



Therapeutic Class ReviewSM

Women's Health – Estradiol gel 0.06% (Elestrin[®])

December 2007

New Product for Review:

Estradiol gel 0.06% (Elestrin[®])

[Kenwood Therapeutics]

Dossier Provided by Manufacturer:

Dossier Evaluation: (2, missing PE model)

- 1 - Dossier missing significant clinical trial(s).
- 2 - Mfg. provided all relevant trials; Missing pharmacoeconomic model.
- 3 - Mfg. provided all relevant trials and information.

Available Therapeutic Alternatives:

Preferred/Formulary	Non-Preferred/Non-Formulary
Oral Estrogen Replacement Products	
Conjugated equine estrogens (CEE) (Premarin [®]) [Wyeth]	esterified estrogens (Menest [®]) [Monarch]
Conjugated estrogens A, synthetic (Cenestin [®]) [Duramed]	
estradiol (generics)	
estropipate (generics)	
Oral Combination Products	
CEE/medroxyprogesterone (MPA) (Premphase [®]) [Wyeth]	estradiol/norethindrone (Activella [®]) [Novo-nordisk]
CEE/MPA (Prempro [®]) [Wyeth]	estradiol/norgestimate (Prefest [®]) [Monarch]
ethinyl estradiol/norethindrone (EE/NE) (FemHrt [®]) [Galen]	esterified estrogen/methyltestosterone (Estratest [®]) [Solvay]
	drospirenone 0.5mg/estradiol 1mg (Angeliq [®]) [Berlex]
Transdermal Products	
<i>Twice weekly patch</i>	
estradiol (generics)	estradiol/norethindrone (CombiPatch [®]) [Novartis]
estradiol (Alora [®]) [Watson]	
estradiol (Esclim [®]) [Women's First Health]	
estradiol (Estraderm [®]) [Novartis]	
estradiol (Vivelle [®] /Vivelle Dot [®]) [Novartis]	
<i>Once weekly patch</i>	
estradiol (generic)	estradiol (Climara [®]) [Berlex]
<i>Topical gel or emulsion</i>	
	estradiol gel 0.06% (Elestrin [®]) [Kenwood Therapeutics]
	estradiol topical emulsion (Estrasorb [®]) [Esprit Pharma]
	estradiol gel 0.06% (EstroGel [®]) [Ascend Therapeutics]

Available Therapeutic Alternatives (Continued):

Preferred/Formulary	Non-Preferred/Non-Formulary
Vaginal Products	
conjugated estrogen cream (Premarin®) [Wyeth]	estradiol (Estring®) [Pfizer]
estradiol vaginal tablets (Vagifem®) [Novo Nordisk]	estradiol (FemRing®) [WC Prof Prod]
	estradiol cream (Estrace®) [WC Prof Prod]
Progestin Products	
medroxyprogesterone (generics)	progesterone, micronized (Prometrium®) [Schering]
	norethindrone (Aygestin®) [Duramed]

Executive Summary

General considerations:

- Current recommendations for hormone replacement therapy (HRT) are to use the lowest effective dose of estrogen for the shortest period of time for relief of menopausal symptoms.
- There is no evidence to support superior efficacy of any estrogen product on the market for relief of menopausal symptoms.
- Women with an intact uterus should use a progestin to help protect against endometrial proliferative effects seen with estrogen monotherapy.
- Topical estrogens do not necessarily carry a lower risk of serious adverse effects compared to oral preparations.

Estradiol gel 0.06% (Elestrin)

- Estradiol gel 0.06% (Elestrin) is the third topical estrogen gel or emulsion to be approved by the FDA for the treatment of vasomotor symptoms associated with menopause.
- Estradiol gel 0.06% (Elestrin) contains the same estrogen (estradiol) present in many oral, vaginal and transdermal medications used to treat the symptoms of menopause.
- The FDA approved estradiol gel 0.06% (Elestrin) in December 2006 for relief of moderate to severe vasomotor symptoms associated with menopause. Approval was based on one clinical trial evaluating the ability of estradiol gel 0.06% (Elestrin) to significantly reduce the number and severity of hot flushes compared to placebo.
- Transdermal estrogen products, like estradiol gel 0.06% (Elestrin), account for \$250 million of the \$1.3 billion dollars spent on hormone replacement therapies each year.

Evidence

- The randomized, placebo-controlled clinical trial for estradiol gel 0.06% (Elestrin) in postmenopausal women was a dose ranging trial that established 0.87gm of gel (containing 0.52mg estradiol) as the lowest effective dose for treatment of vasomotor symptoms.
 - This trial was critically appraised as possibly useful (Low Grade B).
 - Other doses of gel used in this trial were 1.7gm and 2.6gm. Of note, the 2.6gm dose was not FDA approved.

- Outcomes used in this trial (number and severity of hot flushes) are of clinical significance to patients.
- Statistically significant differences between treatment and placebo were seen at 5 weeks for subjects in the low dose group and these differences were maintained through the end of the trial (week 12).

Safety relative to available therapeutic options¹

- There is a potential risk of accidental exposure to children and other individuals, as demonstrated in a skin transfer study.
- Concomitant use with sunscreen can result in a 2-fold increase in serum estradiol levels.
- The gel is flammable for about 5 minutes after application, posing a potential risk for burns.

Medical value relative to available options:

- There are several less expensive formulary/preferred options available with comparable safety and efficacy profiles.
- There are formulary/preferred transdermal patches for patients who prefer topical therapy for vasomotor symptoms.
- Considerations in subpopulations:
 - **Pediatrics:** not for use in pediatrics; however, there is potential for accidental exposure to children.
 - **Geriatrics:** an insufficient number of females ≥ 65 years of age were in clinical trials to determine any differences in response vs. younger subjects.
 - **Gender:** for use in menopausal women only.
 - **Race, ethnicity:** no dosage adjustment is necessary based on race or ethnicity.

Product value

Estradiol gel 0.06% (Elestrin) provides another treatment option for women experiencing vasomotor symptoms associated with menopause. It does not provide protection against endometrial proliferation as do several of the preferred/formulary options containing progestins.

Conclusion

- Estradiol gel 0.06% (Elestrin) is non-preferred/non-formulary because:
 - There is no evidence that estradiol gel 0.06% (Elestrin) offers superior efficacy or safety over available preferred/formulary alternatives.
 - There are formulary/preferred options to satisfy patient preference for topical estrogen therapy.

Products²

Drug Products	FDA approval ^a	Patent Expiration(s) ^c	FDA approved indications	Potential Off-label Uses ^d
Elestrin	Dec 2006	Dec 2009	Vasomotor symptoms	Products in this class have been used for the following conditions: <ul style="list-style-type: none"> - Vasomotor symptoms associated with menopause - Osteoporosis prevention - Atopic Vaginitis - Kraurosis Vulvae - Female hypogonadism - Female Castration - Primary Ovarian Failure - Metastatic Breast Cancer (Palliative) - Prostate Cancer (Palliative in Advanced disease)
EstroGel	Feb 2004	Feb 2007	Vasomotor symptoms	
Estrasorb	Oct 2003	Jan 2015	Vasomotor symptoms, atopic vaginitis, kraurosis vulvae	
Premarin	< Jan 1982	July 2006	Vasomotor symptoms, osteoporosis, atopic vaginitis, female hypogonadism, female castration, ovarian failure	
Cenestin	March 1999	Feb 2007	Vasomotor symptoms, atopic vaginitis, kraurosis vulvae	
Enjuvia	Dec 2004	April 2010	Vasomotor symptoms	
Menostar	June 2004	June 2010	Osteoporosis	
Prempro	Nov 1995	Jan 2015	Vasomotor symptoms, osteoporosis, atopic vaginitis, kraurosis vulvae	
Premphase	Dec 1994	Feb 2012	Vasomotor symptoms, osteoporosis, atopic vaginitis, kraurosis vulvae	
Angeliq	Sept 2005	Aug 2017	Vasomotor symptoms	
FemHrt	Oct 1999	May 2010	Vasomotor symptoms, osteoporosis	
CombiPatch	Aug 1998	Dec 2012	Vasomotor symptoms, atopic vaginitis, kraurosis vulvae, female hypogonadism, female castration, ovarian failure	
Climara Pro	Nov 2003	Oct 2010	Vasomotor symptoms	

^a Date applies to approval date for the original brand name medication where there are now generics available.

^b Cost estimate based on AWP (average wholesale price) listed in First Data Bank as of July for 1 month of therapy.

^c Based on patents listed in Orange Book as of 07/31/2007.

^d As listed in © 1974 - 2007 Thomson MICROMEDEX database or as referenced.

Products Availability, Dosing Regimen and Approximate Cost

Estrogen Products	Dose/Route	AWP Cost*
Oral estrogens		
estradiol oral 0.5mg, 1mg, 2mg	0.5mg - 2mg orally QD	\$15
estropipate oral 0.75mg, 1.5mg, 3mg, 6mg	0.75mg - 6mg orally QD	\$30
conjugated equine estrogens (Premarin) 0.3mg, 0.45mg, 0.625mg, 0.9mg, 1.25mg	0.3mg - 2.5mg orally QD	\$44
conjugated estrogens A, synthetic (Cenestin) 0.3mg, 0.625mg, 0.9mg, 1.25mg	0.3mg - 2.5mg orally QD	\$46
conjugated estrogens B, synthetic (Enjuvia) 0.3mg, 0.45, 0.625mg, 1.25mg	0.3mg - 1.25mg orally QD	\$40
esterified estrogens (Menest) 0.3mg, 0.625mg, 1.25mg, 2.5mg	0.3mg - 2.5mg orally QD	\$69
Transdermal estradiol patches		
Generics 0.05mg/day, 0.1 mg/day	1 patch topically twice weekly	\$79
Alora 0.025 mg/day, 0.05 mg/day, 0.075 mg/day, 0.1mg/day	1 patch topically twice weekly	\$44
Estraderm 0.05mg/day, 0.1mg/day		\$58
Vivelle, Vivelle Dot 0.025mg/day, 0.0375mg/day, 0.05mg/day, 0.075mg/day, 0.1mg/day	1 patch topically twice weekly	\$56
Climara 0.025mg/day, 0.0375mg/day, 0.05mg/day, 0.06mg/day, 0.075mg/day, 0.1mg/day	1 patch topically twice weekly	\$50
Menostar 0.014 mg/day	1 patch topically once weekly	\$56
Topical estrogens		
estradiol topical gel (Elestrin)	0.87-1.7g topically once daily	\$37.94 - \$75.89
estradiol topical gel (EstroGel)	1.25g topically once daily	\$106 (2 mo supply)
Estradiol topical emulsion (Estrasorb)	3.48 gm (2 foil pouches = 1 dose) daily	\$71.40

Products Availability, Dosing Regimen and Approximate Cost (Continued)

Estrogen Products	Dose/Route	AWP Cost*
Combination estrogens/progestins*		
CEE/MPA (Prempro, Prempro low-dose): 0.3mg/1.5mg, 0.45mg/1.5mg, 0.625mg/2.5mg, 0.625mg/5mg, Premphase 0.625mg; 0.625mg/5mg	CEE 0.3mg/MPA 1.5mg orally QD CEE 0.45mg/MPA 1.5mg orally QD CEE 0.625/MPA 2.5mg orally QD CEE 0.625mg/5mg orally QD CEE 0.625mg days 1-14; CEE 0.625mg CEE/MPA 5mg days 15-28; orally	\$56 \$56
EE 1mg/drsp 0.5mg (Angeliq)	1mg EE/drsp 0.5mg orally once daily	\$69
EE/NE (FemHrt) 5mcg/1mg	5mcg EE/1mg NE orally once daily	\$55
estradiol/NE (Activella) 1mg/0.5mg	1mg estradiol/0.5mg NE orally once daily	\$56
estradiol/norgestimate oral (Prefest) 1mg/0mg; 1mg/0.09	1mg estradiol orally QD x 3days, then 1mg estradiol/0.09mg norgestimate QD x 3 days; repeat regimen continuously	\$53
estradiol/NE transdermal (CombiPatch): 0.05/0.14 mg/day, 0.05/0.25 mg/day	0.05mg estradiol/0.14mg NE transdermal system applied days 1-14. May increase to 0.05 estradiol 0.05mg/0.25mg NE days 15-28, if greater progestin dose desired. Transdermal system is replaced twice weekly during the 28 day cycle.	\$47
estradiol/levonorgestrel transdermal (Climara Pro) 0.045/0.015 mg/day	0.045mg estradiol/0.015mg levonorgestrel per day transdermal system applied and replaced once weekly.	\$50
Vaginal estrogens		
CEE cream (Premarin) estropipate (Estrace®)	½ to 2grams intravaginally, depending on symptoms (3 weeks on; 1 week off).	\$48 \$48
estradiol vaginal tablets (VagiFem)	1 tablet vaginally once daily for the first 2 weeks, then 1 tablet twice weekly. Every 3 to 6 months, the doctor will see if the dosage can be reduced or discontinued.	\$38
estradiol vaginal ring (Estring) estradiol vaginal ring (FemRing)	1 ring inserted for 3 months 1 ring inserted for 3 months	\$138 (3 mo supply) \$156 (3 mo supply)
Progestin Products		
medroxyprogesterone 2.5mg, 5mg, 10mg	5-10mg orally cyclic administration; 2.5mg orally daily continuous regimen	\$9.39
norethindrone (Aygestin) 5mg	1-10mg orally cyclic regimen; 0.5mg orally daily continuous regimen.	\$67
Progesterone, micronized (Prometrium) 100mg, 200mg	200mg orally cyclic regimen; 100mg orally every day.	\$45

*AWP (average wholesale price) based on First Data Bank as of July 2007 for 1 month of therapy.

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