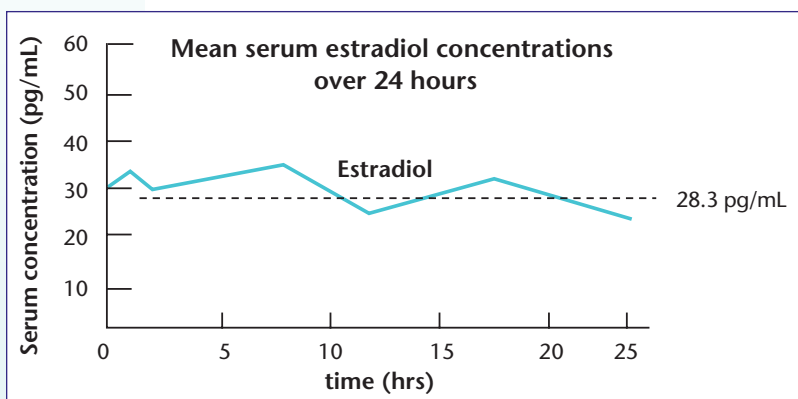


FIGURE 2. Mean serum concentrations of estradiol on day 14 in 24 women receiving the estradiol gel 0.06%, 1.25-g dose daily for 14 days.³

Gel had a significant reduction in mean number of moderate-to-severe hot flashes per day from 10.3 to 2.8 (± 3.7), compared with a reduction from 11.0 to 5.2 (± 6.5) observed in placebo recipients ($P < .05$).

As shown in Figure 3, 65% of EstroGel recipients had $\geq 50\%$ reduction in frequency of hot flashes by week 4, with the proportion increasing to approximately 85% at week 12.³ EstroGel treatment was also associated with a significant reduction in severity of hot flashes at weeks 4 and 6 to 12 compared with placebo. Vaginal cytology showed a significant ($P < .001$) upward shift in maturation values, a marker for improvement in vaginal atrophy, in EstroGel recipients. In the second study, 90 women received EstroGel in a 1.25-g dose and 80 received a standard-dose estradiol transdermal system patch (delivers 0.05 mg/d) for 12 weeks. The treatments had similar efficacy in reducing moderate-to-severe hot flashes. The estradiol:estrone ratio with EstroGel 0.06% treatment approached 1:1, in a manner similar to that observed with patch treatment.

EstroGel 0.06% was well tolerated in these pivotal trials. The primary adverse effects with EstroGel 0.06% treatment were headache, infection, breast pain, vaginitis, abdominal pain, pain, and rash. The frequency of application site reactions was markedly lower with EstroGel 0.06% compared with the estradiol patch (0.6% versus 20.7%).³

A number of other transdermal products have recently been FDA-approved, including estradiol gel 0.1% (marketed as Divigel), another estradiol gel 0.06% (marketed as Elestrin), and estradiol spray (marketed as Evamist). It should be noted that EstroGel 0.06% has

two FDA-approved indications: treatment of moderate to severe vasomotor symptoms associated with menopause and treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause (when prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered), while both Elestrin and Divigel have one (treatment of moderate-to-severe vasomotor symptoms associated with menopause).

In summary, EstroGel 0.06% provides a number of advantages in hormone therapy. The product is the original estradiol product formulated in a gel formulation. The once-daily

application to the arm using a metered-dose pump is convenient and travel-friendly. The clear, colorless gel dries in 2 to 5 minutes and is odorless once dry. There is a low incidence of application site reactions. The transdermal route of delivery avoids first-pass hepatic metabolism and provides stable levels of estradiol in the circulation throughout the dosing interval. Clinical significance of the avoidance of first-pass metabolism has not been determined. EstroGel 0.06% is well tolerated and significantly reduces the frequency and severity of moderate-to-severe vasomotor symptoms and moderate-to-severe symptoms of vulvar and vaginal atrophy associated with menopause (when prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered). □

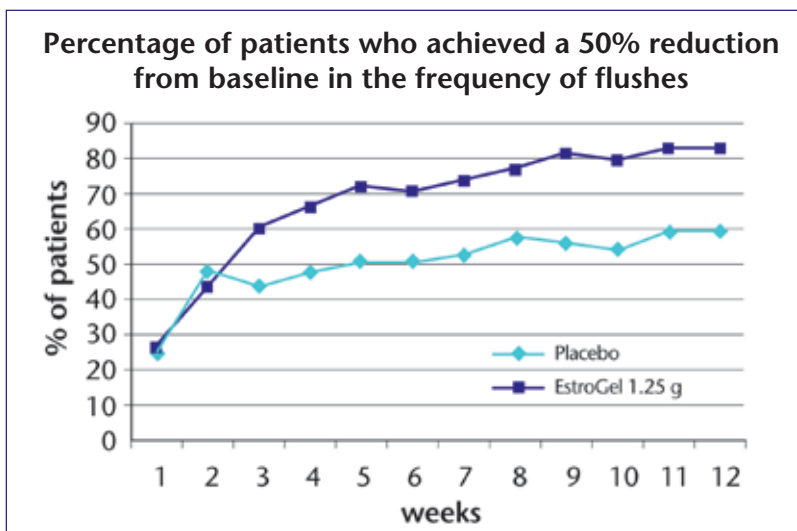


FIGURE 3. Percentage of patients with $\geq 50\%$ reduction in frequency of moderate-to-severe hot flashes during 12 weeks of treatment with estradiol gel 0.06%, 1.25-g dose or placebo gel.³

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IMPORTANT SAFETY INFORMATION¹

EstroGel is contraindicated for patients with any of the following conditions: undiagnosed abnormal genital bleeding; known, suspected, or history of breast cancer; known or suspected estrogen-dependent neoplasia; active deep vein thrombosis, pulmonary embolism, or history of these conditions; active or recent arterial thromboembolic disease; liver dysfunction or disease; known hypersensitivity to ingredients in EstroGel; known or suspected pregnancy.

Estrogens with or without progestins should not be used for the prevention of cardiovascular disease. The estrogen-alone substudy of the Women's Health Initiative (WHI) reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (aged 50-79 years) during 6.8 and 7.1 years, respectively, of treatment with oral conjugated estrogens (CE 0.625 mg) per day, relative to placebo.

The estrogen-plus-progestin substudy of the WHI reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (aged 50-79 years) during 5.6 years of treatment with oral conjugated estrogens (CE 0.625 mg) combined with medroxyprogesterone acetate (MPA 2.5 mg) per day relative to placebo.

The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with CE 0.625 mg alone and during 4 years of treatment with CE 0.625 mg combined with MPA 2.5 mg, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women.

Other doses of conjugated estrogens with medroxyprogesterone acetate, and other combinations and dosage forms of estrogens and progestins were not studied in the WHI clinical trials and, in the absence of comparable data, these risks

should be assumed to be similar. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman.

Because of the risk of endometrial cancer, close clinical surveillance of all women taking estrogens is important.

Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of "natural" estrogens results in a different endometrial risk profile than synthetic estrogens at equivalent estrogen doses.

Increase in the risk of breast cancer, gallbladder disease, hypercalcemia in patients with breast cancer and bone metastases, and retinal vascular thrombosis have been reported in patients receiving estrogens. Alcohol-based gels are flammable. Avoid fire, flame, or smoking until the gel has dried.

In clinical studies, the most commonly reported adverse events for EstroGel were headache, infection, breast pain, vaginitis, abdominal pain, pain, and rash.

Blood pressure should be monitored during estrogen use. Precautions should be taken when administering to nursing mothers, to patients over 65 years of age and in patients with hypertriglyceridemia, impaired liver function and past history of cholestatic jaundice, hypocalcemia, hypothyroidism, conditions that might be influenced by fluid retention, hypocalcemia, endometriosis, asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic hemangiomas. The risk of ovarian cancer may also be increased.

REFERENCE: 1. EstroGel 0.06% [package insert]. Herndon, VA: ASCEND Therapeutics, Inc; 2007.