FSRH CEU new product review: Drovelis® estetrol/drospirenone combined oral contraceptive

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Introduction

A new combined oral contraceptive (COC), Drovelis® is brought to the UK market by Gedeon Richter on 24/10/22.

Drovelis is a cyclical regimen of 24 daily active tablets (pink) containing estetrol 14.2mg and drospirenone 3mg, followed by 4 daily inactive tablets (white).

Estetrol (E4) is a new active substance (which means that it has not previously been used in licensed contraceptives or menopausal hormone therapy. E4 is an estrogen produced by the fetal liver and present in maternal serum during pregnancy. It is 10-20 times less potent than ethinylestradiol (EE) and is also less potent than estradiol (E2). (E4 in Drovelis is manufactured but is identical to the natural estetrol molecule).

Drospirenone (DRSP) is a synthetic progestogen already used for contraception at a dose of 3mg in combination with EE, and more recently as a 4mg progestogen-only pill. DRSP effectively suppresses ovulation. It also has antimineralocorticoid and mild antiandrogenic activity.

Like other COCs, the main mechanism of contraceptive action of the E4/DRSP COC is suppression of ovulation.

What studies are relevant?

Phase II studies informed E4 dose and choice of progestogen required to achieve ovarian suppression and to optimise bleeding pattern and tolerability. Effect on haemostatic parameters, lipids and glycaemic control was investigated and comparison was made with existing COCs.[1,2,3]

Two subsequent large, multicentre, single arm phase III studies [4, 5] have reported on contraceptive effectiveness, bleeding pattern, safety and side effects. These studies investigated 1553 subjects aged 18-50 in Europe and Russia[4], and 1864 subjects aged 16-50 in the USA and Canada[5] who used E4/DRSP for up to 13 cycles. The studies (which did not compare E4/DRSP with other COCs) together contribute data for a total of 2735 observed woman-years (35,677 cycles) of use of E4/DRSP.

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How does Drovelis compare to existing combined hormonal contraceptives?

Contraceptive effectiveness

Key information: Ovarian suppression by E4/DRSP and reported Pearl Indices are similar to those with other combined hormonal contraceptives.

Evidence

A phase II randomised controlled trial[6] of 82 subjects compared E4/DRSP to EE20mcg/DRSP over 3 cycles of use, demonstrating similar suppression of ovarian function in the two groups. In the E4/DRSP group, the earliest return to ovulation in the post-treatment cycle occurred 9 days after the last (placebo) tablet (the majority ovulated at day 12-15).

The European/Russian phase III study[4] observed 5 on-treatment pregnancies, all in subjects aged 18-35. The overall Pearl Index was 0.42 (CI^{95} 0.14 - 0.99) for those aged 18-35. Method failure rate (representing perfect use) in this study was 0.29 (CI^{95} 0.06 - 0.83) per 100 woman- years.

In the US/Canadian study phase III study[5], there were 28 on-treatment pregnancies. Overall Pearl Index for users aged 16-35 was 2.19 (CI^{95} 1.43 - 3.2). Method failure Pearl Index was 1.43 (CI^{95} 0.78 – 2.39).

As is often the case in studies of user-dependent contraception, Pearl Indices in the US study are higher than in the European study. There is lower reported adherence to correct use in the US/Canadian study, but other contributing factors are unidentified.

Pooling the data from the two phase III studies, the Pearl Index for E4/DRSP in 16-35 year olds is 1.52 (1.04 – 2.16) pregnancies per 100 woman-years based on a total of 26,455 cycles of use by 2,837 subjects. The pooled Pearl Index for method failure (reflecting pregnancy risk with perfect use) is 0.84 (CI^{95} 0.49 – 1.34) for subjects aged 16-35.[7]

Safety

Key information: The available evidence suggests that E4/DRSP COC has a comparable safety profile to that of other COCs. Use of combined hormonal contraception is associated with increased risk of venous thromboembolism (VTE) and arterial thrombotic events. The evidence is too limited to inform whether there is any significant difference in risk between the COC containing E4 and those containing EE or E2.

Evidence

Evidence suggests that COC containing E4 could (at least at lower doses) have a more neutral effect on haemostasis, lipid profile, SHBG, cortisol binding globulin and thyroid binding globulin and angiotensinogen than COC containing EE.[8,9,10,11,12] Further evidence would be required to inform whether this is of clinical relevance.

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In the single arm phase III studies of E4/DRSP[4,5], only one VTE event was observed. There were no incident myocardial infarctions or cerebrovascular accidents. As the incidence of these significant health

events amongst women of reproductive age is low, very large comparative studies would be required to give robust evidence regarding the effect of E4/DRSP on risk and to allow comparison with other COC.

Endometrial suppression is maintained during use of E4/DRSP.[6]

DRSP is an aldosterone antagonist and could affect serum potassium. Drovelis has not been studied in users with renal disease, but the manufacturer advises avoiding use by individuals with severe renal impairment or acute renal failure.

Bleeding pattern

Key information: Bleeding patterns during established use of E4/DRSP appear similar to those with other COC.

Evidence

The European/Russian phase III study[4] reported scheduled bleeds starting during or just after the placebo pills in 92-94% of users, with unscheduled bleeding in 19.2% at cycle 2 and 12.8% at cycle 11. In the US/Canadian phase III study[5], most established users of E4/DRSP experienced scheduled withdrawal bleeding/spotting lasting about 5 days. About 15% per cycle reported absence of the withdrawal bleed. Unscheduled bleeding or spotting (the majority was spotting) was reported by about 15-20% of established users. Discontinuation due to bleeding was 2.6%.

Side effects

In the published studies, reported side effects, similar to those with other COC, include irregular bleeding, acne, headache, mastalgia, emotional lability and weight gain. In the European/Russian phase III study[4], 9.1% discontinued because of apparent side effects of E4/DRSP.

Drug interaction

Key information: As with other CHC, the contraceptive effectiveness of E4/DRSP could be reduced by concurrent use of enzyme-inducing drugs.

E4 is metabolised chiefly by glucuronidation and exposure could be affected by use of drugs that induce glucuronidation. Cytochrome P450 appears not to play a role in E4 metabolism. Metabolism of, and exposure to DRSP are, however, dependent on cytochrome P450 activity.

Other excipients

Like other oral contraceptives, Drovelis contains lactose derived from milk and magnesium stearate (may be of animal origin). See the Summary of Product Characteristics at Drovelis 3 mg/14.2 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

FSRH CEU Conclusion and Guidance

Drovelis® E4/DRSP COC offers (user-dependent) contraceptive effectiveness comparable to that of other combined hormonal contraceptives. The limited evidence available suggests similar safety profile, bleeding pattern and side effects to existing combined oral contraceptives. It is hoped that the ongoing International Active Surveillance Study which will report at 1 and 7.5 years will provide further evidence and may help to clarify whether the apparent lesser effect of E4-containing COC on e.g. haemostatic parameters impacts on associated health outcomes, particularly thrombotic risk.

Medical eligibility: FSRH CEU advises that UKMEC recommendations relating to medical eligibility for use of combined hormonal contraception apply also to Drovelis. (see UKMEC 2016 at UKMEC April 2016 (Amended September 2019) - Faculty of Sexual and Reproductive Healthcare (fsrh.org)). Users should be advised about potential associated health risks including venous thromboembolism as for all combined hormonal contraceptives. DRSP is an aldosterone antagonist that could increase serum potassium. No studies have been undertaken in users with renal impairment, but the manufacturer advises avoiding use by individuals with severe renal impairment or acute renal failure.

Starting Drovelis, correct use and managing missed pills: If Drovelis is started on Day 1 of a natural menstrual cycle no additional contraceptive precautions are required. As with estradiol-containing COCs if Drovelis is quick started after Day 1, additional contraceptive precautions are required for 7 days. See the Summary of Product Characteristics at Drovelis 3 mg/14.2 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)).

Pills should be taken daily without a break (the 4 inactive pills confer a hormone-free interval). A pill is missed when it is taken >24 hours late. The manufacturer-recommended missed pill rules should be followed (see the Summary of Product Characteristics at Drovelis 3 mg/14.2 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)).

Useful links

See the full European Medicines Agency report on Drovelis at Drovelis, INN-drospirenone/estetrol (europa.eu)

See the Summary of Product characteristics for Drovelis Drovelis 3 mg/14.2 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

See the Patient Information for Drovelis Drovelis 3 mg/14.2 mg film-coated tablets - Patient Information Leaflet (PIL) - (emc) (medicines.org.uk)

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The Clinical Effectiveness Unit (CEU) was formed to support the Clinical Effectiveness Committee of the Faculty of Sexual and Reproductive Healthcare (FSRH), the largest UK professional membership organisation working at the heart of sexual and reproductive healthcare. The CEU promotes evidence based clinical practice and it is fully funded by the FSRH through membership fees. It is based in Edinburgh and it provides a member's enquiry service, evidence based guidance, new SRH product reviews and clinical audit/research. *Find out more here.*