

New Transdermal Estrogen Products

by Greta Nemergut, PharmD

Column Editor: Lee Vermeulen, MS, RPh, Director, Center for Drug Policy, University of Wisconsin Hospital and Clinics

Several new topical estrogen products have been approved by the FDA in recent years. The products offer varying amounts of estrogen as well as a variety of dosage forms, allowing for a more customized dosing regimen for women. Each product contains the same estrogen component, estradiol, which is also the estrogen component of the traditional transdermal patch. Table 1 summarizes the new products.¹

INDICATIONS

Each of the products is FDA labeled for treatment of moderate to severe vasomotor symptoms associated with menopause.²⁻⁶ EstroGel is also indicated to treat vulvar/vaginal atrophy symptoms associated with menopause.⁶ The transdermal patches have an additional indication for the prevention of postmenopausal osteoporosis and treatment of hypoestrogenism.⁷

PHARMACOLOGY/PHARMACOKINETICS

Endogenous estrogens are primarily responsible for the development and maintenance of the female reproductive system. Estradiol is the main intracellular human estrogen and is more potent than its metabolites, estrone and estriol, at the receptor level. Estrogens exert their action by binding to nuclear receptors in estrogen-responsive tissues.²⁻⁶

TABLE 1. TRANSDERMAL ESTROGEN PRODUCTS	
Medication	Systemic Estradiol Dose Delivered
Evamist (estradiol transdermal spray)	1 spray ~ 0.021 mg/day 2 sprays ~ 0.029 mg/day 3 sprays ~ 0.04 mg/day
Divigel (estradiol gel, 0.1%)	Unknown
Elestrin (estradiol gel, 0.06%)	0.87 gm dose = 0.0125 mg/day 1.7 gm dose = 0.0375 mg/day
Estrasorb (estradiol topical emulsion)	2 foil pouches = 0.05 mg/day
EstroGel (estradiol gel, 0.06%)	0.035 mg/day

The primary source of estrogen in the reproductive adult women is the ovarian follicle, which secretes 70 to 500 mcg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, the majority of endogenous estrogen is produced by the conversion of androstenedione, which is secreted by the adrenal cortex, to estrone by peripheral tissues. Estrone and estrone sulfate are the most abundant circulating estrogens in postmenopausal women.²⁻⁶

The pituitary secretion of gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH) are modulated by circulating estrogens through a negative feedback mechanism. Estrogens reduce the elevated levels of these hormones that occur in postmenopausal women.²⁻⁶

Since the action of estradiol in the body is the same when any form of exogenous estrogen is administered, the main difference among products is their kinetic profiles. While each demonstrates varying drug concentration values, the best indicator of total estro-

TABLE 2. PHARMACOKINETIC PARAMETERS

	AUC (pg-hr/mL)	Cmax (pg/mL)	Cavg (pg/mL)	Cmin (pg/mL)	Tmax (hr)	E2:E1	Systemic estradiol dose (mg/day)
Evamist							
1 spray	471	36.4	19.6	11.3	20	unknown	0.021
2 sprays	736	57.4	30.7	18.1	18	unknown	0.029
3 sprays	742	54.1	30.9	19.6	20	unknown	0.04
Divigel							
0.25 gm	236	14.7	9.8	unknown	16	0.42	unknown
0.5 gm	504	28.4	21	unknown	10	0.65	unknown
1 gm	732	51.5	30.5	unknown	8	0.65	unknown
Elestrin							
0.87 gm	335.2	21.6	15.4	9.4	18	0.53	0.0125
1.7 gm	940.2	66.7	39.2	21.1	4	0.98	0.375
Estrasorb	unknown	unknown	unknown	unknown	unknown	unknown	0.05
EstroGel	unknown	46.4	28.3	unknown	unknown	unknown	0.035

E2:E1=estradiol to estrone ratio

TABLE 3. CLINICAL TRIALS

Trial	Design	Outcome		Comment
Evamist (estradiol transdermal spray). EST-01 ¹	Phase 3, MC, R, DB, PC, PG n=458 post-menopausal women 18 and older estradiol vs placebo 1 spray 2 sprays 3 sprays Postmenopausal, 8 or more vasomotor symptoms per day assessed by diary Duration: 12 weeks	Mean decrease in vasomotor symptoms per day from baseline: Frequency: Week 12 1 spray estradiol: 8.10 (69%) placebo: 4.76 (38%) p=0.004* 2 sprays estradiol: 8.66 (68%) placebo: 6.19 (51%) p=0.0099* 3 sprays estradiol: 8.44 (78%) placebo: 5.32 (42%) p<0.0001*	Severity**: Week 12 1 spray estradiol: 1.04 (41%) placebo: 0.26 (10%) p<0.0001* 2 sprays estradiol: 0.92 (36%) placebo: 0.54 (21%) p=0.0406* 3 sprays estradiol: 1.07 (41%) placebo: 0.31 (12%) p<0.0001*	High placebo response Results not published 1 spray did not demonstrate significance over placebo at week 4 *p values are for estradiol vs placebo **Severity calculated as: SS2 = (2 x number moderate + 3 x number severe)/(number moderate + number severe) Adverse events: headache (10.6%), breast tenderness (5.8%), nipple pain (3.5%), back pain (3.5%), arthralgia (2.2%), nausea (2.2%), application site reactions (<2%)
Divigel (estradiol gel, 0.1%) ³	R, DB, PC n=495 post-menopausal women 18 and older estradiol 0.25 gm/day estradiol 0.5 gm/day estradiol 1 gm/day. Placebo 50 moderate to severe hot flushes at baseline per week Duration: 12 weeks	Mean decrease in vasomotor symptoms per day from baseline: Frequency: Week 12 0.25 gm/day: 6.88 (71%) 0.5 gm/day: 7.29 (79%) 1 gm/day: 8.35 (87%) placebo: 4.48 (48%), p<0.001 for each active group vs placebo	Severity: Week 12 0.25 gm/day: 0.33 (13%) p=0.021 0.5 gm/day: 0.56 (22%) p=0.002 1 gm/day: 1.69 (67%) p<0.001 placebo: 0.13 (5%)	Results only available in package insert p values all active treatment vs placebo
Elestrin (estradiol gel, 0.06%) ⁸	R, DB, PC, MC, PG n=484 post-menopausal women 18 and older estradiol 0.87 gm/day estradiol 1.7 gm/day estradiol 2.6 gm/day placebo 60 moderate to severe vasomotor symptoms per week Duration: 12 weeks	Mean decrease in vasomotor symptoms per day from baseline: Frequency: Week 5 0.87 gm/day: 7.7 (58%) placebo: 5.5 (41%), p<0.001 Week 3 1.7 gm/day: 8.2 (63%), p=0.007 2.6 gm/day: 9.5 (74%), p<0.001 placebo: 5.4 (40%) p values estradiol vs placebo	Severity: Week 4 (50% reduction) 0.87 gm/day: ~55%, p<0.01 1.7 gm/day: ~70%, p<0.001 2.6 gm/day: ~75%, p<0.001 placebo: ~40% Week 12 (50% reduction) 0.87 gm/day: ~80%, p<0.001 1.7 gm/day: ~85%, p<0.001 2.6 gm/day: ~90%, p<0.001 placebo: ~45% Week 12 (100% reduction) 0.87 gm/day: ~25%, p<0.001 1.7 gm/day: ~37%, p<0.001 2.6 gm/day: ~55%, p<0.001 placebo: ~8%	0.87 gm did not demonstrate significance over placebo at week 4 Frequency results reported for first week active treatment demonstrated significance over placebo Severity measured on 4 point scale: 0=none, 1=mild, 2=moderate, 3=severe Assessed vaginal atrophy symptoms, but study not powered to assess Adverse events: More significant in treatment groups vs placebo (p<0.001) breast tenderness, metrorrhagia, vaginal discharge, endometrial hypertrophy, nipple pain; incidence of each increased with increasing dose
Estrasorb (estradiol topical emulsion) ⁵	R, PC n=200 post-menopausal women, average age 52 estradiol 3.45 gm (2.5 mg) placebo Duration: 12 weeks	Mean decrease in vasomotor symptoms per day from baseline: Frequency: Week 12 3.45 gm: 11.11 (85%) placebo: 7.20 (53%) p<0.001 (estradiol vs placebo)	Severity: Week 12 3.45 gm: 1.44 (61%) placebo: 0.55 (23%) p<0.001 (estradiol vs placebo)	Results only available from package insert
EstroGel (estradiol gel, 0.06%) ⁶	PC n=145 only women age 29 to 67 years old estradiol gel 1.25 gm (0.75 mg) placebo Duration: 12 weeks	Mean decrease in vasomotor symptoms per day from baseline: Frequency: Week 12 1.25 gm/day: 7.55 (73%) placebo: 5.84 (53%) p=0.043 (estradiol vs placebo)	Severity: Week 12 1.25 gm/day: 1.03 (44%) placebo: 0.54 (23%) p<0.001 (estradiol vs placebo)	Results only available from package insert Vulvar and vaginal atrophy: vaginal wall cytology showed significant increase (p<0.001) of superficial epithelial cells from baseline. No change seen in placebo group.

MC=multicenter,R=randomized,DB=double-blind,PC=placebo-controlled,PG=parallel-group

diol exposure is systemic estradiol dose. Based on the results of several long-term randomized and observational studies, the current recommendation for treatment of vasomotor symptoms associated with menopause is the lowest dose of estrogen for the shortest amount of time to alleviate the symptoms. Table 2 compares the kinetic parameters of the new transdermal agents.²⁻⁶ The estradiol patch total estrogen exposure corresponds to the product description, therefore, the systemic estradiol exposure ranges from 0.025 mg to 0.1 mg, depending on which patch is worn.

CLINICAL TRIALS

Each of the five new transdermal estrogen products was evaluated in a randomized, placebo-controlled trial evaluating the efficacy of low dose estradiol for the treatment of vasomotor symptoms of menopause. The trials are summarized in Table 3.^{1, 3, 5, 6, 8} All of the trials were of similar design and all demonstrated statistically significant improvement of both frequency and severity of vasomotor symptoms from baseline when comparing the active treatment to placebo. Placebo response was large, with patients in the placebo groups experiencing a 40% to 50% reduction in the frequency of their symptoms, and a 5% to 23% reduction in the severity.

The North American Menopause Society published an updated position statement in March of 2007 regarding the use of estrogen and progestogen in peri- and postmenopausal women.⁹ Recommendations for treatment include considering using lower-than-standard doses of estrogen or progestogen therapy, defined as 0.3 mg of conjugated estrogen, 0.25-0.5 mg of oral estradiol, or 0.025 mg estradiol patch, or equivalent. Many studies demonstrate similar efficacy with the lower doses of estrogen in vasomotor symptom relief and preservation of bone mineral density. Lower doses are better tolerated and may have a better risk-benefit ratio than standard doses; however, they have not been studied long term. Nonoral estrogen may be associated with a lower risk of venous thromboembolism and does not go through first-pass metabolism, minimizing estrogen metabolites. Again, no long term risk-benefit data are available regarding the use of non-oral estrogens, and observational studies have shown similar risk of breast cancer for non-oral and oral estrogen. The position statement recommends that the use of estrogen or progestogen therapy should be consistent with individual treatment goals, benefits and risks. One should take into account the time since menopause, cause of menopause, symptoms that may have an impact on quality of life, and the underlying risk of cardiovascular disease, stroke, venous thromboembolism, diabetes, and other conditions.

DRUG INTERACTIONS

No drug interaction studies were completed for any of the products. Estrogens are metabolized partially by CYP450 3A4. Inducers of CYP3A4, such as St. Johns Wort, phenobarbital, carbamazepine, and rifampin may reduce plasma serum concentrations of estrogen, resulting in decreased efficacy. Inhibitors of CYP3A4, including erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir, and grapefruit juice may increase plasma levels and may cause an increase in side effects.²⁻⁶

CONTRAINDICATIONS/WARNINGS/PRECAUTIONS

The contraindications, warnings, and precautions do not differ among products in regard to estrogen supplementation. They each contain a black box warning indicating estrogens increase the risk for endometrial cancer, as well as, increase the risk of cardiovascular events, including myocardial infarction and stroke. The black box warning also includes the potential for increased risk of invasive breast cancer, pulmonary emboli, venous thromboembolism, and dementia. They are not recommended for the prevention of cardiovascular disease or dementia and should be given at the lowest dose possible for the shortest duration consistent with treatment goals.²⁻⁶ The only difference is the warnings and precautions that apply to the dosage form and skin exposure/contact. These differences are listed in Table 3.²⁻⁶

ADVERSE EVENTS

As mentioned in the contraindications/warnings/precautions section, all estrogen products carry the black box warning of increased cardiovascular events, including MI, stroke and venous thromboembolism, and dementia. The new transdermal products have not been directly evaluated for any of these outcomes. The adverse event data for specific products were derived from the individual 12 week studies completed for each product. The most common adverse events seen were nasopharyngitis, sinusitis, headache, breast tenderness and metrorrhagia.²⁻⁶ Application site reactions occurred in 1.3% of patients treated with Evamist, <1% of patients on Divigel, 1-4% (dryness and erythema) on Elestrin, and 0.6% on EstroGel. Estrasorb reported 4% of patients experiencing pruritis; however, it was not recorded if this occurred only at the application site or other body sites.²⁻⁶ The type of skin reactions was not defined for the products, except for Elestrin, where most patients experienced either dryness or erythema at the site. In comparison, 3.2% of patients using estradiol patches reported application site reactions.⁷

COST, DOSE, AND HOW SUPPLIED

A summary of available dosage forms, administration, and cost for each new transdermal estrogen product is provided in Table 5. As with any hormone replacement therapy, women who have a uterus need to also take a progestin to minimize the risk of uterine cancer.

CONCLUSIONS

Direct clinical evidence demonstrating efficacy for each of the new estrogen products is minimal, with only one published trial available. However, the mechanism of estrogen in the body is well established. While not compared head-to-head, each transdermal product appears to have similar efficacy in reducing the frequency of vasomotor symptoms associated with menopause.

Estradiol daily exposure is the most important kinetic factor, as the therapy goal is to have minimal estradiol exposure in order to minimize adverse events, while still allowing for symptom control. For long-term use, no data currently exist to determine



TABLE 4. APPLICATION WARNINGS AND PRECAUTIONS

	Evamist	Divigel	Elestrin	Estrasorb	EstroGel
Sunscreen Application	When sunscreen applied 1 hour after, 11% decrease in estradiol exposure, no change seen when sunscreen applied 1 hour prior	Not clinically evaluated	Estradiol absorption increased if sunscreen applied 10 minutes prior, should not be applied to same site at least 25 min after, concomitant administration for greater than 7 days may increase absorption and should be avoided	Do not use in close proximity, as estradiol absorption may be increased	Not clinically evaluated
Flammable	Avoid fire, flame, or smoking until spray has dried, has alcohol component	Avoid fire, flame, or smoking until gel has dried, has alcohol component	Avoid fire, flame, or smoking until gel has dried, has alcohol component	No, no alcohol base	Avoid fire, flame, or smoking until gel has dried, has alcohol component
Occlusion	Allow to dry for 2 minutes before dressing	Occlusion with clothing or other barriers not recommended until gel completely dried	Allow to dry for 5 minutes before dressing	Allow to dry completely before covering with clothing	Allow to dry for 5 minutes before dressing
Potential for estradiol transfer	No significant transfer demonstrated	Potential for drug transfer, avoid skin contact with others until gel dried, site of application should be covered after drying	Do not allow others to come in contact with application site for at least 2 hours	Potential for drug transfer, males who contacted site 2 and 8 hours post-application had increase of 25% in serum estradiol, to reduce chance of transfer avoid skin contact with others until gel dried, site of application should be covered after drying	No transfer demonstrated 15 minutes after application
Effects of washing	Site washing 1 hour after 3 spray administration did not have significant effect on serum estradiol levels; allow 30 min before washing	Washing site 1 hour after administration resulted in 30 to 38% decrease in mean 24 hour exposure to estradiol; refrain from washing up to 1 hour after administration	Not evaluated	Estradiol detected on skin 2 and 8 hours after administration, washing 8 hours after administration removed detectable estradiol from site	Site washing 1 hour after administration resulted in a 22% decrease in serum estradiol concentrations

TABLE 5. COST, DOSE, AND HOW SUPPLIED

Medication	Available Dosage Forms	Dosage/Administration	Cost*
Evamist (estradiol transdermal spray)	Metered dose pump; each spray delivers 90 mcL (1.53 mg estradiol); each pump contains 8.1 mL, will deliver 56 sprays	Initiate with 1 spray (1.53 mg estradiol)/day May use 1, 2, or 3 sprays applied each morning on adjacent non-overlapping 20 cm ² areas on inner surface of forearm starting near the elbow Allow to dry for about 2 min; site should not be washed for 30 min	\$54.12 / pump
Divigel (estradiol gel, 0.1%)	Single dose foil packets of 0.25 gm (0.25 mg estradiol), 0.5 gm (0.5 mg estradiol) and 1 gm (1 mg estradiol)	Start at 0.25 gm daily, adjust dose to patient response Apply entire contents of packet once daily on skin of either right or left upper thigh (alternate sites daily). The site should be 200 cm ²	\$60.80 / 30 packets
Elestrin (estradiol gel, 0.06%)	Non-aerosol metered dose pump; each spray delivers 0.87 gm (0.52 mg estradiol); each pump contains 144 gm of gel, will deliver 100 metered doses	Start with 1 metered dose; apply to skin in thin layer of upper arm (approx 320 cm ²). Dose adjustments based on patient response	\$67.03 / pump
Estrasorb (estradiol topical emulsion)	Foil pouches containing 1.7 gm	Daily dose of 2 packets—on to each leg every morning, rub into entire leg for at least 3 min, rub excess on buttocks.	\$62.49 / 60 packets
EstroGel (estradiol gel, 0.06%)	Non-aerosol metered-dose pump, 3 pumps sizes: 93 gm, 50 gm and 25 gm; each dose of 1.25 gm contains 0.75 mg estradiol	Applied over arm from wrist to shoulder in thin layer, area should be 750 cm ²	\$69.88 / pump

Evamist formulary dossier¹; *based on AWP

if transdermal estrogen is safer than oral estrogen in regard to risk-benefit ratios. Current recommendations advise using estrogen products, regardless of route of administration, for the shortest amount of time needed to adequately control symptoms of menopause.

All transdermal estrogen products offer similar estrogen exposure and are efficacious. Having multiple dosage forms allows women to choose a preferred product, taking into account tolerability, ease of use, and cost. ●

Greta Nemergut is a clinical pharmacist and medication use policy analyst in the Center for Drug Policy, UW Hospital and Clinics.

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Considering Variety

Redefining the pharmacy clerkship experience

by Laura Jester

As pharmacy students entering the last year of school, we prepare to leave the safety of the School of Pharmacy and head into the real world. Suddenly we are being asked, "What do you want to do when you graduate?" We are given the following advice: Here are available clerkship sites. Decide where you want to go. And, one more thing — consider variety.

Being fortunate enough to have no idea what I would like to do upon graduation, I took the last point to heart. Considering a variety of clerkship sites is how I ended up at the doorstep of the Pharmacy Society of Wisconsin. I had no idea what to expect, but since that first day I have found myself in the middle of some exciting issues on the forefront of pharmacy.

This rotation provided me with a unique view of pharmacy practice and gave me a chance to redefine it. When I thought about all of the students who may not be aware of what PSW can offer as a rotation site and professional organization, I decided to share my own discov-

eries with them. Here is a list of my top five experiences as a student at PSW.

1. **Viewing pharmacy from a different perspective.** The PSW clerkship is a back-stage pass to the world of pharmacy. I was able to see all of the effort that goes into running meetings and projects smoothly and efficiently.
2. **Staying abreast of current legislation**



Laura Jester (center, participating in the WPQC student training) spent part of her summer on rotation at the PSW office.

and regulation. Ever want to know how laws affecting pharmacy get into legislation? This is a great opportunity to see the whole process and how pharmacists are shaping the legal landscape.

3. **Understanding what professional organizations provide to their mem-**

bers. Planning and managing programs to advance pharmacy is a major undertaking. PSW provides members with continuing education, resources and tools, and up-to-date information, and advocates for the pharmacy profession in Wisconsin for all types of pharmacists.

4. **Meeting pharmacists who are making a difference.** The people I have met on this rotation are practicing pharmacy in new and exciting ways. Some of the most innovative people walk through the doors of PSW daily.
5. **Getting my feet wet. This rotation is hands-on.** I have created policy, developed resources, participated in

board meetings, traveled to pharmacies, and written for *Fast Facts* and *JPSW*. The unique opportunities to get involved are endless.

If I had not heeded the advice to consider a variety of clerkship experiences I may not have had the opportunity to discover another side of pharmacy. The perspective and skills I have gained during this rotation can be applied in any pharmacy setting in my future career. By seeing pharmacy practice from many angles, the picture becomes clearer.

So consider variety when choosing clerkship sites and redefine what pharmacy means to you. ●

Laura Jester is a fourth-year PharmD student at the UW School of Pharmacy. She wrote this article during her PSW elective clerkship.