



## Faculty of Sexual & Reproductive Healthcare New Product Review from the Clinical Effectiveness Unit

20mcg ethinylestradiol/3mg drospirenone - Eloine<sup>®</sup>, Daylette<sup>®</sup>

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### Product Summary

#### Description:

- 20mcg ethinylestradiol/3mg drospirenone (20mcgEE/3mgDRSP) is a combined estrogen and progestogen contraceptive pill licensed for contraceptive use.
- 20mcgEE/3mgDRSP comes in a calendar pack with 24 consecutive active tablets containing ethinylestradiol 20mcg and drospirenone 3mg followed by four placebo tablets.
- Drospirenone is a synthetic progestogen that has antimineralocorticoid activity similar to that of progesterone and mild antiandrogenic activity.
- There is no pill-free interval: the subsequent pill packet is started the day after the last tablet of the previous packet has been taken. A four day hormone-free interval is provided by the four placebo tablets.

#### Therapeutic indications:

- In the UK, 20mcgEE/3mgDRSP is licensed for use for contraception only.
- In the USA, the FDA has approved Yaz<sup>®</sup> for use in treatment of symptoms of Premenstrual Dysphoric Disorder (PMDD ie severe premenstrual mood symptoms) and moderate acne vulgaris. However this applies only if the woman also wishes to use an oral contraceptive as her method of contraception. Evidence supporting use of 20mcgDRSP/3mgDRSP for these indications is very limited and other combined oral contraceptives which may also be effective have been much less extensively studied.

#### Manufacturer:

- Eloine is manufactured by Bayer and has the same composition as Yaz<sup>®</sup> (previously available on private prescription only and now withdrawn in the UK, replaced by Eloine).
- Consilient Health has also recently launched a generic preparation named Daylette<sup>®</sup>.

#### Cost:

- Eloine costs £14.70 for a packet of 3x 28 tablets.
- Daylette is £10.50 for 3 x28 tablets.

### **How effective is 20mcgEE/3mgDRSP as contraception?**

20mcgEE/3mg DRSP is of comparable effectiveness to other combined oral contraceptives. [1,2,3]

A large US observational study reports lower failure rates amongst users of a 24/4 EE/DRSP regimen than a 21/7 EE/DRSP regimen. The study also suggests greater contraceptive effectiveness of a 24/4 EE/DRSP regimen than with a 24/4 regimen containing EE in combination with norethisterone. The dose of EE is not specified. The authors postulate that this reflects the greater ovarian suppression achieved with a shorter hormone-free interval and a progestogen with a longer half life.[4]

Ovarian suppression was observed to be similar over three cycles amongst 146 women randomised to either EE20mcg/LNG as a 21/7 regimen or EE20mcg/3mgDRSP as a 24/4 regimen. [5] Comparing different regimens of EE20mcg/3mgDRSP, ovarian suppression has been observed to be greater with a 24/4 regimen than with a 21/7 regimen. [6]

It must be remembered that with typical use of a combined oral contraceptive, the contraceptive failure rate has been reported to be about 9%.

### **How acceptable do women find 20mcgEE/3mgDRSP?**

The bleeding pattern associated with use of EE20mcg/3mgDRSP in a 24/4 regimen has been reported to be equivalent to that of EE20mcg/3mgDSG in a 21/7 regimen. Pooled data from women taking part in four clinical trials of EE20mcg/3mgDRSP 24/4 (n=1285) demonstrates similar cycle control to that achieved with EE20mcg/3mgDSG 21/7.[1]

### **Contraindications to use:**

The contraindications to use of combined hormonal contraceptives set out in the UKMEC 2009 [7] and in the FSRH guideline Combined Hormonal Contraception 2011[8] apply to 20mcgEE/3mgDRSP.

### **Interaction with other medications:**

These are in line with other combined hormonal contraceptives.

In addition, the manufacturers note that concomitant use of EE20mcg/3mgDRSP with aldosterone antagonists or potassium-sparing diuretics has not been studied. As drospirenone has antimineralocorticoid activity, the Summary of Product characteristics suggests that serum potassium should be checked in the first cycle in women using these drugs. [9,10]

### **What health risks are associated with use of 20mcgEE/3mgDRSP?**

#### **Venous thromboembolism (VTE):**

The FSRH advises that, in common with combined hormonal contraceptives (CHC) containing desogestrel and gestodene, use of drospirenone-containing CHC increases VTE risk by 4.5 to 6 fold to 9-12 VTE events per 10,000 woman years.[11] Similarly, a recent large UK database study reports an adjusted odds ratio of 4.12 (3.43-4.96) for current use of CHC containing drospirenone compared to no use of CHC within the previous year.[12]

**Arterial disease:**

It has been postulated that the antimineralocorticoid activity of drospirenone might be beneficial for blood pressure. Small, short term studies have not observed a significant change in blood pressure over time with use of EE20mcg/3mgDRSP[12,13] and some data suggest that the preparation does not negatively affect risk factors for cardiovascular disease [13,14,15]. However data are extremely limited and there is no substantive evidence to suggest that risk of arterial disease is any different to that with other combined hormonal contraceptives.

The health risks associated with all combined hormonal contraception [8] should be considered to apply to 20mcgEE/3mgDRSP.

**What additional benefits may 20mcgEE/3mgDRSP offer?**

In the USA, 20mcgEE/3mgDRSP is licensed for use in the treatment of symptoms of PMDD and moderate acne vulgaris in women who choose COC as their contraceptive method. It should be noted that because of the initial suggestion that the antimineralocorticoid activity of DRSP and claims made regarding additional benefits of Yasmin®, more studies have considered use of EE/DRSP than other combined oral contraception for premenstrual symptoms and acne. This may have distorted the available evidence.

**PMDD:**

There is limited evidence suggesting that EE20mcg/3mgDRSP may be beneficial for women with symptoms of PMDD (severe premenstrual mood symptoms). However there is no conclusive evidence that EE20mcg/DRSP is more effective than other combined oral contraceptives.

Cochrane review in 2012 [16] concludes that “Drospirenone 3 mg plus ethinyl estradiol 20 µg may help treat premenstrual symptoms in women with severe symptoms, that is, premenstrual dysphoric disorder. The placebo also had a large effect. We do not know whether the combined oral contraceptive works after three cycles, helps women with less severe symptoms, or is better than other oral contraceptives”.

Since then, an open label trial of 90 Thai women randomised to either 20mcgEE/3mgDRSP or 20mcgEE/desogestrel demonstrated an improvement over six cycles in Women’s Health Assessment Questionnaire scores with both preparations.[17] A significantly greater effect was reported in the drospirenone group. Conversely, the abstract of a Chinese randomised study of 187 women with PMDD reports no significant difference in symptoms between treatment with 20mcgEE/DRSP and placebo. The complete article is not available for review.[18]

**Acne:**

EE20mcg/3mgDRSP may reduce acne lesions in moderate acne vulgaris. It is not known how effective it is compared to other combined hormonal contraceptives and to non-hormonal acne treatments.

A 2012 Cochrane Review [19] identifies two randomised controlled trials that compare use of EE20mcg/3mgDRSP to placebo for moderate acne: Koltun et al observe a significant reduction in inflammatory and non-inflammatory lesions and in total lesion count with EE20mcg/3mgDRSP compared to placebo amongst 893 women.[20] A small trial (n=25) reported by Palli et al demonstrates a significant reduction in truncal acne lesions with EE20mcg/3mgDRSP versus placebo.[21]

Considering all EE/DRSP combined oral contraceptives (not just 20mcg preparations), the Cochrane review for treatment of acne [19] concludes that all “A drospirenone COC appeared to be more effective than norgestimate or nomegestrol acetate plus 17 $\beta$ -estradiol but less effective than cyproterone acetate”. All six COCs evaluated in placebo-controlled trials have been found to be effective in reducing inflammatory and non-inflammatory facial acne lesions. Few important and consistent differences are found between COC types in their effectiveness for treating acne. How COCs compare to alternative acne treatments is unknown since only one trial addressed this issue”.[19]

Reporting on data from a US healthcare database, Joish et al suggest that EE/DRSP is cost-effective versus other acne treatments.[22]

It should be noted that many of the studies which demonstrated the above non-contraceptive benefits of EE/DRSP were directly funded by the pharmaceutical industry.

### **Weight:**

There is no significant evidence that 20mcgEE/3mgDRSP is less likely to be associated with weight gain than other combined hormonal contraceptives.

### **References**

1. Anttila L1, Bachmann G, Hernádi L, Kunz M, Marr J, Klipping C. Contraceptive efficacy of a combined oral contraceptive containing ethinylestradiol 20  $\mu$ g/drospirenone 3mg administered in a 24/4 regimen: a pooled analysis of four open-label studies. *Eur J Obstet Gynecol Reprod Biol.* 2011 Apr;155(2):180-2. doi: 10.1016/j.ejogrb.2010.12.037. Epub 2011 Feb 1.
2. Caiyan W1, Wen D, Qingping L, Huan S, Ziyang H, Liangdan T, Zheng'ai X, Yufeng L, Shulan Z, Baihua D, Xiaoyan X, Mulan R, Xiaomao L, Youdi X, Zhisong M, Meiqing X, Hongyu W, Zirong H2. [Efficacy and safety of a combined oral contraceptive containing drospirenone 3 mg and ethinylestradiol 20  $\mu$ g in a 24+4-day regimen in China]. *Zhonghua Fu Chan Ke Za Zhi.* 2014 May;49(5):355-9.[Article in Chinese]
3. Anttila L1, Kunz M, Marr J. Bleeding pattern with drospirenone 3 mg+ethinyl estradiol 20 mcg 24/4 combined oral contraceptive compared with desogestrel 150 mcg+ethinyl estradiol 20 mcg 21/7 combined oral contraceptive. *Contraception.* 2009 Nov;80(5):445-51. doi: 10.1016/j.contraception.2009.03.013. Epub 2009 May 9.
4. Dinger J<sup>1</sup>, Minh TD, Buttman N, Bardenheuer K. Effectiveness of oral contraceptive pills in a large U.S. cohort comparing progestogen and regimen. *Obstet Gynecol.* 2011 Jan;117(1):33-40.
5. Seidman L<sup>1</sup>, Kroll R<sup>2</sup>, Howard B<sup>3</sup>, Ricciotti N<sup>4</sup>, Hsieh J<sup>5</sup>, Weiss H<sup>6</sup>. Ovulatory effects of three oral contraceptive regimens: a randomized, open-label, descriptive trial. *Contraception.* 2015 Jun;91(6):495-502. doi: 10.1016/j.contraception.2015.03.001. Epub 2015 Mar 6.

6. Klipping C<sup>1</sup>, Duijkers I, Trummer D, Marr J. Suppression of ovarian activity with a drospirenone-containing oral contraceptive in a 24/4 regimen. *Contraception*. 2008 Jul;78(1):16-25. doi: 10.1016/j.contraception.2008.02.019. Epub 2008 May 27.
7. UK Medical Eligibility Criteria for Contraceptive Use 2009  
<http://www.fsrh.org/pdfs/UKMEC2009.pdf> (accessed 16/11/2015)
8. FSRH Combined Hormonal Contraception 2011  
<http://www.fsrh.org/pdfs/CEUGuidanceCombinedHormonalContraception.pdf> (accessed 16/11/2015)
9. Summary of Product Characteristics, Eloine. <https://www.medicines.org.uk/emc/medicine/30637> (accessed 16/11/2015)
10. Summary of Product Characteristics, Daylette.  
<http://www.mhra.gov.uk/home/groups/spcpil/documents/spcpil/con1438925897137.pdf> (accessed 26/11/2105)
11. FSRH statement Nov 2014: VTE and hormonal contraception  
<http://www.fsrh.org/pdfs/FSRHStatementVTEandHormonalContraception.pdf> (accessed 16/11/15)
12. Vinogradova Y<sup>1</sup>, Coupland C<sup>2</sup>, Hippisley-Cox J<sup>2</sup>. Use of combined oral contraceptives and risk of venous thromboembolism: nested case-control studies using the QResearch and CPRD databases. *BMJ*. 2015 May 26;350:h2135. doi: 10.1136/bmj.h2135.
13. Giribela CR<sup>1</sup>, Consolim-Colombo FM, Nisenbaum MG, Moraes TL, Giribela AH, Baracat EC, Melo NR. Effects of a combined oral contraceptive containing 20 mcg of ethinylestradiol and 3 mg of drospirenone on the blood pressure, renin-angiotensin-aldosterone system, insulin resistance, and androgenic profile of healthy young women. *Gynecol Endocrinol*. 2015 Jul 25:1-4. [Epub ahead of print]
14. de Nadai MN<sup>1</sup>, Nobre F, Ferriani RA, Vieira CS. Effects of two contraceptives containing drospirenone on blood pressure in normotensive women: a randomized-controlled trial. *Blood Press Monit*. 2015 Dec;20(6):310-5. doi: 10.1097/MBP.000000000000139.
15. El-Haggag SM<sup>1</sup>, Mostafa TM. Cardiovascular risk in Egyptian healthy consumers of different types of combined oral contraceptives pills: A comparative study. *Endocrine*. 2015 Aug;49(3):820-7. doi: 10.1007/s12020-014-0507-4. Epub 2014 Dec 25.
16. Lopez LM<sup>1</sup>, Kaptein AA, Helmerhorst FM. Oral contraceptives containing drospirenone for premenstrual syndrome. *Cochrane Database Syst Rev*. 2012 Feb 15;2:CD006586. doi: 10.1002/14651858.CD006586.pub4.
17. Wichianpitaya J<sup>1</sup>, Taneepanichskul S. A comparative efficacy of low-dose combined oral contraceptives containing desogestrel and drospirenone in premenstrual symptoms. *Obstet Gynecol Int*. 2013;2013:487143. doi: 10.1155/2013/487143. Epub 2013 Feb 20.
18. Fu Y<sup>1</sup>, Mi W, Li L, Zhang H<sup>2</sup>, Wang J, Cheng W, Sun L, Li L, Xie S, Zhang J. [Efficacy and safety of a combined oral contraceptive containing drospirenone 3 mg and ethinylestradiol 20 µg in the treatment of premenstrual dysphoric disorder: a randomized, double blind placebo-controlled study]. [Article in Chinese] *Zhonghua Fu Chan Ke Za Zhi*. 2014 Jul;49(7):506-9.

19. Arowojolu AO<sup>1</sup>, Gallo MF, Lopez LM, Grimes DA. Combined oral contraceptive pills for treatment of acne. *Cochrane Database Syst Rev.* 2012 Jul 11;7:CD004425. doi:10.1002/14651858.CD004425.pub6.
20. Koltun W<sup>1</sup>, Maloney JM, Marr J, Kunz M. Treatment of moderate acne vulgaris using a combined oral contraceptive containing ethinylestradiol 20 µg plus drospirenone 3mg administered in a 24/4 regimen: a pooled analysis. *Eur J Obstet Gynecol Reprod Biol.* 2011 Apr;155(2):171-5. doi: 10.1016/j.ejogrb.2010.12.027. Epub 2011 Feb 2.
21. Palli MB<sup>1</sup>, Reyes-Habito CM, Lima XT, Kimball AB. A single-center, randomized double-blind, parallel-group study to examine the safety and efficacy of 3mg drospirenone/0.02 mg ethinyl estradiol compared with placebo in the treatment of moderate truncal acne vulgaris. *J Drugs Dermatol.* 2013 Jun 1;12(6):633-7.
22. Joish VN<sup>1</sup>, Boklage S, Lynen R, Schmidt A, Lin J. Use of drospirenone/ethinyl estradiol (DRSP/EE) among women with acne reduces acne treatment-related resources. *J Med Econ.* 2011;14(6):681-9. doi: 10.3111/13696998.2011.617803. Epub 2011 Sep 5.