UKMi UK Medicines Information

New Medicines Profile

NHS

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Qlaira

Concise evaluated information to support the managed entry of new medicines in the NHS

Summary

- 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 appears to be similar to that reported for other COCs.
- Clinical trial data suggest that side effects and tolerability are also comparable to those of other COCs.
- Fewer women experienced withdrawal bleeding with Qlaira than with a low dose ethinylestradiol and levonorgestrel comparator. Individual women may perceive this as either an advantage or disadvantage. Pregnancy should be ruled out if withdrawal bleeding is missed in two consecutive cycles.
- There are no long term safety data for Qlaira.
- Qlaira is significantly more expensive than other COCs and there is currently no evidence of clinically significant benefits over ethinylestradiol containing alternatives.
- The starting regimen for Qlaira differs slightly from that recommended for other COCs.
- Standard guidance on missed pills cannot be applied to Qlaira and the manufacturer's advice is complex.

Brand Name, (Manufacturer): Qlaira®▼, (Bayer)

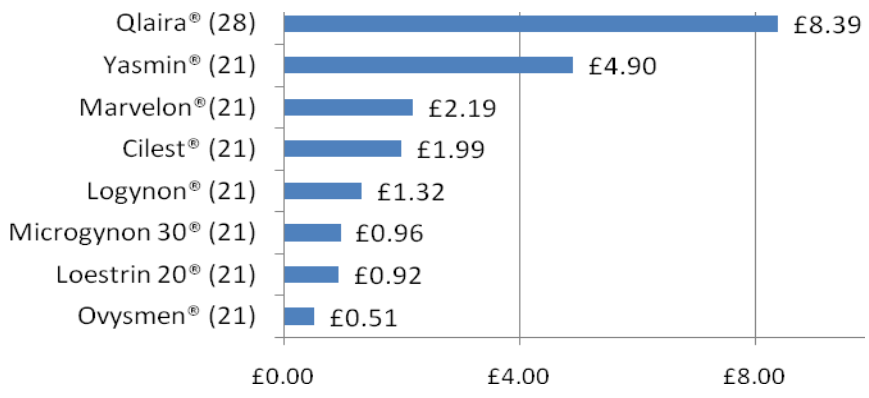
BNF Therapeutic Class: 7.3.1 Combined hormonal contraceptives

Licensed Indications: Oral contraception

Dosage and Administration: One tablet daily for 28 days, subsequent packs to be started without a pill-free break. There are five different tablet types per 28 day cycle (see Appendix I), including two placebo tablets, and use is continuous.

Marketed: May 2009

Cost Comparisons: Cost for 28 days treatment (prices from NHS dictionary of medicines & devices October 2009)



NB. Doses shown for general comparison and do not imply therapeutic equivalence

Introduction

Qlaira is a new combined oral contraceptive (COC).[1] 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.[2] Previous attempts to develop estradiol based COCs have been hampered by unacceptable bleeding.[3]

Evidence

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.[3-6] 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.[3-6] Inclusion and exclusion criteria were otherwise similar (Appendix I). Contraceptive efficacy was assessed using the Pearl Index (see box).

Pearl Index (PI)[7]

A statistical estimate of the number of unintended pregnancies per 100 women-years of use.

Unadjusted PI – includes all pregnancies and all cycles of contraceptive use except those in which additional barrier methods have been used.

Adjusted PI (or PI for method failure) – excludes pregnancies that can be reliably attributed to non-compliance and associated cycles.[8,9]

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.[4] The SmPC quotes an adjusted PI for women aged 18-50 of 0.42 (UL CI = 0.77).

These values are within the range quoted for COCs in general,[5] 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.[4] However, indirect comparisons of contraceptive efficacy may not be reliable, due to possible differences between populations and the effect of trial duration.[7,8] Particular difficulties arise for the Qlaira trials, as the age range (and thus fertility) of participants differs from the norm. Figures are usually calculated for the age ranges 18-40 or 18-45, rather than the 18-35 or 18-50 data provided for Qlaira.[4]

Reliable control of uterine bleeding is regarded as an additional aim of COC use, and irregular intracyclic (breakthrough) bleeding as a significant undesirable effect.[10] Bleeding irregularities are the principal reason given for women discontinuing COCs.[11] Cycle and bleeding pattern control with Qlaira was investigated over seven cycles (two 90 day periods) in an active comparator study.[3,4] Qlaira was compared 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[12]). Lower doses of both oestrogen and progestogen components of COCs may be associated with increased levels of intracyclic bleeding.[10,13,14]

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 approximatly 14% (range 10.5-18.6%) and 12% (9.9-17.1%) of women per cycle, respectively.

Women taking Qlaira experienced fewer scheduled withdrawal bleeds than those taking the comparator ($p<0.0001$). 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.[3] 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.

Safety

Pooled analysis of two of the three efficacy trials revealed 65 serious adverse events effecting 48 out of a total of 1776 women treated with Qlaira, five of which were classified as possibly drug-related.[4] Overall, the pattern of serious adverse events in these short-term trials did not differ from that seen with other COCs.[5,6] 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.

In the active comparator trial, 3.3% of women in either group discontinued treatment due to adverse effects.[3] There were no discontinuations due to bleeding disorders. Table 1 shows the rates of drug related adverse events occurring in ≥ 1% of women.

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)

NHS Impact

The Office of National Statistics estimate that 18% of women in the UK aged 16-49 were using COCs during 2007/08.[15] 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.[16] Although unlicensed, FSRH guidelines suggest advising women to 'tricycle' COCs to prevent or delay withdrawal bleeding or to reduce adverse effects associated with oestrogen withdrawal.[16] 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.[17]

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 Elligibility Criteria for Contraceptive Use (UKMEC) categories assumed to apply.[18,19]

Qlaira offers an additional – more expensive – COC choice, which may reduce the likelihood of withdrawal bleeding. Some women may perceive this as an advantage, whereas others may see it as a disadvantage. Pregnancy must be ruled out if the first absence follows imperfect use or if withdrawal bleeding is missed in two consecutive cycles.[1] There is currently no evidence of clinically significant benefits over other COCs

Appendix I: Table of Key Clinical Trials

Risk Management Issues:

Standard Missed Pill guidance does not apply.[1,20] Advice in the SPC is complex, with four different courses of action – according to point in the cycle. Unique starting regimen.[1]

Produced for the UK Medicines Information Service

By Regional Drug & Therapeutics Centre, Newcastle upon Tyne

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Key papers are highlighted in bold

Appendix I

Table 1: Key Trials

<table>
<tr><th>Ref No</th><th>Trial Design</th><th>Trial Population</th><th>Treatment</th><th>Primary Outcomes</th></tr>
<tr><td>4 & 3

Trial A35644 in PAR</td><td>Multi-centre, double blind, double dummy, randomised.</td><td>798 healthy women aged 18-50 years. Cigarette consumption up to 10 per day permitted up to age 30. Smokers aged >30 years excluded.
Other exclusion criteria:
Pregnancy; lactation; < 3 menstrual cycles following childbirth, abortion or lactation; current use of IUD; BMI > 30kg/m^2; use of long-acting progestins within 6 months prior to study entry; hypersensitivity to any of the stud drug ingredients and known or suspected malignant or pre-malignant disease.</td><td>Qlaira
[Estradiol valerate (E2V) 3mg on days 1-2, E2V 2mg/Dienogest (DNG) 2mg on days 3-7, E2V 2mg/DNG 3mg on days 8-24, E2V 1mg on days 25-36 and placebo on days 27-28]
OR
Comparator
[Ethinyl estradiol 20 micrograms / levonorgestrel 100 micrograms (EE/LNG) on days 1-21 and placebo on days 22-28].
Participants received 7-cycles of treatment.</td><td>Intracyclic bleeding incidence: Qlaira = 10.5-18.6%; Comparator = 9.9-17.1% (p>0.05).
Proportion of women experiencing scheduled withdrawal bleeding per cycle: Qlaira = 77.7-83.2%; Comparator = 89.5-93.8% (p<0.0001).
<table>
<tr><td></td><td colspan="2">Bleeding/spotting days
Mean ± SD (95% CI)</td><td colspan="2">Bleeding/spotting episodes
Mean ± SD (95% CI)</td></tr>
<tr><td>Reference Period</td><td>Qlaira (n=399)</td><td>Comparator (n=399)</td><td>Qlaira (n=399)</td><td>Comparator (n=399)</td></tr>
<tr><td>Period 1 (days 1-90)</td><td>17.3±10.4 (16.3 – 18.3)</td><td>21.5±8.6 (20.6 – 22.3)</td><td>17.3±10.4 (16.3 – 18.3)</td><td>21.5±8.6 (20.6 – 22.3)</td></tr>
<tr><td>Period 2 (days 91-180)</td><td>13.4±9 (12.4 – 14.3)</td><td>15.9±7 (15.2 – 16.6)</td><td>13.4±9 (12.4 – 14.3)</td><td>15.9±7 (15.2 – 16.6)</td></tr>
</table>
Satisfaction rating
Somewhat or very satisfied: Qlaira = 79.4%; Comparator = 79.9%.
Very satisfied: Qlaira = 39.8%; Comparator = 35.3%.</td></tr>
<tr><td>4 & 6

Trial A35179 in PAR</td><td>Open-label, multicentre, uncontrolled non-comparative study.</td><td>1377 healthy women aged 18-50 years. Smokers aged >30 years excluded. Women with undiagnosed vaginal bleeding excluded. Other exclusion criteria focussed on pregnancy, lactation, liver disease, vascular disease, uncontrolled thyroid disorder, uncontrolled hypertension, diabetes mellitus, tumors (known or suspected), other severe diseases that might interfere, substantial overweight, prohibited concomitant medication.</td><td>Qlaira taken continuously for 20 cycles, with the interval between tablets as close to 24hours as possible.</td><td>13 pregnancies occurred during 23,368 cycles. 6 of these were attributed to method failure. 12 of the pregnancies occurred in women aged 18-35years (5 attributed to method failure).
<table>
<tr><td>Age Group</td><td>Unadjusted Pearl Index (upper limit of 95% CI)</td><td>Adjusted Pearl Index (upper limit of 95% CI)</td><td>Kaplan-Meier estimate for cumulative failure rate over 20 cycles (95% CI)</td></tr>
<tr><td>18-35 years</td><td>0.94 (1.65)</td><td>0.40 (0.92)</td><td>0.0142 (0.0080-0.0251)</td></tr>
<tr><td>18-50 years</td><td>0.73 (1.24)</td><td>0.34 (0.73)</td><td>0.0109 (0.0063-0.0188)</td></tr>
</table></td></tr>
<tr><td>4 & 5

Trial A39818 in PAR</td><td>Open-label, multicentre, uncontrolled non-comparative study.</td><td>490 women aged 18-35years. Smokers aged >30 years excluded. Other exclusions as per contraindications.</td><td>Qlaira taken continuously for 13 cycles, with the interval between tablets as close to 24hours as possible.</td><td>Number of unintended pregnancies during treatment –presented as unadjusted and adjusted Pearl indices and Kaplan-Meier survival curves.
Unadjusted Pearl Index for women aged 18-35 years = 1.45 (upper limit 95% CI 3.16). Adjusted Pearl Index (Method Failure) = 1.00 (upper limit 95% CI 2.57).</td></tr>
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