



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

### Women's Health Drospirenone 0.5mg /Estradiol 1 mg (Angeliq)<sup>®</sup>

February 2007

**New Product for Review:**

Drospirenone (drsp) 0.5mg/estradiol (EE) 1mg  
(Angeliq<sup>®</sup>) [Berlex] (1X28 day cycle)

**Dossier Provided by Manufacturer:**

**Dossier Evaluation: 2**

- 1- dossier w/missing components
- 2- all components present, except pharmaco-economic model
- 3- all components present (comprehensive)

**Available Therapeutic Alternatives**

Preferred/Formulary	Non-Preferred/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]
	drospirenone 0.5mg/estradiol 1mg (Angeliq <sup>®</sup> ) [Berlex]
<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]

## Available Therapeutic Alternatives (Continued)

Preferred/Formulary	Non-Preferred/Non-Formulary
<b>Progestin Products</b>	
medroxyprogesterone (generics)	progesterone, micronized (Prometrium <sup>®</sup> ) [Schering]
	norethindrone (Aygestin <sup>®</sup> ) [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.
- Hormone replacement products should provide an opportunity to titrate estrogen dose safely and effectively according to this recommendation.
- There is no evidence to support superior efficacy of any estrogen product on the market for relief of menopausal symptoms.

#### *Drsp 0.5mg/EE 1mg (Angeliq)*

- Drsp 0.5mg/EE 1mg (Angeliq) is the first hormone replacement therapy with drsp to be approved by the FDA.
- Drsp 0.5mg/EE 1mg (Angeliq) contains the same progestin (0.5mg drsp) found in the birth control pill YAZ (3mg drsp) and is packaged in a similar fashion.
- The FDA approved drsp 0.5mg/EE 1mg (Angeliq) in September 2005 for relief of moderate to severe vasomotor symptoms and vulvar/vaginal atrophy associated with menopause. Approval was based on:
  - Proven bioequivalence of the estrogen component (estradiol 1mg).
  - One clinical trial evaluating drsp's ability to protect the endometrium from hyperplasia.

#### Evidence

- The randomized, active comparative clinical trial for drsp 0.5mg/EE 1mg (Angeliq) in endometrial safety was a dose ranging trial that established drsp 0.5mg as the lowest effective dose that protects against endometrial hyperplasia.
  - This trial was critically appraised as not useful (Grade X) due to the high drop-out rate (26%).
- Efficacy in treating menopausal symptoms is implied from estradiol bioequivalence trial results.
- There is no evidence that the dose of progestin has any additional health benefits.

#### *Safety relative to available therapeutic options*

- As a set dose combination, drsp 0.5mg/EE 1mg (Angeliq) does not offer flexibility to titrate to lowest effective dose per recommendations.

- There is a risk of elevated serum potassium levels.
  - Minimal in healthy subjects, given the low dose of drsp in drsp 0.5mg/EE 1mg (Angeliq), 1/6 the dose found in YAZ.
  - Higher in patients with predisposing risk factors; conditions such as renal insufficiency, hepatic dysfunction and adrenal insufficiency.

*Medical value relative to available options is poor considering drsp 0.5mg/EE 1mg (Angeliq):*

- Confers the same efficacy as ethinyl estradiol 1mg in treatment of menopausal symptoms.
- Cost is several times that of other estrogen/progestin products.

### **Conclusion**

Drsp 0.5mg/EE 1mg (Angeliq) is non-formulary/non-preferred because there is:

- No useful evidence that this product provides additional clinical value over existing therapies for relief of menopausal symptoms.
- Added potential for hyperkalemia.

**Products** 1-23

<b>Medication Product</b>	<b>FDA Approval Date<sup>a</sup></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				
estropiate oral	5/19/77	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>														
<b>Oral</b>														
CEE/MPA (Prempro)* (Premphase)*	12/30/94 11/17/95	X	X	X	X									
EE 1mg/drsp 0.5mg (Angeliq)	9/28/05	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									
<b>Transdermal</b>														
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

<sup>a</sup> Date applies to approval date for the original brand name medication where there are now generics available.

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

## Products Availability, Dosing Regimen and Approximate Cost

Estrogen Products	Dose/Route	AWP Cost*
<b>Oral estrogens</b>		
estradiol oral 0.5mg, 1mg, 2mg	0.5mg - 2mg orally QD	\$1.80 (MAC)
estropipate oral 0.75mg, 1.5mg, 3mg, 6mg	0.75mg - 6mg orally QD	\$7.40 (MAC)
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	\$35
<b>Transdermal estradiol patches</b>		
Generics 0.05mg/day, 0.1 mg/day	1 patch topically twice weekly	\$49 (MAC)
Alora 0.025 mg/day, 0.05 mg/day, 0.075 mg/day, 0.1mg/day	1 patch topically twice weekly	\$42
Estraderm 0.05mg/day, 0.1mg/day		\$52
Vivelle, Vivelle Dot 0.025mg/day, 0.0375mg/day, 0.05mg/day, 0.075mg/day, 0.1mg/day	1 patch topically twice weekly 1 patch topically twice weekly	\$45
Climara 0.025mg/day, 0.0375mg/day, 0.05mg/day, 0.06mg/day, 0.075mg/day, 0.1mg/day	1 patch topically once weekly	\$44
Generics 0.05mg/day, 0.1mg/day,	1 patch topically once weekly	\$39
Menostar 0.014 mg/day	1 patch topically once weekly	\$56
<b>Topical estrogens</b>		
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	\$55
<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	\$56
Premphase 0.625mg; 0.625mg/5mg	CEE 0.625mg days 1-14; CEE 0.625mg CEE/MPA 5mg days 15-28; orally	\$56
EE 1mg/ drsp 0.5mg (Angeliq)	1mg EE/ drsp 0.5mg orally once daily	\$74
EE/NE (FemHrt) 5mcg/1mg	5mcg EE/1mg NE orally once daily	\$51
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.	\$44
<b>Vaginal estrogens</b>		
CEE cream (Premarin)	½ to 2grams intravaginally, depending on symptoms (3 weeks on; 1 week off).	\$45
estropipate (Estrace®)		\$41
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.	\$36
estradiol vaginal ring (Estring)	1 ring inserted for 3 months	\$132 (3 mo supply)
estradiol vaginal ring (FemRing)	1 ring inserted for 3 months	\$135 (3 mo supply)

\*AWP (average wholesale price) based on First Data Bank or Maximum Allowable Cost (MAC) as of January 2007 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	\$4 (MAC)
norethindrone (Aygestin) 5mg	1-10mg orally cyclic regimen; 0.5mg orally daily continuous regimen.	\$75
Progesterone, micronized (Prometrium) 100mg, 200mg	200mg orally cyclic regimen; 100mg orally every day.	\$45

\*AWP (average wholesale price) based on First Data Bank or Maximum Allowable Cost as of January 2007 for 1 month of therapy.

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11. Estraderm prescribing information. Novartis Pharmaceuticals Corporation, East Hanover, NJ, April 2004.
12. Femhrt prescribing information. Warner Chilcott, Inc., Rockaway, NJ, January 2004.
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