



## Therapeutic Class Review<sup>SM</sup>

### Hormone Replacement Therapy

March 2005

#### New Product(s) for Review

estradiol/levonorgestrel patch (Climara Pro<sup>®</sup>) [Berlex]  
 estradiol (Menostar<sup>®</sup>) [Berlex]  
 estradiol gel (EstroGel<sup>®</sup>) [Solvay]  
 estradiol topical emulsion (Estrasorb<sup>®</sup>) [Novavax]  
 conjugated estrogens B, synthetic (Enjuvia<sup>®</sup>) [Elan]

#### Dossier Provided by Manufacturer:

**Dossier:** yes  
**Dossier:** requested -- Not received  
**Dossier:** yes  
**Dossier:** requested -- Not received  
**Dossier:** requested -- Not received

#### Available Therapeutic Alternative(s)

Preferred/Formulary	Non-Prefer/Non-Formulary
<b>Oral Estrogen Replacement Products</b>	
conjugated equine estrogens (CEE) (Premarin <sup>®</sup> ) [Wyeth]	esterified estrogens (Menest <sup>®</sup> ) [Monarch];
conjugated estrogens A, synthetic (Cenestin <sup>®</sup> ) [Duramed]	
estradiol (generics)	
estropipate (generics)	
<b>Oral Combination Products</b>	
CEE/medroxyprogesterone (MPA) (Premphase <sup>®</sup> ) [Wyeth]	estradiol/norethindrone (Activella <sup>®</sup> ) [Novo-nordisk]
CEE/MPA (Prempro <sup>®</sup> ) [Wyeth]	estradiol/norgestimate (Prefest <sup>®</sup> ) [Monarch]
ethinyl estradiol/norethindrone (EE/NE) (FemHrt <sup>®</sup> ) [Galen]	esterified estrogen/methyltestosterone (Estratest <sup>®</sup> ) [Solvay]
<b>Transdermal Products</b>	
<i>Twice weekly patch</i>	
estradiol (generics)	
estradiol (Alora <sup>®</sup> ) [Watson]	
estradiol (Esclim <sup>®</sup> ) [Women's First Health]	
estradiol (Estraderm <sup>®</sup> ) [Novartis]	
estradiol (Vivelle <sup>®</sup> /Vivelle Dot <sup>®</sup> ) [Novartis]	
estradiol/norethindrone (Combipatch <sup>®</sup> ) [Novartis]	
<i>Once weekly patch</i>	
estradiol (generic)	estradiol (Climara <sup>®</sup> ) [Berlex]
<b>Vaginal Products</b>	
conjugated estrogen cream (Premarin <sup>®</sup> ) [Wyeth]	estradiol (Estring <sup>®</sup> ) [Pfizer]
estradiol cream (Estrace <sup>®</sup> ) [WC Prof Prod]	estradiol (FemRing <sup>®</sup> ) [WC Prof Prod]
	estradiol vaginal tablets (Vagifem <sup>®</sup> ) [Novo Nordisk]
<b>Progestin Products</b>	
medroxyprogesterone (generics)	progesterone, micronized (Prometrium <sup>®</sup> ) [Schering] norethindrone (Aygestin <sup>®</sup> ) [Duramed]

## Executive Summary

- Current evidence suggests that other than for short-term control of symptoms associated with menopause, the harms of long-term estrogen therapy (with or without progestins) for prevention of chronic diseases (greater than five years) in postmenopausal women outweigh clinical benefits.
- Because of long-term safety concerns, the FDA and National Treatment Guidelines recommend that hormone replacement therapy be used in the lowest effective doses and for the shortest duration of treatment.
- Different product formulations (oral, transdermal patch or gels) demonstrate comparable short-term safety and efficacy (from 3 months, up to at least 3 years) in relieving hot flashes and night sweats, vaginal atrophy and associated dyspareunia.
- Vaginally administered products (creams, rings, vaginal tablets) provide effective estrogen options that can be administered locally (minimizing systemic absorption) when menopausal symptoms are limited to vaginal atrophy without vasomotor symptoms.
- Oral and transdermal patch formulations of estrogens with or without progestins have been shown to consistently increase bone mineral density and reduce the risk of osteoporotic fracture.
- There is no evidence showing certain estrogen products confer superior clinical advantages in safety or efficacy because of a lowest effective dose or route of administration.
  - While transdermal delivery offers a convenient form of administration, there is no compelling evidence that transdermal delivery of estrogen or estrogen/progestin products (in avoiding first-pass hepatic effects) confers better long-term safety than oral administration.
  - There is no evidence that the addition of different progestin products confers differences in clinical efficacy or safety, when used in combination with estrogen for prevention of endometrial hyperplasia in women with a uterus.
- Other than convenience, newer product formulations offer no significant clinical advantages over currently available estrogen products.
  - The efficacy estradiol gel and emulsion products (Estrogel, Estrasorb) appears to be similar to oral and transdermal estrogen products in relieving vasomotor symptoms.
  - The gel and emulsion products have less potential for administration site reactions commonly associated with transdermal patches.
  - There is no evidence that synthetic conjugated estrogens B (Enjuvia) differs in efficacy or safety from other oral or transdermal estrogen products when used for relief of vasomotor symptoms.
  - Other than convenience of once-weekly administration, transdermal estradiol/levonorgestrel (Climara Pro) offers no superior clinical advantages over other systemic hormone replacement products in the short-term treatment of vasomotor symptoms in postmenopausal women.

- Low-dose transdermal estradiol (Menostar) increases BMD in post-menopausal women.
  - o There is no evidence that low-dose transdermal estradiol (Menostar) differs in efficacy from other low-dose systemic estrogen products in increasing bone mineral density.
  - o Long-term studies to determine fracture risk reduction with low-dose transdermal estradiol (Menostar) are not available.
  - o When used in women with an intact uterus, low-dose transdermal estradiol (Menostar) without progestin therapy has shown a low incidence of clinically significant endometrial hyperplasia (0.5%); however product labeling for low-dose transdermal estradiol (Menostar) recommends that women with a uterus receive a progestin for at least 14 days every six or 12 months.

### **Conclusion**

EstroGel, Menostar, Enjuvia, and Climara Pro are non-formulary/non-preferred because these products do not offer any significant clinical advantages over other formulary/preferred estrogen or combination estrogen/progestin products in short-term treatment of vasomotor symptoms or reducing fracture risk in women with osteoporosis.

**Products**

<b>Medication Product</b>	<b>FDA Approval Date</b>	<b>Vasomotor sx's associated with menopause</b>	<b>Osteoporosis prevention</b>	<b>Atopic Vaginitis</b>	<b>Kraurosis Vulvae</b>	<b>Female hypogonadism</b>	<b>Female Castration</b>	<b>Primary Ovarian Failure</b>	<b>Metastatic Breast Cancer (Palliative)</b>	<b>Prostate Cancer (Palliative in Advanced disease)</b>	<b>Prevention of endometrial hyperplasia</b>	<b>Secondary Amenorrhea</b>	<b>Abnormal Uterine Bleeding</b>	<b>Endometriosis</b>
<b>Oral estrogens</b>														
estradiol oral	7/28/75	X	X	X	X	X	X	X	X	X				
estropipate oral	5/19/77	X	X	X	X	X	X	X	X					
conjugated equine estrogens (Premarin)	5/08/42	X	X	X		X	X	X	X	X				
conjugated estrogens A, synthetic (Cenestin)	3/24/99	X		X	X									
Conjugated estrogens B, synthetic (Enjuvia)	5/10/04	X												
esterified estrogens (Menest)	09/28/77	X		X	X	X	X	X	X	X				
<b>Transdermal estrogens</b>														
estradiol generics, Alora, Climara, Esclim, Estraderm, Vivelle, Vivelle Dot	9/10/86 and after	X	X	X	X	X	X	X						
Menostar	6/8/2004		X											
<b>Combination estrogens/progestins*</b>														
<i>Oral</i>														
CEE/MPA (Prempro)* (Premphase)*	12/30/94 11/17/95	X	X	X	X									
EE/NE (FemHrt)*	10/15/99	X	X											
estradiol/NE (Activella)	2/11/00	X	X	X	X									
estradiol/norgestimate oral (Prefest)	10/22/99	X	X	X	X									
<i>Transdermal</i>														
estradiol/NE transdermal (Combipatch)*	8/7/98	X		X	X	X	X	X						
estradiol/levonorgestrel transdermal (Climara Pro)*	11/21/03	X												
<b>Topical estrogen products</b>														
Estradiol topical gel (EstroGel)	2/9/04	X												
Estradiol topical emulsion (Estrasorb)	10/9/03	X		X	X									
<b>Vaginal estrogens</b>														
CEE cream (Premarin)	10/16/78			X	X									
estradiol vaginal tablets/cream (VagiFem, Estrace)	3/26/99			X	X									
estradiol vaginal ring (Estring, FemRing)	4/26/96 3/20/03			X	X									
<b>Progestins</b>														
medroxyprogesterone*	6/18/59										X	X		X
norethindrone (Aygestin)*	4/21/82											X	X	X
micronized progesterone (Prometrium)*	5/14/98										X	X		X

\*For women with an intact uterus; CEE = conjugated equine estrogens; EE = ethinyl estradiol; NE = norethindrone

## Products Availability, Dosing Regimen and Approximate Cost

<b>Estrogen Products</b>	<b>Dose/Route</b>	<b>AWP Cost*</b>
<b>Oral estrogens</b>		
estradiol oral 0.5mg, 1mg, 2mg	0.5mg - 2mg orally QD	\$2.10 (MAC)
estropipate oral 0.75mg, 1.5mg, 3mg, 6mg	0.75mg - 6mg orally QD	\$5.10 (MAC)
conjugated equine estrogens (Premarin) 0.3mg, 0.45mg, 0.625mg, 0.9mg, 1.25mg	0.3mg - 2.5mg orally QD	\$33
conjugated estrogens A, synthetic (Cenestin) 0.3mg, 0.625mg, 0.9mg, 1.25mg	0.3mg - 2.5mg orally QD	\$32
conjugated estrogens B, synthetic (Enjuvia) 0.3mg, 0.45, 0.625mg, 1.25mg	0.3mg - 1.25mg orally QD	Pricing not yet available
esterified estrogens (Menest) 0.3mg, 0.625mg, 1.25mg, 2.5mg	0.3mg - 2.5mg orally QD	\$28
<b>Transdermal estradiol patches</b>		
Generics 0.05mg/day, 0.1 mg/day	1 patch topically twice weekly	\$33 (MAC)
Alora 0.025 mg/day, 0.05 mg/day, 0.075 mg/day, 0.1mg/day	1 patch topically twice weekly	\$41
Esclim 0.025mg/day, 0.0375mg/day, 0.05mg/day, 0.06mg/day, 0.075mg/day, 0.1mg/day	1 patch topically twice weekly	\$36
Estraderm 0.05mg/day, 0.1mg/day	1 patch topically twice weekly	\$42
Vivelle, Vivelle Dot 0.025mg/day, 0.0375mg/day, 0.05mg/day, 0.075mg/day, 0.1mg/day	1 patch topically twice weekly	\$38, \$40
Climara 0.025mg/day, 0.0375mg/day, 0.05mg/day, 0.06mg/day, 0.075mg/day, 0.1mg/day	1 patch topically once weekly	\$38
Generics 0.05mg/day, 0.1mg/day,	1 patch topically once weekly	\$26
Menostar 0.014 mg/day	1 patch topically once weekly	\$50
<b>Topical estrogens</b>		
estradiol topical gel (EstroGel)	1.25g topically once daily	\$98 (2 mo supply)
Estradiol topical emulsion (Estrasorb)	3.48 gm (2 foil pouches = 1 dose) daily	\$49
<b>Combination estrogens/progestins*</b>		
CEE/MPA (Prempro, Prempro low-dose): 0.3mg/1.5mg, 0.45mg/1.5mg, 0.625mg/2.5mg, 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	\$42
Premphase 0.625mg; 0.625mg/5mg	CEE 0.625mg days 1-14; CEE 0.625mg CEE/MPA 5mg days 15-28; orally	\$42
EE/NE (FemHrt) 5mcg/1mg	5mcg EE/1mg NE orally once daily	\$40
estradiol/NE (Activella) 1mg/0.5mg	1mg estradiol/0.5mg NE orally once daily	\$39
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	\$42
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.	\$41
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.	\$38
<b>Vaginal estrogens</b>		
CEE cream (Premarin)	½ to 2grams intravaginally, depending on symptoms (3 weeks on; 1 week off).	\$39
estropipate (Estrace®)		\$72
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.	\$26
estradiol vaginal ring (Estring)	1 ring inserted for 3 months	\$118 (3 mo supply)
estradiol vaginal ring (FemRing)	1 ring inserted for 3 months	\$122 (3 mo supply)

\*AWP (average wholesale price) based on First Data Bank or Maximum Allowable Cost (MAC) as of January 2005 for 1 month of therapy.

## Products Availability, Dosing Regimen and Approximate Cost (continued)

Progestin Products		
medroxyprogesterone 2.5mg, 5mg, 10mg	5-10mg orally cyclic administration; 2.5mg orally daily continuous regimen	\$5
norethindrone (Aygestin) 5mg	1-10mg orally cyclic regimen; 0.5mg orally daily continuous regimen.	\$64
Progesterone, micronized (Prometrium) 100mg, 200mg	200mg orally cyclic regimen; 100mg orally every day.	\$40

\*AWP (average wholesale price) based on First Data Bank or Maximum Allowable Cost as of January 2005 for 1 month of therapy.

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