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THE WOMEN'S HEALTH ALLIANCE

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Advances in Transdermal Estrogen-Only Therapy for Vasomotor Symptoms

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What are the key challenges for clinician providers who care for the older woman past reproductive age or those who are surgically menopausal?

Menopausal symptoms are a concern for a substantial number of women in the United States. Annually, 11 million women reach the age of natural menopause—approximately 51.3 years.[1,2] In addition, more than 500,000 women undergo a hysterectomy each year, with removal of the ovaries in more than 50%.[3] Whether menopause occurs naturally or is surgically-induced, more than 85% of these women experience symptoms associated with estrogen deficiency, including, but not limited to, hot flushes and night sweats.[4,5]

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How can moderate to severe hot flushes impact the day-to-day function of menopausal women?

Vasomotor symptoms (i.e., hot flushes and night sweats) are the number one complaint of menopausal women and the main reason that they seek treatment.[6,7] Vasomotor symptoms (VMS) may also contribute to sleep difficulty, another common complaint affecting more than 40% of menopausal women, and nearly 50% of surgically menopausal women.[8,9] Sleep disturbances increase as the frequency and severity of VMS increases.[10] In a related study by Ohayon, of the 982 women sampled, about half experienced mild hot flashes, a third moderate hot flashes, and 15.5% reported severe hot flashes. The World Health Organization defines severe hot flashes as occurring most of the time, characterized by a sen-

continued on page S3

minivelle®
(estradiol transdermal system)

INDICATION

MINIVELLE™ (estradiol transdermal system) is indicated for treatment of moderate to severe vasomotor symptoms due to menopause.

IMPORTANT SAFETY INFORMATION

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

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**
- **Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia**
- **The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT)**
- **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**

Estrogen Plus Progestin Therapy

- **Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia**
- **The WHI estrogen plus progestin substudy reported increased risks of stroke, DVT, pulmonary embolism (PE), and myocardial infarction (MI)**
- **The WHI estrogen plus progestin substudy reported increased risks of invasive breast cancer**
- **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**

Estrogens should not be used in women with 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 history of arterial thromboembolic disease (e.g., stroke or MI); known anaphylactic reaction or angioedema with MINIVELLE, liver dysfunction or disease; known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders; or known or suspected pregnancy.

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. Postmenopausal women should be re-evaluated periodically as clinically appropriate to determine if treatment is still necessary.

Estrogens increase the risk of gallbladder disease. Discontinue estrogen if severe hypercalcemia, loss of vision, severe hypertriglyceridemia or cholestatic jaundice occurs. Monitor thyroid function in women on thyroid replacement therapy.

In clinical trials with Vivelle® (estradiol transdermal system), the most common side effects (≥5%) were headache, breast tenderness, back pain, pain in limb, nasopharyngitis, dyspepsia, nausea, sinusitis, and intermenstrual bleeding.

Please see accompanying full Prescribing Information including Boxed WARNING.

continued from page S1

sation of heat with sweating, and causing the woman to stop her activity.[9] Half (50.9%) of the women in the Ohayon study experienced both night sweats and daytime hot flashes.

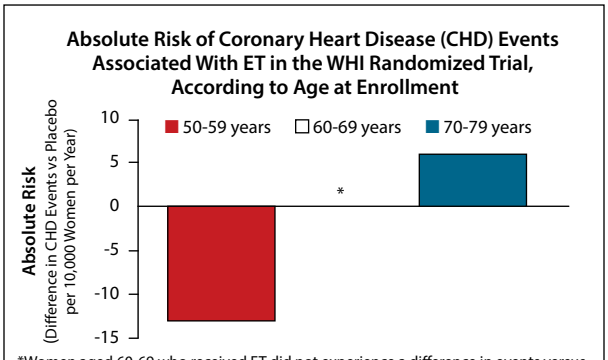
Hormone therapy (HT):
A term that includes both estrogen monotherapy (ET) and estrogen + progestogen combination therapy (EPT)[11]

Do we know more about the risks of hormone therapy since the initial Women's Health Initiative (WHI) findings from 2002?

The original reports from the WHI provided an understanding of the benefits and risks of hormone therapy (HT).[12,13] More detailed analyses of the WHI data, and results from subsequent studies help provide additional insight on the benefits and risks associated with treatment. Unlike the original reports from WHI, these analyses attempt to clarify the risk-benefit ratio of therapy and age and time since menopause with respect to the initiation and use of HT.[11, 14-16] Other evidence suggests that the dose and route of administration also affect the risks of HT.[15]

A secondary analysis of the WHI data included 77.9% of participants in the conjugated estrogen-only (ET) group (n=3778) and 78.4% of participants in the placebo group (n=3867) who continued into the postintervention extension phase and were followed for a mean of 10.7 years.[14] One of the objectives of the extension was to examine the relationship of age at study randomization on health outcomes.[14] As clinicians, it is important to understand that risk of disease can be calculated in several ways. The original and follow-up analyses demonstrated a trend for risk in terms of hazard ratios (**FIGURE 1**). When expressed in terms of absolute rate per 10,000 women annualized over the average follow-up of 10.7 years, women aged 50 to 59 who received ET compared with women who received placebo had 13 fewer coronary heart disease (CHD) events. The women aged 60 to 69 who received ET did not experience a difference in events versus those on placebo (plotted zero in **FIGURE 1**). By contrast, women aged 70 to 79 years who received ET compared to women who received placebo had 6 excess events ($P = 0.05$ for every age interaction).[14] Understanding the absolute risks of these events may allow clinicians to better counsel their patients on the risks and benefits associated with therapy.

FIGURE 1 Age-specific intervention results for a mean follow-up of 10.7 years[14]



*Women aged 60-69 who received ET did not experience a difference in events versus those on placebo (plotted zero here).

Adapted from LaCroix AZ, et al. *JAMA*. 2011;305(13):1305-1314.

How do we appropriately communicate these new findings on the benefits and absolute risks of estrogen therapy into a clinical context?

Experts in menopause management consider ET with or without a progestogen to be the most effective treatment for moderate to severe VMS and related conditions.[17] Indeed, one of the primary indications for ET is the treatment of moderate to severe VMS.[17] Estrogen alone is recommended for hysterectomized women, but women with an intact uterus should receive concomitant progestogen (EPT) to protect the endometrium from the risk of unopposed estrogen causing hyperplasia and endometrial cancer.[4,17] The WHI estrogen-alone substudy, stratified by age, showed in women 50 to 59 years of age a nonsignificant trend toward reduced risk for CHD.[18]

What is the optimum duration of HT and how does it differ for estrogen alone versus estrogen plus progestogen?

The recommendation for the duration of HT differs for EPT and ET. For EPT, the duration is limited by the increased risk of breast cancer and breast cancer mortality associated with 3 to 5 years of use.[17] For ET, a more favorable benefit-risk profile was observed during a mean of 7 years of use and 4 years of follow-up, findings that allow more flexibility in duration of use.[17]

What are the different routes of estrogen administration?

All FDA-approved estrogen products are approved for the treatment of VMS, though the doses approved for VMS that have demonstrated efficacy vary by product.[19] The most common routes for the administration of estrogen are oral and transdermal.[4]

ET products may contain natural or synthetic conjugated equine estrogens (CE), 17β-estradiol (E_2), or other synthetic estradiol derivatives.[20] A number of oral and transdermal estrogen products are available. There also are topical options, including several gels, an emulsion, and a spray, all of which contain 17β-estradiol (E_2) (**TABLE 1** and **TABLE 2** on pages S4 and S5).

The wide variety of ET products permits individualization of therapy, as recommended by the North American Menopause Society (NAMS), the American Association of Clinical Endocrinologists (AACE), and the US Food and Drug Administration.[4,17,21] All agree that the lowest effective dose should be prescribed for the shortest duration of time, consistent with treatment goals and individual risks.[5,17,21-23] The decision to discontinue ET should be made jointly by the health care provider and the patient. However, clinical experience indicates that some women may require extended therapy

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TABLE 1 Oral estrogen therapy options for women with surgical menopause (i.e., those without a uterus): Products available in the United States[20]

Composition	Available dosages/day (mg)	FDA-approved indications
Conjugated estrogens (1 brand)	0.3, 0.45, 0.625, 0.9, 1.25	PMO, VMS, VVA, HE
Synthetic conjugated estrogens, A (1 brand)	0.3, 0.45, 0.625, 0.9, 1.25	VMS, VVA (0.3 mg/day dosage is indicated for VVA only)
Synthetic conjugated estrogens, B (1 brand)	0.3, 0.45, 0.625, 0.9, 1.25	VMS, VVA
Esterified estrogens (1 brand)	0.3, 0.625, 1.25, 2.5	VMS, VVA, HE
17β -estradiol (1 brand and various generics)	0.5, 1.0, 2.0	PMO, VMS, VVA, HE (indications for tablets only)
Estradiol acetate (1 brand)	0.45, 0.9, 1.8	VMS
Estropipate (1 brand and various generics)	0.625 (0.75 estropipate, calculated as sodium estrone sulfate 0.625), 1.25 (1.5), 2.5 (3.0), 5.0 (6.0)	PMO, VMS, VVA, HE

Composition and dosages are adapted from The North American Menopause Society. Hormone products for postmenopausal use in the United States and Canada. November 19, 2012. Indications are from manufacturers' prescribing information.

PMO = Prevention of postmenopausal osteoporosis; VMS = Treatment of moderate to severe vasomotor symptoms associated with menopause; VVA = Treatment of moderate to severe symptoms of vulvar and vaginal atrophy; HE = Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure.

because of persistent symptoms.[4,17,22] Women choosing to continue ET must be made aware of the risks and monitored appropriately.

Is there important counseling information for patients about potential short-term side effects of estrogen therapy?

One of the best ways to ensure compliance with a recommended product is for the healthcare provider to fully inform the patient about the potential risks and side effects. This may help alleviate patient concerns and dispel any misconceptions they may have while providing an appropriate risk-benefit perspective. Common side effects of ET include headache, breast pain and tenderness, and nausea and vomiting.[24] For a complete list of side effects and potential risks, clinicians should consult the labeling for the specific ET formulation prescribed. The clinician should properly manage the patient's expectations ahead of time. If the patient understands that she may be experiencing manageable side effects, this may reduce the likelihood that the patient will discontinue therapy without first consulting her clinician. In addition, it is advisable to schedule a follow-up visit to determine whether any dose adjustment is needed and to discuss any side effects that the patient may be experiencing. Patients should be reevaluated periodically (typically 3-6 months) to determine if ongoing treatment is still needed.

What advice should we provide to patients regarding the use of estrogen therapy?

In addition to using an ET product with proven efficacy for their symptoms, patients may want to learn how features of different formulations fit in with their preferences. A wide variety of oral and transdermal ET options are available.[25] Transdermal ET options include gels, sprays, and patches. The gel formulations include 2 delivered via pump and 1 supplied in foil packets. An estradiol spray is approved at a dosage of 1 to 3 sprays per day for the treatment of moderate to severe VMS.[25]

Considerations for the use of an oral option include potential interactions with food, as well as convenience in remembering to take the medication on a regular daily basis. Transdermal patches also have considerations that should be discussed with patients if a patch is their desired form of therapy. Patches should only be applied to skin that is clean, dry, and free of any powder, oil, or lotion.[18] The patch should be applied to a different area of the abdomen or buttocks each time. Patients should not use the same application site 2 times in the same week.[18] Upon removal of the patch, if any adhesive residue remains on the skin, the area needs to dry for 15 minutes. Then, patients can gently rub the area with oil or lotion to remove the adhesive from the skin.[18] Finally, for other topical nonpatch products, there is a wait time before patients who use gels or sprays can bathe or swim. Users of gels and sprays need to allow at least 2 to 5 minutes for these products to dry before dressing, and users of gels must wash their hands after application.[25] Because all of the gels and sprays are alcohol-based, users are cautioned to avoid fire, flame, or smoking until they have dried.[25] Gels and sprays may have specific instructions regarding the application of sunscreen.

Specific product label information should be consulted to determine how best to counsel patients.[25] Certainly, clinicians can advise a patient about ET options that

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TABLE 2 Selected transdermal and topical estrogen therapy options for women with surgical menopause (i.e., those without a uterus): Products available in the United States[20]

Composition	Delivery rate (mg/day) (mg)	Dosing frequency	FDA-approved indications
17 β-estradiol (E_2) matrix patches			
5 branded products	0.025, 0.0375, 0.05, 0.06, 0.075, 0.1	Once weekly	PMO, VMS, VVA, HE
	0.025, 0.0375, 0.05, 0.075, 0.1	Twice weekly	
	0.025, 0.05, 0.075, 0.1	Twice weekly	
1 branded product	0.0375, 0.05, 0.075, 0.1	Twice weekly	VMS only
2 branded products	0.025, 0.014	Once weekly	PMO only
Generic products	0.1, 0.05	Once or twice weekly	VMS, VVA
17β -estradiol (1 brand and various generics)	0.5, 1.0, 2.0	PMO, VMS, VVA, HE (indications for tablets only)	
Topical E_2			
3 branded gels	0.35	Daily application: 1 metered pump	VMS, VVA
	0.0125	Daily application: 1-2 metered pumps	VMS
	0.025, 0.05, 0.1	Daily application: 1 packet	VMS
1 branded emulsion	0.05 (2 packets)	Daily application: 2 packets	VMS
1 branded spray	1.53-4.59 (one spray contains 1.53 mg E_2 per 90 mcL)	Initial dose: 1 spray, increase to 2 to 3 sprays/day as needed	VMS

References for composition and dosages are adapted from The North American Menopause Society. Hormone products for postmenopausal use in the United States and Canada. November 19, 2012. Indications are from manufacturers' prescribing information.

PMO = Prevention of postmenopausal osteoporosis; VMS = Treatment of moderate to severe vasomotor symptoms associated with menopause; VVA = Treatment of moderate to severe symptoms of vulvar and vaginal atrophy; HE = Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure.

may help address her specific menopausal symptoms. However, patients may not know what questions to ask; therefore, it is equally important for clinicians to proactively ask their patients about their concerns in order to best individualize treatment. For example, some patients may make decisions themselves based on incomplete information. A case in point comes from a telephone survey of 670 women from an HMO following the news of the WHI in 2002.[26] Whereas 93% of those surveyed had heard about the long-term HT study in the lay press, less than one-fourth understood the study in detail with regard to results on relative risks and benefits of ET.[26] Despite lack of knowledge of the study, over half of these women attempted to discontinue their HT within 6 to 8 months of that study report.[26] Unfortunately, many patients decide to stop HT on their own, and often don't inform their health care clinician about their questions or concerns. Patients may not realize that there is a chance of recurring symptoms when HT is discontinued, regardless of their age or duration of use, or whether ET is discontinued abruptly or gradually.[17,27-29] Symptom management should be balanced with an informed discussion regarding HT and its associated risks and benefits.

What are the differences between oral and transdermal delivery of estrogen?

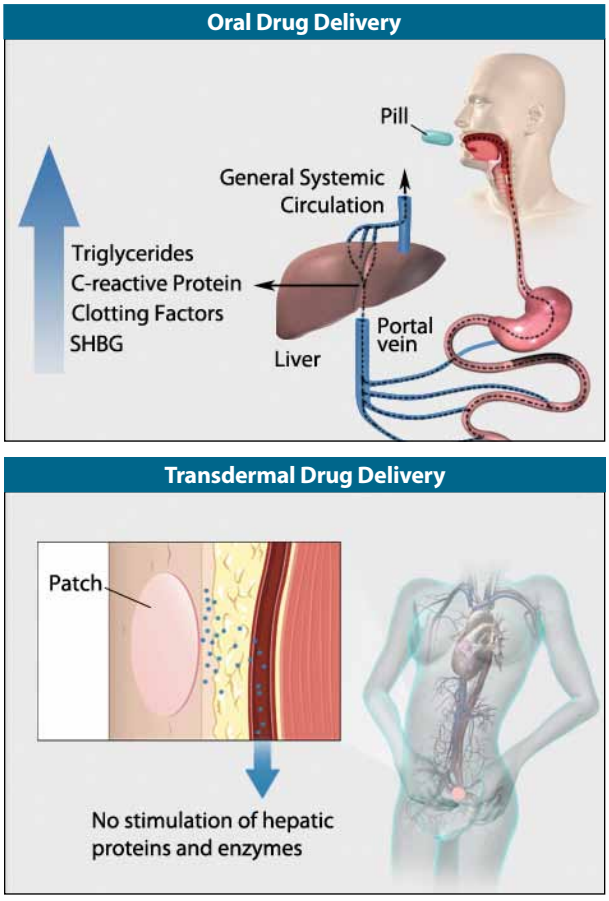
For the treatment of VMS, dosages of oral conjugated estrogen (CE) formulations range from 0.3 to 0.625 mg daily and micronized 17β-estradiol formulations range from 0.5 to 2.0 mg (**TABLE 1**).[19] In contrast, dosages of transdermal estrogen formulations approved for the treatment of VMS range from 0.025 to 0.1 mg/day (**TABLE 2**).[18-20] Oral estrogens are absorbed from the gastrointestinal tract and transported to the liver, whereas transdermal estrogens are absorbed directly into the subcutaneous capillaries of the skin (**FIGURE 2**).[4,19]

When metabolized, oral estrogens produce an estrone/estradiol ratio that is 5 times higher than the ratio in menstruating women.[30] The estrone/estradiol ratio resulting from transdermal estrogens is similar to the physiologic ratio in menstruating women (**FIGURE 2** and **TABLE 3** on page S6).[5,18,30-34] These differences do not imply differences in safety or efficacy.

What is the local tolerability and adhesion profile of the current drug-in-adhesive transdermal patch technology?

The transdermal route of administration is ideally suited to small, potent, lipophilic drugs, which include estrogen. Trans-

FIGURE 2 Oral and transdermal drug delivery



dermal drug delivery has evolved from the first-generation reservoir patch introduced in 1986, followed by the solid-matrix system, and then the drug-in-adhesive transdermal patches employed in many of today's estrogen products. (**FIGURE 3** and **FIGURE 4**)

Absorption through the skin results in a gradual increase in serum drug concentration, which avoids the peaks and troughs associated with oral administration, and that can be long-lasting. The estrogen release characteristics produce a range of plasma estradiol concentrations observed during the early follicular phase of the menstrual cycle.[36]

TABLE 3 Characteristics of oral and transdermal estrogens*

Oral estrogens (CEE and micronized 17β-estradiol)	Transdermal estrogens
Largest total doses of estrogen[5]	Smallest total estrogen doses[18,33]
Absorbed from gastrointestinal tract and delivered directly to liver[5,31]	Absorbed directly into circulation via skin[34]
Produce estrone/estradiol ratios 5 times higher than in menstruating women[32]	Produce estrone/estradiol ratios similar to those in menstruating women[30,32]

*These differences do no imply differences in safety or efficacy of oral or transdermal agents.

The newest drug-in-adhesive transdermal patch for ET, Minivelle® (estradiol transdermal system), contains estradiol in the same DOT matrix adhesive platform as Vivelle-Dot®.[18,37] Minivelle is indicated for the treatment of moderate to severe VMS due to menopause. Four dosage strengths are available to provide nominal *in vivo* delivery rates of 0.0375, 0.05, 0.75, or 1.0 mg of estradiol per day via the skin. Each corresponding system has an active surface area of 2.48, 3.30, 4.95, or 6.6 cm^2 and contains 0.41, 0.62, 0.83, 1.24, or 1.65 mg of estradiol USP, respectively.[18]

The DOT matrix delivery system is designed to release estradiol continuously.[18,30] Estradiol levels may increase above baseline with 4 hours after application.[38] The wavy score protective liner is designed for ease of handling during the application process. The adhesive layer is composed of estradiol mixed with acrylic and silicone in precise ratios to control the rate of delivery. The concentration gradient between the

FIGURE 3 Reservoir patch

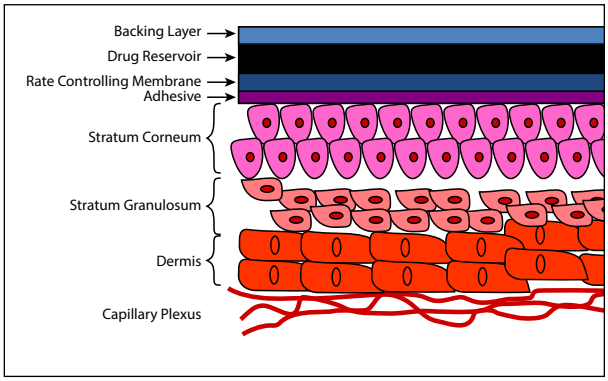
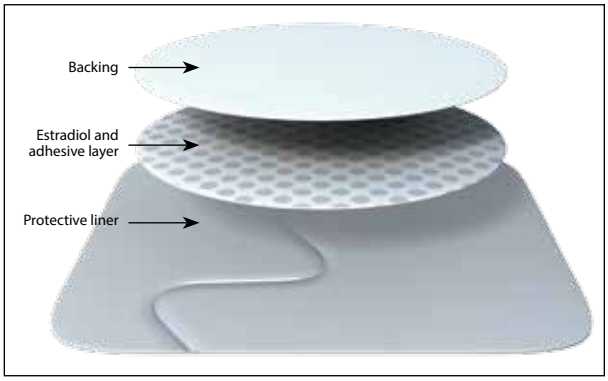


FIGURE 4 Matrix patch



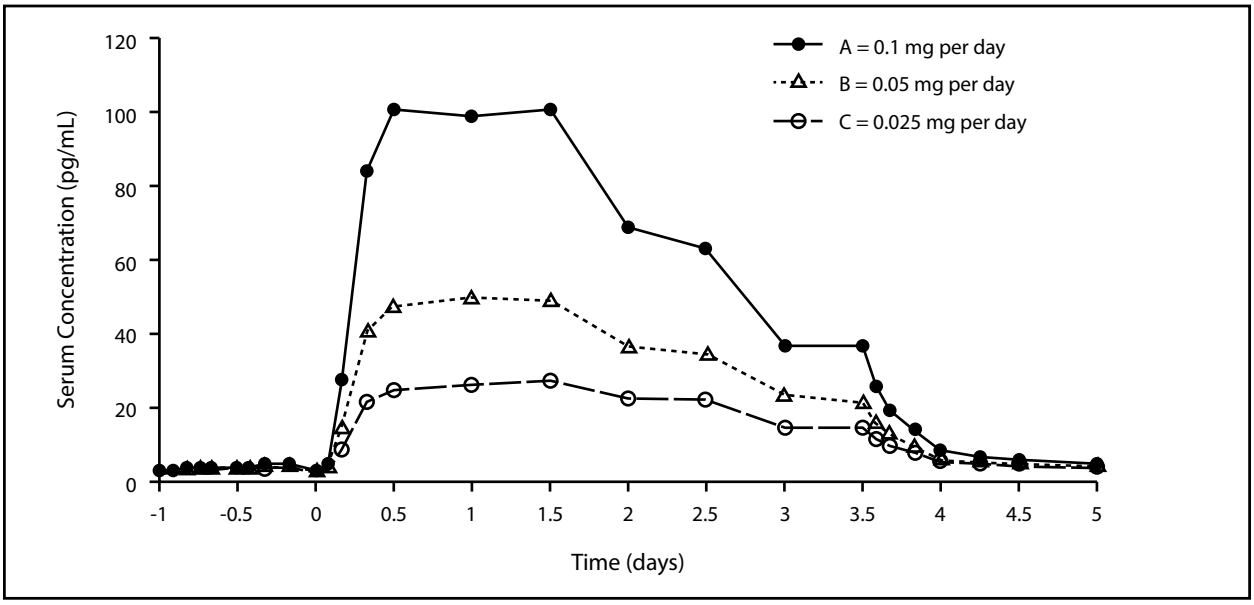
estradiol in the patch and skin results in highly efficient diffusion through the skin into systemic circulation.[35]

Patch application is twice-a-week.[18] The recommended starting dose for patients initiating use of ET for moderate to severe VMS is 0.0375 mg/day. When switching patients with VMS on Vivelle-Dot® to Minivelle®, use the same corresponding Minivelle dose for the indication (1:1 switch).[37]

Minivelle 0.05 mg/day provides a dose of estrogen that is 92% less than conjugated equine estrogens (Premarin®) 0.625 mg/day.[37]

Minivelle (estradiol transdermal system) is bioequivalent to Vivelle® which has demonstrated safety and efficacy for the treatment of VMS.[37] In a single-dose, two-way crossover study conducted in 96 healthy, non-smoking, non-fasting, postmenopausal women, Minivelle (0.1 mg/day) was bioequivalent to Vivelle (0.1 mg/day) based on estradiol exposure (AUC_{0-84}) and estradiol peak concentration (C_{max}) following a single dose on the lower abdomen for 84 hours.[18,37] Patients should not start using Minivelle if they have unusual vaginal bleeding, currently have or have had certain cancers, had a stroke or heart attack, currently have or have had blood clots, currently have or have had liver problems, have been diagnosed with a bleeding disorder, are allergic to Minivelle or any of its ingredients, or think they may be pregnant. The most common adverse events (≥ 5%) include headache, breast tenderness, back pain, pain in the limbs, nasopharyngitis, dyspepsia, nausea, sinusitis, and intermenstrual bleeding.[18] Estradiol pharmacokinetics were characterized in a separate open-label, single-center, randomized, single-dose, three-way, crossover study con-

FIGURE 5 Mean baseline-uncorrected estradiol serum concentration-time profile following a single dose of Minivelle® 0.1 mg/day (A), 0.05 mg/day (B), and 0.025 mg/day (C). (N=36)[18]



In a dose-proportionality study, it was shown that concentrations increase linearly with increasing doses from smallest (0.025 mg/day) through a middle dose (0.05 mg/day) to the highest dose (0.1 mg/day).

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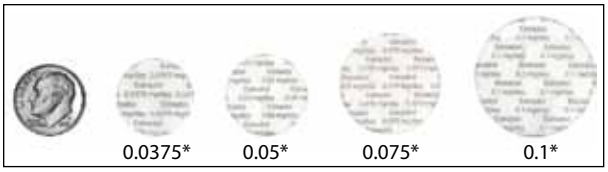
FIGURE 6 **Minivelle® (estradiol transdermal system) is currently the smallest patch available for ET**



Dime and patches are proportional, but not shown at actual size

*mg/day

ducted in 36 healthy, nonsmoking postmenopausal women (aged 40 to 65 years). Minivelle patches delivering nominal estradiol of approximately 0.025 mg, 0.05 mg, and 0.1 mg per day were applied to the lower abdomen under fed conditions in a crossover fashion for 84 hours. The mean baseline-uncorrected estradiol serum concentrations of Minivelle at three dosage strengths are shown in **FIGURE 5** on Page S7.[18,37]

Reduced patch size: Minivelle is currently the smallest ET patch and is 34% smaller than Vivelle-Dot® (**FIGURE 6**).[39-41]

Local tolerability profile: During the clinical pharmacology studies with Minivelle, 35% or less of subjects experienced barely perceptible erythema. No transdermal systems were removed due to irritation. Three subjects (2.2 %) reported mild discomfort while wearing Minivelle (N=136).[18]

Adhesion data: The smooth, curved edges (**FIGURE 7**) may help prevent the Minivelle patch from lifting or snagging associated with everyday wear. The Minivelle patch stays in place during showering and exercising. In pharmacokinetic studies, nearly 100% of subjects reported complete adhesion over the wear period. This is based on combined data from a bioequivalence and dose-proportionality study consisting of 208 observations.[37]

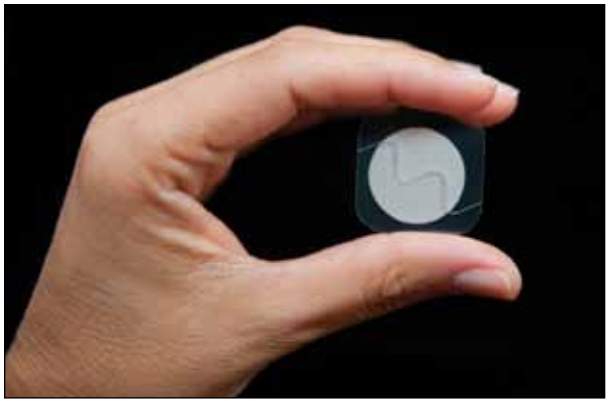
Overall summary

Menopausal symptoms are a concern for a substantial number of women in the United States, and hot flushes and night sweats are the number one complaint and the main reason that they seek treatment.[6,7]

While original reports from the WHI helped to provide an understanding of the benefits and risks of HT, more recent and detailed analyses of the WHI data, as well as results from subsequent studies, help provide additional insight on the benefits and risks associated with treatment.[11,12] These more recent analyses attempt to clarify the benefits and risks of therapy and age and time since menopause with respect to the initiation and use of HT, as well as dose and route of administration.[13-16]

Experts in menopause management consider ET with or without a progestogen to be the most effective treatment for moderate to severe VMS.[17] For EPT, the duration is limited by the increased risk of breast cancer and breast cancer mortality associated with 3 to 5 years of use.[17] For ET, a more

FIGURE 7 **Minivelle and its wavy score protective liner**



favorable risk-benefit profile was observed during a mean of 7 years of use and 4 years of follow-up, findings that allow more flexibility in duration of use.[17] The most common routes for the administration of estrogen are oral and transdermal. Transdermal drug delivery has evolved from the first-generation reservoir patch introduced in 1986, followed by the solid-matrix system, and then the drug-in-adhesive transdermal patches employed in many of today's estrogen products. The newest drug-in-adhesive transdermal patch for ET, Minivelle (estradiol transdermal system), contains estradiol in the same DOT matrix adhesive platform as Vivelle-Dot.[18] Minivelle is indicated for the treatment of moderate to severe VMS. Four dosage strengths are available to provide nominal in vivo delivery rates of 0.0375, 0.05, 0.75, or 1.0 mg of estradiol per day via the skin.[18] The recommended dose for patients initiating use of ET for moderate to severe VMS is 0.0375 mg/day. Patch application is twice-a-week.[18]

Minivelle 0.05 mg/day provides a dose of estrogen that is 92% less than conjugated equine estrogens (Premarin®) 0.625 mg/day.[37] Minivelle is bioequivalent to Vivelle and offers the same demonstrated efficacy.[37] Minivelle is the smallest patch currently available for ET, and is 34% smaller than Vivelle-Dot.[37] In pharmacokinetic studies, nearly 100% of subjects reported complete adhesion over the wear period. This is based on combined data from a bioequivalence and dose-proportionality study consisting of 208 observations.[37] Minivelle may be a safe and effective treatment option for women who suffer from moderate to severe vasomotor symptoms due to menopause.

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Please see full Important Safety Information on page S2.
Please see accompanying full Prescribing Information including Boxed WARNING.

MINIVELLE® (estradiol transdermal system) **Rx Only**

Brief Summary; Consult package insert for full Prescribing Information

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.

Cardiovascular Disorders and Probable Dementia

Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or 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.

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.

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.

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.

The WHIMS estrogen plus progestin ancillary study of the WHI, reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CE (0.625 mg) combined with MPA (2.5 mg), relative to placebo. It is unknown whether this finding applies to younger postmenopausal women.

Breast Cancer

The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer. 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.

INDICATIONS AND USAGE

MINIVELLE® (estradiol transdermal system) is indicated for the treatment of moderate to severe vasomotor symptoms due to menopause.

CONTRAINDICATIONS

MINIVELLE® (estradiol transdermal system) 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 a history of these conditions
- Active arterial thromboembolic disease (for example, stroke and MI), or a history of these conditions
- Known anaphylactic reaction or angioedema with MINIVELLE
- Known liver impairment
- Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders
- Known or suspected pregnancy

WARNINGS AND PRECAUTIONS

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. Should a stroke occur or be suspected, estrogen-alone therapy should be discontinued immediately.

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).

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 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, 14.2)]*. The increase in risk was demonstrated after the first year and persisted. 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 *[see Clinical Studies (14.2)]*.

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).

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). An increase in relative risk was demonstrated in year 1, and a trend toward decreasing relative risk was reported in years 2 through 5.

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

Venous Thromboembolism

In the WHI estrogen-alone substudy, the risk of VTE (DVT and PE), was increased for women receiving daily CE (0.625 mg)-alone compared to placebo (30 versus 22 per 10,000 women-years), although only the increased risk of DVT reached statistical significance (23 versus 15 per 10,000 women years). The increase in VTE risk was demonstrated during the first 2 years *[see Clinical Studies (14.2)]*. 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 *[see Clinical Studies (14.2)]*. 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 surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

Malignant Neoplasms

Endometrial cancer

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

Clinical surveillance of all women using estrogen-alone or estrogen plus 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 postmenopausal estrogen therapy 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] 0.80) [see Clinical Studies (14.2)]*.

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. 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 *[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. However, these studies have not 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 increased 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. 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.

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, 0.83-2.65). The absolute risk of probable dementia for CE-alone versus placebo was 37 versus 25 cases per 10,000 women-years *[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 percent CI, 1.21-3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 cases per 10,000 women-years *[see Use in Specific Populations (8.5), and Clinical Studies (14.3)]*.

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 (14.3)]*.

Gallbladder Disease

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

Hypercalcemia

Estrogen administration may lead to severe hypercalcemia in women 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.

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.

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.

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.

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.

Hepatic Impairment and/or Past History of Cholestatic Jaundice

Estrogens may be poorly metabolized in patients 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.

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 their free thyroid hormone levels in an acceptable range.

Fluid Retention

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

Hypocalcemia

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

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.

Hereditary Angioedema

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

Exacerbation of Other Conditions

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

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.

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 TBG 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 free 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 triglycerides levels.

Impaired glucose tolerance.

ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in labeling:

- Cardiovascular Disorders *[see Boxed Warning]*
- Endometrial Cancer *[see Boxed Warning]*

Clinical Trials Experience

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

There were no clinical trials conducted with MINIVELLE® (estradiol transdermal system). MINIVELLE is bioequivalent to Vivelle® (estradiol transdermal system). The following adverse reactions have been reported with Vivelle:

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

	Vivelle 0.0375 mg/day† (N=130) N (%)	Vivelle 0.05 mg/day† (N=103) N (%)	Vivelle 0.075 mg/day† (N=46) N (%)	Vivelle 0.1 mg/day† (N=132) N (%)	Placebo (N=157) N (%)
Gastrointestinal disorders					
Constipation	5 (3.8)	4 (3.9)	3 (6.5)	2 (1.5)	4 (2.5)
Dyspepsia	12 (9.2)	3 (2.9)	2 (4.3)	0	10 (6.4)
Nausea	8 (6.2)	4 (3.9)	0	7 (5.3)	5 (3.2)
General disorders and administration site conditions***					
Influenza-like illness	6 (4.6)	8 (7.8)	0	3 (2.3)	10 (6.4)
Pain NOS*	8 (6.2)	0	2 (4.3)	7 (5.3)	7 (4.5)
Infections and infestations					
Influenza	4 (3.1)	6 (5.8)	0	10 (7.6)	14 (8.9)
Nasopharyngitis	16 (12.3)	10 (9.7)	9 (19.6)	11 (8.3)	24 (15.3)
Sinusitis NOS*	17 (13.1)	13 (12.6)	3 (6.5)	7 (5.3)	16 (10.2)
Upper respiratory tract infection NOS*	8 (6.2)	11 (10.7)	4 (8.7)	6 (4.5)	9 (5.7)
Investigations					
Weight increased	5 (3.8)	2 (1.9)	2 (4.3)	0	3 (1.9)

continued

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

	Vivelle 0.0375 mg/day† (N=130) N (%)	Vivelle 0.05 mg/day† (N=103) N (%)	Vivelle 0.075 mg/day† (N=46) N (%)	Vivelle 0.1 mg/day† (N=132) N (%)	Placebo (N=157) N (%)
Musculoskeletal and connective tissue disorders					
Arthralgia	11 (8.5)	4 (3.9)	2 (4.3)	5 (3.8)	9 (5.7)
Back pain	10 (7.7)	9 (8.7)	4 (8.7)	14 (10.6)	10 (6.4)
Neck pain	4 (3.1)	4 (3.9)	0	6 (4.5)	2 (1.3)
Pain in limb	10 (7.7)	7 (6.8)	2 (4.3)	6 (4.5)	9 (5.7)
Nervous system disorders					
Headache NOS*	35 (26.9)	32 (31.1)	23 (50.0)	34 (25.8)	37 (23.6)
Sinus headache	12 (9.2)	5 (4.9)	5 (10.9)	2 (1.5)	8 (5.1)
Psychiatric disorders					
Anxiety NEC**	5 (3.8)	0	0	2 (1.5)	4 (2.5)
Depression	4 (3.1)	7 (6.8)	0	4 (3.0)	6 (3.8)
Insomnia	6 (4.6)	4 (3.9)	2 (4.3)	2 (1.5)	9 (5.7)
Reproductive system and breast disorders					
Breast tenderness	10 (7.7)	8 (7.8)	3 (6.5)	17 (12.9)	0
Dysmenorrhea	0	0	3 (6.5)	0	0
Intermenstrual bleeding	9 (6.9)	6 (5.8)	0	14 (10.6)	7 (4.5)
Respiratory, thoracic and mediastinal disorders					
Sinus congestion	4 (3.1)	3 (2.9)	3 (6.5)	6 (4.5)	7 (4.5)
Vascular disorders					
Hot flushes NOS*	0	3 (2.9)	0	0	6 (3.8)
Hypertension NOS*	0	3 (2.9)	0	0	2 (1.3)

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

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

DRUG INTERACTIONS

No drug interaction studies have been conducted for MINIVELLE.

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 estrogens and may result in side effects.

USE IN SPECIFIC POPULATIONS

Pregnancy

MINIVELLE 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.

Nursing Mothers

MINIVELLE 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 estrogens have been identified in the breast milk of women receiving estrogen therapy. Caution should be exercised when MINIVELLE is administered to a nursing woman.

Pediatric Use

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

Geriatric Use

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

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 probable dementia in women receiving estrogen-alone or estrogen plus progestin when compared to placebo *[see Warnings and Precautions (5.3), and Clinical Studies (14.3)]*.

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 *[see Warnings and Precautions (5.3), and Clinical Studies (14.3)]*.

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 MINIVELLE therapy with institution of appropriate symptomatic care.

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information and Instructions for Use)

References: 1. U.S. Food and Drug Administration. Estrogen and estrogen with progestin therapies for postmenopausal women. http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm135318.htm#.U14ZzYBzKnM.email.Accessed July 25, 2013. **2.** European Monthly Prescribing Reference. Hormone replacement therapies chart. http://www.empr.com/hormone-replacement-therapy-chart/article/123738/. Accessed on July 25, 2013. **3.** Pharmaceuticals and Medical Devices Agency, Japan. Pharmaceuticals and Medical Devices Safety Information, No. 252, November 2008. http://www.pmda.go.jp/english/service/pdf/precautions/PMDSI-252.pdf. Accessed July 25, 2013. **4.** Minivelle [package insert]. New York, NY: Noven Therapeutics, LLC; 2012.

For information, visit www.minivelle.com or call 1-800-455-8070.

noven THERAPEUTICS, LLC

From the manufacturer of Vivelle-Dot®

Minivelle® – the planet's smallest estrogen therapy patch[1-3]

For the treatment of moderate to severe vasomotor symptoms due to menopause

Good things come in small patches

Discreet design

34% smaller than Vivelle-Dot® and about the size of a dime at the 0.0375 mg/day dose

Effective relief

Effectively relieves moderate to severe hot flashes and night sweats due to menopause[4]

Staying power

Stays in place during showering and exercising, and round shape may help prevent snagging associated with everyday wear[4]

Less skin exposed

Causes almost no skin irritation and leaves almost no sticky residue behind on the skin[4]

Visit www.minivelle.com to learn more and to find out how eligible patients can *save big* on this small patch.*

*For eligible patients only. Restrictions may apply. See offer for the full terms and conditions.

minivelle™
(estradiol transdermal system)
0.0375, 0.05, 0.075, 0.1 mg/day
Good things come in small patches

INDICATION

MINIVELLE® (estradiol transdermal system) is indicated for treatment of moderate to severe vasomotor symptoms due to menopause.

IMPORTANT SAFETY INFORMATION

WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, BREAST CANCER AND PROBABLE DEMENTIA
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**
- **Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia**
- **The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT)**
- **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**

Estrogen Plus Progestin Therapy

- **Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia**
- **The WHI estrogen plus progestin substudy reported increased risks of stroke, DVT, pulmonary embolism (PE), and myocardial infarction (MI)**
- **The WHI estrogen plus progestin substudy reported increased risks of invasive breast cancer**
- **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**

Estrogens should not be used in women with 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 history of arterial thromboembolic disease (e.g., stroke or MI); known anaphylactic reaction or angioedema with MINIVELLE, liver dysfunction or disease; known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders; or known or suspected pregnancy.

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. Postmenopausal women should be re-evaluated periodically as clinically appropriate to determine if treatment is still necessary.

Estrogens increase the risk of gallbladder disease. Discontinue estrogen if severe hypercalcemia, loss of vision, severe hypertriglyceridemia or cholestatic jaundice occurs. Monitor thyroid function in women on thyroid replacement therapy.

In clinical trials with Vivelle® (estradiol transdermal system), the most common side effects (≥5%) were headache, breast tenderness, back pain, pain in limb, nasopharyngitis, dyspepsia, nausea, sinusitis, and intermenstrual bleeding.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Please see Brief Summary of full Prescribing Information, including Boxed WARNING, on the following pages.

Please see adjacent page for references.