

# NEW DRUG EVALUATION

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## QLAIRA

**Qlaira is a novel combined oral contraceptive (COC) for continuous administration, with a complex quadriphasic dose regimen. It is the first COC to combine the oestrogen estradiol valerate and the progestogen dienogest. Contraceptive efficacy, side-effects and tolerability appear to be similar to other COCs. Withdrawal bleeding occurred less often and was less predictable with Qlaira than with a very low dose ethinylestradiol COC, although breakthrough bleeding rates were similar. There are no long term safety data available. Qlaira is significantly more expensive than other COCs and there is currently no evidence of clinically significant benefits over alternatives.**

### What is it?

Qlaira is a new combined oral contraceptive (COC).<sup>1</sup> It is one of only two COCs available worldwide to contain the 'natural' oestrogen estradiol valerate, and the first in the UK with the antiandrogenic progestogen dienogest.<sup>2</sup> Previous attempts to develop estradiol-based COCs have been hampered by unacceptable bleeding.<sup>3</sup>

### How effective is it?

The Public Assessment Report (PAR) produced by the Medicines Evaluation Board in the Netherlands refers to three trials of contraceptive efficacy, only one of which has been fully published.<sup>3-6</sup> Studies ranged in duration from seven to 20 cycles. Only one had an active comparator arm; the other two were of open-label, non-comparator design. Two of the trials enrolled healthy women aged 18-50 years; the third enrolled healthy women aged 18-35 years.<sup>3-6</sup> Inclusion and exclusion criteria were otherwise similar. Contraceptive efficacy is assessed using the Pearl Index (PI), a statistical estimate of the number of unintended pregnancies per 100 women-years of use.<sup>7</sup> The unadjusted PI includes all pregnancies and all cycles of contraceptive use except those in which additional barrier methods have been used. The adjusted PI (or PI for method failure) excludes pregnancies that can be reliably attributed to non-compliance and associated cycles.<sup>8,9</sup>

The unadjusted and adjusted PIs for women aged 18-35 based on pooled data from all three studies were 1.01 (upper limit of 95% CI = 1.59) and 0.51 (UL CI = 0.97), respectively.<sup>4</sup> The SPC quotes an adjusted PI for women aged 18-50 of 0.42 (UL CI = 0.77).<sup>1</sup>

These values are within the range quoted for COCs in general,<sup>5</sup> but the PAR notes that the trial data suggest lower contraceptive efficacy for Qlaira than for approved second and third generation standard dose ethinylestradiol COCs.<sup>4</sup> However, indirect comparisons of contraceptive efficacy may not be reliable, due to possible differences between populations and the effect of trial duration.<sup>7,8</sup> Particular difficulties arise for the Qlaira trials, as the age range (and thus fertility) of participants differs from the norm (usually 18-40 or 18-45).<sup>4</sup>

Reliable control of uterine bleeding is regarded as an additional aim of COC use, and irregular intracyclic

(breakthrough) bleeding as a significant undesirable effect.<sup>10</sup> Bleeding irregularities are the principal reason given for women discontinuing COCs.<sup>11</sup> Cycle and bleeding pattern control were investigated over seven cycles (two 90 day periods) in a study comparing Qlaira with a very low dose monophasic ethinylestradiol/levonorgestrel combination (EE 20 µg /LNG 100 µg – a lower dose of progestogen than currently available in the UK).<sup>3,4,12</sup> Lower doses of both oestrogen and progestogen components of COCs may be associated with increased levels of intracyclic bleeding.<sup>10,13,14</sup>

The proportion of women experiencing intracyclic bleeding per cycle and the maximum intensity of that bleeding was similar in the Qlaira and comparator groups ( $p > 0.05$ ). Intracyclic bleeding with Qlaira and the comparator occurred in approximately 14% (range 10.5-18.6%) and 12% (9.9-17.1%) of women per cycle, respectively.

Over seven cycles, the proportion of women experiencing withdrawal bleeding per cycle ranged from 77.7-83.2% for Qlaira and from 89.5-93.8% for the comparator ( $p < 0.0001$  in each cycle). The mean proportions of women who did not experience a withdrawal bleed were 19.4% and 7.7% per cycle, respectively.<sup>3</sup> Scheduled withdrawal bleeds were also shorter with Qlaira (mean length = 4.1-4.7 vs. 5.0-5.2 days,  $p < 0.05$ ). Accordingly, women taking Qlaira reported fewer bleeding and spotting days ( $p < 0.0001$ ) and episodes ( $p < 0.0001$  to  $p < 0.05$ ) in each of the 90 day reference periods.

### How safe is it?

In the active comparator trial, 3.3% of women in either group discontinued treatment due to adverse effects.<sup>3</sup> There were no discontinuations due to bleeding disorders. The rates of drug related adverse events occurring in  $\geq 1\%$  of women were:

Adverse Event [N (%)]	Qlaira (N=399)	EE/LNG (N=399)
breast pain	13 (3.3)	4 (1.0)
headache	7 (1.8)	7 (1.8)
acne	5 (1.3)	9 (2.3)
alopecia	3 (0.8)	4 (1.0)
migraine	2 (0.5)	5 (1.3)
↑ body weight	2 (0.5)	4 (1.0)

Pooled analysis of two of the three efficacy trials revealed 65 serious adverse events effecting 48 out of a total of 1,776 women treated with Qlaira, five of which were classified as possibly drug-related.<sup>4</sup> Overall, the pattern of serious adverse events in these short-term trials did not differ from that seen with other COCs.<sup>5,6</sup> There are no longer term safety data and the relative risks of venous thromboembolism, breast and cervical cancer with this novel combination of hormones remain to be established.

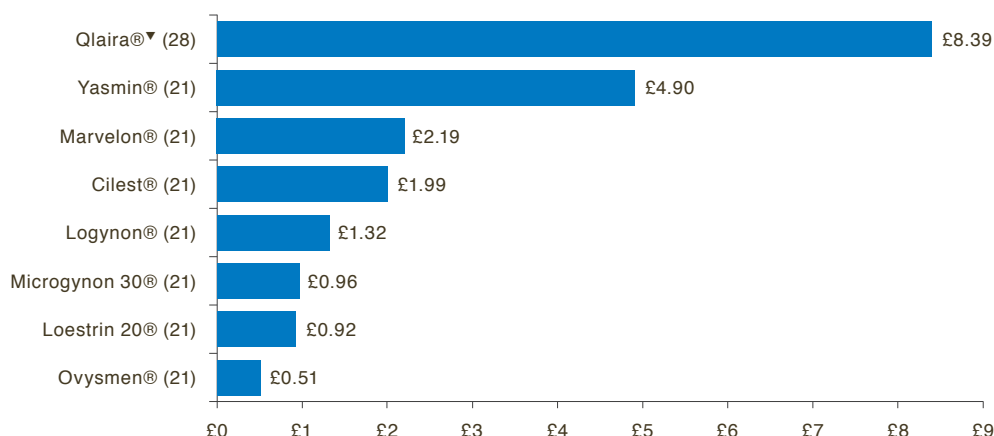
All suspected adverse reactions to black triangle drugs such as Qlaira should be reported to the MHRA via the Yellow Card Scheme ([www.yellowcard.gov.uk](http://www.yellowcard.gov.uk)).

### What other options are there?

Faculty of Sexual and Reproductive Healthcare (FSRH) guidance on first prescription of COC recommends a monophasic COC containing 30 µg EE with norethisterone or levonorgestrel as a suitable first pill.<sup>15</sup> Although unlicensed, FSRH guidelines suggest advising women to 'tricycle' COCs to prevent or delay withdrawal bleeding or to reduce adverse effects associated with oestrogen

### How much does it cost?

Cost of 28 days treatment (Drug Tariff/dm+d October 2009)



N.B. Doses shown are for general comparison only and do not imply therapeutic equivalence

withdrawal.<sup>15</sup> NICE guidance on long-acting reversible contraception (LARC) emphasises that all LARC methods are more cost-effective than COCs and that increased uptake of LARC will reduce unintended pregnancies.<sup>16</sup>

### When should it be used?

In the absence of evidence to the contrary, the risks and benefits of Qlaira, and the indications and contraindications, are assumed to be the same as for other COCs, and UK Medical Eligibility Criteria for Contraceptive Use (UKMEC) categories assumed to apply.<sup>17,18</sup>

Qlaira offers an additional – more expensive – COC choice, which may reduce the likelihood of withdrawal bleeding, which some women may perceive as an advantage. Pregnancy must be ruled out if the first absence follows imperfect use or if withdrawal bleeding is missed in two consecutive cycles.<sup>1</sup> Standard missed pill guidance does not apply and some women may have difficulty with the manufacturer's advice.<sup>1,19</sup> There is currently no evidence of clinically significant benefits of Qlaira over other COCs and no data on long-term safety is available.

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KEY RCT-randomised controlled trial, G-Guidance, O-Open study, MA-Meta analysis, R-Review, Abs - abstract, E - Editorial.

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