Faculty of Sexual and Reproductive Healthcare
Clinical Effectiveness Unit

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FACULTY STATEMENT FROM THE CLINICAL EFFECTIVENESS UNIT

The estradiol valerate / dienogest combined pill, Qlaira®

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Summary

Qlaira® (Bayer Schering Pharma) is a combined oral contraceptive (COC) recently launched in the UK. It is the first COC to contain estradiol valerate which is metabolised to estradiol, an estrogen hormone that also exists naturally in the human body. Qlaira's complex, quadraphasic dosage regimen was designed to give optimal cycle control. The continuous 28-day cycle consists of 26 active tablets with a sequence of reducing estrogen and increasing progestogen dose, followed by 2 placebo tablets (table 1).

Clinical trials suggest that Qlaira is as effective as other combined pills and has similar cycle control to a low dose (20μg) COC. Qlaira has different missed pill rules and is priced at a higher cost than any of the COCs currently available in the UK.

The introduction of Qlaira to the UK market provides additional choice for women seeking hormonal contraception. The concept of a natural estrogen pill may appeal to some women but there is currently no evidence of clinically significant benefits over pills containing synthetic estrogen. Until further data emerge the indications and contraindications to use of Qlaira must be assumed to be the same as for other combined hormonal contraceptives.

Further Information

Content

In addition to being the first combined oral contraceptive pill to contain estradiol valerate (E2V), Qlaira is the first pill within the UK to contain the synthetic progestogen dienogest (DNG). Dienogest has anti-androgenic activity of approximately one third of that of cyproterone acetate. It has no significant mineralocorticoid or glucocorticoid activity.[1] A COC containing dienogest has been available for more than 10 years in countries outside the UK.

Table 1 Contents and order of pills contained in each wallet of Qlaira

Number of pills	Colour	Estradiol Valerate (mg)	Dienogest (mg)
2	Dark yellow	3	0
5	Medium red	2	2
17	Light yellow	2	3
2	Dark red	1	0
2	White	0	0

Evidence Reviewed

Efficacy

In a large open label European study, the adjusted (per protocol) Pearl Index for Qlaira users was 0.34 failures per 100 women-years in subjects aged 18-50 years, and 0.4 in those aged 18-35 years.[2] These failure rates are similar to those reported for COCs containing ethinylestradiol.[3]

Benefits

In theory, a COC containing estradiol may be less likely to cause the alterations in lipid metabolism, coagulation factors and glucose regulation that are seen with COCs containing synthetic estrogen. Theoretically, Qlaira may also be less likely to cause side-effects such as mood change and headache that occur due to estrogen withdrawal in the pill-free week of traditional 21/7 COC formulations.

Currently, the evidence for any actual advantages of Qlaira over other COCs is very limited. Some comparative studies have demonstrated smaller changes in lipid profiles, haemostatic variables and levels of sex hormone binding globulin with Qlaira than with COCs containing ethinylestradiol (EE).[2;4] However, most values have been within the normal range for both COC groups, and most differences between groups have been statistically non-significant. One study has shown a significantly smaller intra-individual rise in D-dimer levels with Qlaira than with Microgynon ($p=0.01$), but the clinical relevance of this finding is unknown.[5]

Pharmacokinetic studies show stable levels of estradiol throughout the cycle of Qlaira users.[6] Clinical trial data suggest that side effects and tolerability are comparable to those of other COCs. In a randomised double-blind study comparing Qlaira to a combined pill containing 20μg EE and 100μg levonorgestrel (LNG), there were significantly fewer bleeding and spotting days amongst those who received E2V/DNG compared with those who received EE/LNG ($p<0.001$).[7] Qlaira users had significantly fewer scheduled withdrawal bleeds, with 77.7-83.2% per cycle in the E2V/DNG group compared with 89.5-93.8% in the EE/LNG group ($p<0.0001$).[7] The absence of withdrawal bleeding may be seen as a disadvantage or advantage by different women. Studies are underway to examine the effect of Qlaira on dysfunctional bleeding and dysmenorrhoea, and to compare Qlaira to a COC containing 30μg EE.[8]

Risks

No epidemiological data have been reported on the effects of COCs containing estradiol. Although estradiol valerate is also found in some hormone replacement therapy (HRT) preparations, the risks that are associated with HRT use do not necessarily apply to the younger, premenopausal population of women who use the COC. Currently the risks and benefits of taking Qlaira have to be assumed to be the same as for other COCs and, therefore, the UK Medical Eligibility Criteria for Contraceptive Use (UKMEC)[9] categories for combined hormonal contraceptives also apply to Qlaira.

Manufacturer's Instructions for Use of Qlaira[1]

Starting regimen

There is no need for additional contraception if Qlaira is started:

- On the first day of menses
- On the day after the last active tablet of a previous combined oral contraception
- On the day a combined patch or combined vaginal ring is removed
- Immediately post termination or miscarriage
- On day 21-28 following delivery or second trimester termination

An individual should be advised to refrain from sexual intercourse or use condoms for **9** days* if Qlaira is started:

- Any day after day 1 of menses (if it is reasonably certain that she is not pregnant)
- Any day when changing from a progestogen-only method
- Any day after the first day post termination or miscarriage
- After day 28 onwards following delivery or second trimester termination

*This differs to other COCs where additional protection is recommended for 7 days

Missed Pills (Principles if missing one pill for more than 12 hours)

Day 1-17 Take missed pill immediately and the next tablet at the usual time (even if means taking two on same day)
Continue with the tablet taking in the normal way
Abstain or use an additional contraceptive method for **9** days

Day 18-24 Discard the rest of the packet
Start taking the Day 1 pill from a new packet immediately and continue taking these pills at the correct time
Abstain or use an additional contraceptive method for **9** days

Day 25-26 Take the missed tablet immediately and the next tablet at the usual time (even if it means taking two tablets on the same day)
Additional contraception is not necessary

Day 27-28 Discard the forgotten table and continue tablet taking in the normal way.
Additional contraception is not necessary.

No more than two tablets are to be taken in any one day. If a woman has forgotten to start a new wallet or if she has missed one or more tablets during Day 3-9 of the wallet she may already be pregnant (provided she has had intercourse in the 7 days before the missed pills). The more tablets (of those with two combined active ingredients on day 3-24) that are missed and the closer they are to the placebo tablet phase, the higher the risk of pregnancy.

Cost

The cost per cycle to the NHS is £8.39.[10] This is considerably more expensive than other COCs which currently range in price from £0.90 to £4.90.[11]

References

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(8) Bayer Healthcare, Bayer Schering Pharma. Qlaira (E2V/DNG). Early Planning Notification for NHS Budget Policy Decision Makers. 2009.

(9) Faculty of Sexual and Reproductive Health Care. UK Medical Eligibility Criteria for Contraceptive Use (UKMEC 2009) In press. 2009.

(10) New Medicines: Qlaira. Pharmaceutical Journal 2009; 282: 609.

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