

FDA-Approved Alternatives to Premarin Derivatives – Are they safer ?

By JANE ALLIN | 9 November 2015

CONTRARY TO popular belief, the FDA has yet to approve any generic as a substitute for Premarin and its daughter products (i.e. Prempro, Premphase, Duavee).

Accordingly no prescription drugs used to treat menopausal symptoms, other than the Premarin family, contain pregnant mare's urine.

However much confusion arises when the subject of HRT is broached, particularly in terms of the safety aspect of FDA-approved versions that are not derived from pregnant mare's urine.

The vast majority of FDA-approved HRT prescription drugs are synthetic bioidenticals - hormones identical on a molecular level to endogenous hormones that are synthesized in the lab from natural plant sources.

These are not to be confused with the compounded bioidenticals, none of which are approved by the FDA. Premarin and its derivatives are also synthetics but, of course, sourced from an animal by-product.

Apart from Brisdelle, the only non-hormonal FDA-approved HRT, the rest fall into three categories of hormone combinations as follows:

- 🕒 Estrogen combinations (e.g. Estrace, Cenestin, Enjuvia, Menest)
- 🕒 Estrogen/Progestin combinations (e.g. Activella)
- 🕒 Estrogen/Androgen combinations (e.g. Menogen, Covaryx)

The estrogen combinations are intended as substitutes for Premarin and Duavee while the estrogen/progestin versions are proposed alternatives to Prempro and Premphase. Estrogen/androgen replacement therapy primarily represents mainstay therapy for young women who have undergone a hysterectomy. See

<http://www.medscape.com/viewarticle/438357>

A good proportion of these drugs contain estradiol or esterified estrogens (non-equine) as the estrogen component (e.g. Estrace, Femtrace, Activella, Femhrt, Angeliq).

However several have identical equine estrogens that are derived from plant-based sources versus pregnant mare's urine.

That said, these drugs are not entirely identical nor are they exactly equivalent in constituents. Cenestin, Enjuvia, and Menest are three such HRTs included in this group.

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Cenestin was originally developed as a generic for Premarin by Duramed/Barr but in 1997, the FDA refused to approve the abbreviated new drug applications from Duramed and Barr Laboratories for a generic version of Premarin.

The FDA's rationale was quite straightforward.

A synthetic generic version of Premarin could not be approved because the exact chemical composition of Premarin could not be fully identified.

This has been a controversial topic for years, a topic The Horse Fund has visited in the past. See <https://tuesdayshorse.wordpress.com/2014/11/14/the-quest-for-a-generic-premarin-a-bitter-pill-to-swallow/>

In any case, all three of these drugs – Cenestin, Enjuvia, and Menest – contain similar estrogen components that are found in Premarin and its derivatives.

Premarin however is a complex mixture of numerous hormonal components, of which only some of the estrogenic components are found in the plant-based synthetics.

The table below compares the ingredients of Premarin, Cenestin and Enjuvia.

I was unable to locate the same information for Menest however the pharmacology is similar to the others and contains a mixture of esterified estrogenic substances, principally estrone, that are of the type excreted by pregnant mares (e.g. sodium estrone sulfate, sodium equilin sulfate).

Pharmacology of Premarin and FDA-approved plant-based synthetics Cenestin and Enjuvia

See <http://surmeno.blogspot.com/2006/03/comparison-of-ingredients-premarin-and.html>

ESTROGEN	PREMARIN	CENESTIN	ENJUVIA
sodium estrone sulfate	✓	✓	✓
sodium equilin sulfate	✓	✓	✓

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ESTROGEN	PREMARIN	CENESTIN	ENJUVIA
sodium 17 alpha-dihydroequilin sulfate	✓	✓	✓
sodium 17 beta-dihydroequilin sulfate	✓	✓	✓
sodium 17 alpha-betahydroequilenin sulfate	✓	✓	✓
sodium 17 beta-betahydroequilenin sulfate	✓	✓	✓
sodium 17 alpha-estradiol sulfate	✓	✓	✓
sodium equilenin sulfate	✓	✓	✓
sodium 17 beta-estradiol sulfate	✓	✓	✓
sodium D8,9-dehydroestrone sulfate	✓		✓
5,7,9 (10) estratrien-3beta, 17 beta-diol	✓		
17 alpha-dihydro-delta, 8,9-dehydroestrone	✓		
17 beta-dihydro-delta, 8,9-dehydroestrone	✓		
5,7,9 (10) estratrien-3beta-ol-17-one	✓		
2-hydroxy-estrone	✓		
2-methoxy-estrone	✓		

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In addition to the extra estrogens contained in Premarin, it also contains six progestin and four androgen equine hormones. See <http://surmeno.blogspot.com/2006/03/comparison-of-ingredients-premarin-and.html>

Despite the fact that these alternatives contain several of the Premarin estrogenic components, a study comparing the pharmacokinetics and relative bioavailabilities of key estrogen components of Premarin with those of synthetic plant-based equivalents concluded that these are not in fact bioequivalent to Premarin and therefore cannot be assumed to be therapeutically equivalent. See <http://www.ncbi.nlm.nih.gov/pubmed/10865186>

But does this mean that these and other FDA-approved synthetics are safe?

Estrogen-only HRT

Premarin (Conjugated Equine Estrogens – CEEs) <http://www.rxlist.com/premarin-drug.htm>

- ⌚ Endometrial cancer, cardiovascular disorders, breast cancer and probable dementia (> 65 yrs).

Enjuvia (plant –derived equine estrogens) <http://www.rxlist.com/enjuvia-drug.htm>

- ⌚ Endometrial cancer, cardiovascular disorders, breast cancer and probable dementia (> 65 yrs).

Estrace (estradiol – plant based) <http://www.rxlist.com/estrace-drug.htm>

- ⌚ Endometrial cancer, cardiovascular disorders, breast cancer and probable dementia (> 65 yrs).

Estrogen –Progestin HRT

Prempro/Premphase (CEEs/progestin) <http://www.rxlist.com/prempro-drug.htm>

- ⌚ Invasive breast cancer, cardiovascular disorders, and probable dementia (> 65 yrs).

Activella (estradiol/progesterone – plant based) <http://www.rxlist.com/activella-drug.htm>

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- ⌚ Invasive breast cancer, cardiovascular disorders, and probable dementia (> 65 yrs).

And let's not forget the newest addition to the Premarin family.

Duavee (CEES/bazedoxifene(SERM)) <http://www.rxlist.com/duavee-drug.htm>

- ⌚ Endometrial cancer, cardiovascular disorders, and probable dementia (> 65 yrs).
- ⌚ The SERM bazedoxifene is believed to inhibit the formation of breast cancer cells by binding to the estrogen receptor thus interfering with its activity.

The picture is clear.

In effect the FDA-approved hormone-containing alternatives carry with them the same risks and warnings associated with drugs derived from conjugate estrogen estrogens, whether that be estrogen alone or combinations .

Albeit the risks may not be of the same significance as those associated with drugs manufactured from pregnant mare's urine.

Nonetheless they still exist , and potentially more so for susceptible individuals.

Although the hormonal ingredients are similar or equivalent, they may or may not function identically for any single given woman. This applies to the Premarin derivatives as well.

And so, as much as it may seem that these hormones are safer than the Premarin family of drugs, there is no solid evidence to prove this.

It is important to note that some of these drugs have been approved by the FDA because data collected from trials has proven their effectiveness in relieving menopausal symptoms and reducing the risk of osteoporosis.

However there have been no long-term studies like the WHI performed to assess their safety profile.

In the absence of comparable data, the risks are generally assumed to be similar to CEEs and other forms of estrogens.

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Moreover, regardless of the source and type of hormones, it is always recommended that estrogens, with or without progestins, should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment.

Brisdelle as an alternative?

As mentioned there is only one FDA-approved non-hormonal HRT. In early June of 2013 the U.S. Food and Drug Administration approved the drug “Brisdelle” (paroxetine - Paxil) manufactured by Noven Pharmaceuticals for the treatment of hot flashes due to menopause.

Brisdelle contains the selective serotonin reuptake inhibitor paroxetine mesylate, making it unique from all other FDA-approved treatment for hot flashes which contain the hormones estrogen or progestin.

Brisdelle poses none of the risks associated with estrogens or estrogen combination therapies. However it is a selective serotonin reuptake inhibitor (SSRIs) (antidepressant), which has been shown to increase the risk of suicidal thoughts and behavior in pediatric and young adult patients when used to treat major depressive disorder and other psychiatric disorders. See <http://www.rxlist.com/brisdelle-drug.htm>

Whether this risk applies to menopausal women is unclear.

As with any drugs and medications there are inherent risks, the nature of which can range from mild to life-threatening. Always consult your doctor to help decide what is best for your particular situation.

Please visit our Alternatives to Premarin page to learn more about options other than drugs containing conjugated equine estrogens. See <http://www.horsefund.org/pmu-alternatives-to-cee-drugs.php>

Comparing the cost of FDA-approved HRT

As an aside and for interest's sake here is a list of some of the more common HRTs available and the costs associated with them.

The list is by no means comprehensive and includes the tablet form of the drug only.

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This information was taken from www.goodrx.com and pertains only to the U.S. Prices are per tablet and converted to monthly costs based on a 30-day interval.

For consistency, all of the costs were taken from Walgreen's with the discount coupons applied.

Obviously prices will vary depending on store, geographic location, available coupons, etc. and are only intended to provide a relative comparison using the same base source.

DRUG NAME	TYPE	GENERIC AVAILABLE?	PATENT EXPIRY DATE	PRICE PER TABLET	MONTHLY COSTS (APPROX)
Prempro / Premphase	CEEs/Progestin	No	Expired	\$5.77	\$173
Brisdelle	SSRI (paroxetine)	No	Apr 2029	\$5.74	\$172
Duavee	CEEs/SERM (bazedoxifene)	No	Oct 2016	\$4.77	\$143
Premarin	CEEs	No	Expired	\$4.33	\$130
Angeliq	Estrogen/Progestin	No	Oct 2017	\$4.31	\$129
Cenestin	CEEs – plant-based	No	Expired	\$3.97	\$119
Prefest	Estradiol/Progestin	No	Mar 2020	\$3.73	\$112
Enjuvia	CEEs – plant-based	No	Feb 2021	\$2.75	\$83
Femtrace	Estradiol acetate	No	Dec 2021	\$2.68	\$80
Activella	Estradiol/Progestin	Yes	Expired	\$2.06	\$78
Menest	CEEs – plant-based	No	Expired	\$1.77	\$53
Femhrt	Estrogen/Progestin	Yes	Expired	\$1.32	\$40
Ogen	Estrogen (estrone)	Yes	Expired	\$0.28	\$8
Estrace	Estradiol	Yes	Expired	\$0.13	\$4

Clearly, Pfizer is laughing all the way to the bank at the expense of women and horses alike.

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