Faculty of Sexual & Reproductive Healthcare

FACULTY STATEMENT FROM THE CLINICAL EFFECTIVENESS UNIT

Estradiol/Nomegestrol Combined Pill, Zoely©

May 2013

Product Summary

Description

- Combined oral contraceptive pill licensed for contraceptive use
- Contains 1.5 mg estradiol (as hemihydrate) and 2.5 mg nomegestrol acetate (NOMAC) per active tablet

Administration and Use

- 28 tablets as 24/4 regimen with no pill free interval
- One white active tablet daily for 24 days
- One yellow placebo (inactive) tablet daily for 4 days

Pharmacology

- 17β-estradiol is identical to the endogenous human estrogen 17β-estradiol.
- Nomegestrol acetate (NOMAC) is a progestogen with strong affinity for the human progesterone receptor, strong anti-gonadotrophic and mild anti-androgenic activity

Efficacy

- Randomised studies suggest that efficacy is comparable to that of the combined oral contraceptive containing drospirenone and ethinylestradiol
- Pearl Index for intention to treat (ITT) use in women ≤ 35 years 0.38 (95% CI 0.1-0.97)

Compliance

- 85-95% compliance reported in clinical trials

Tolerability and acceptability

- Shorter and lighter withdrawal bleeding and higher incidence of absent withdrawal bleeds than EE/DRSP preparations in comparative randomized controlled trials
- Similar rates of unscheduled bleeding to other COCs
- Acne improvement
- Some withdrawal from trials due to weight gain, acne and lack of withdrawal bleeding

Safety

- Frequency and type of adverse events typical for COC
- Smaller effect on lipid and carbohydrate metabolism, haemostatic parameters and markers of endocrine function than established COC
- Clinical relevance of metabolic/haemostatic effects still to be established

Cost

- £5.50 per month

Background
The combined oral contraceptive Zoely® (Merck, Sharp, and Dohme Limited) has been licensed in Europe since 2011 and will be available in the UK from May 2013. Zoely will be the second UK combined oral contraceptive (COC) to contain estradiol and to be formulated as an extended regimen since the introduction of Qlaira® (Bayer plc.) in 2009.[1] Qlaira has a quadraphasic dosage regimen, whereas Zoely will be the first monophasic estradiol pill.

Zoely contains 1.5mg 17β-estradiol (as hemihydrate), a synthetically produced estrogen identical to natural human 17β-estradiol (E2); and 2.5mg nomegestrol acetate (NOMAC).[2] NOMAC is a progestogen derived from 19-norprogesterone. It has strong affinity for the progesterone receptor, strong antigonadotrophic and mild antiandrogenic activity with no estrogenic, androgenic, glucocorticoid or mineralocorticoid activity.[3]

Clinical trial data is limited, and much of the research has been funded by the pharmaceutical industry. Trials have been "open-label" and approximately one-third of participants have been using some other form of combined hormonal contraception (CHC) at the time of recruitment.

Ethinylestradiol, the synthetic estrogen most commonly used in COCs, is associated with alterations in hepatic metabolism and haemostasis. Therefore, COCs containing natural estrogen are potentially safer and more acceptable. NOMAC also has theoretical advantages in that it is structurally similar to natural human progesterone, is highly selective, and has a longer half-life than the progestogens used in other COCs[4]. From the preliminary studies described below there is some evidence of a lack of effect on haemostatic and metabolic variables. However, this has not been shown to be clinically relevant and further large scale clinical trials are required before any benefits over other COCs can be established.

How does Zoely® work?
As with other CHC methods, the primary mode of action is inhibition of ovulation by suppression of gonadotrophins.[5] Increased viscosity of cervical mucus and suppression of endometrial growth are secondary effects[5,6] resulting in reduced sperm penetration and implantation.

How should Zoely® be taken?
One tablet should be taken daily for 28 consecutive days. Each pack starts with 24 white active tablets, followed by 4 yellow inactive tablets. A subsequent pack should be started immediately, without a break, after finishing the previous pack irrespective of presence or absence of withdrawal bleeding. Withdrawal bleeding usually starts on day 2-3 after the last active tablet.

Summary of the manufacturer's instructions for use of Zoely®

Starting regimen
There is no need for additional precautions if Zoely is started:

- On the first day of menses
- On the day after the last active tablets of a previous COC (or at the latest on the day following the usual hormone free interval)
- On or the day after a first trimester abortion
- Between day 21 and 28 following delivery or a second trimester abortion

Women should be advised to avoid sexual intercourse or use additional precautions for 7 days if Zoely® is started any time outside those situations listed above. Seven days of additional precautions are advised when switching from a progestogen-only method. The woman may switch any day from the POP, implant or LNG-IUS. Zoely® should be started on the day after the last pill, or on the day of removal. When changing from an injectable, Zoely® should be started on the day when the next injection would have been due.

More detailed instructions can be found in the summary of product characteristics[2].

Missed or incorrect pill use
Missed pill advice is given in detail in the SPC.[2] The management of missed tablets should be guided by the following two basic rules:

• 7 days of uninterrupted active (white) tablets are required to attain adequate ovulation suppression
• The closer the missed active tablets are to the 4 inactive (yellow) tablets, the higher the risk of pregnancy.

The manufacturer advises that additional precautions are required if a pill is missed by 12 hours. No precautions are required if placebo pills are missed. As withdrawal bleeds are more often absent when using Zoely©, pregnancy testing is more likely to be required after a cycle in which pills have been missed, even if adequate alternative contraceptive methods have been instituted or emergency contraception used.

If an active pill is missed by more than 12 hours. The woman should take the tablet as soon as she remembers and should take further tablets at the usual time.
Day 1-7
The last missed tablet should be taken as soon as possible, even if this means taking two tablets at the same time. A barrier method should be used for the next 7 days. If intercourse has taken place, emergency contraception should be considered.

Day 8-17
The last missed tablet should be taken as soon as possible, even if this means taking two tablets at the same time and the rest of the pack taken in the usual manner
Provided that pills have been taken correctly in the 7 days preceding the first missed pill, no extra contraceptive precautions are required.
Day 18-24
If the preceding 7 pills have been taken correctly, reduced contraceptive protection can still be prevented by:
Taking the last pill as soon as possible, continuing with the active pills but omitting the inactive phase and starting the next pack immediately. A withdrawal bleed is likely to be absent.
Or
Discarding the remainder of active pills in the current pack and proceeding to use the inactive pills before starting a new active pack.
With either of these options extra contraceptive methods should not be required. If no withdrawal bleed occurs, the possibility of pregnancy should be considered.

Can Zoely® be taken continuously?

If a woman wishes to omit her "pill (hormone)-free interval" to delay or abolish her withdrawal bleed, the SPC[2] advises that the inactive pills from the pack may be safely omitted and a new active phase started immediately. In common with other COCs, breakthrough bleeding is more likely in the subsequent months for as long as hormone-free intervals are excluded.

The COC has been shown to be safe and effective in continuous use.[7] In one poorly-controlled RCT[8] continuous use of NOMAC/E2 implants as HRT has been shown to be safe and effective, with good cycle control.

How effective is Zoely®?

<u>Efficacy</u>
A small randomised open-label comparative study over six cycles[5] showed NOMAC/E2 to be as effective in suppressing ovulation as a COC with established efficacy (drospirenone and ethinylestradiol). Efficacy rates similar to those for DRSP/EE have also been reported: Pearl index 1.27 (95% confidence interval [CI] 0.66-2.22) for NOMAC/E2, and 1.89 (95% CI 0.69-4.11) for DRSP/EE.[9] Similar findings were reported in a multicentre RCT comparing NOMAC/E2 with DRSP/EE in 2152 women[10], with PI of 0.38 (95% CI 0.1-0.97) for NOMAC /E2 (ITT analysis).

An RCT[6] comparing NOMAC/E2 in a 24/4 pattern with a 21/7 pattern, in 76 French women aged 18-38, showed a shorter pill-free interval to be associated with greater inhibition of follicular growth, and a shorter withdrawal bleed than a 21 day regimen. This suggests that the shorter pill-free interval in Zoely results in a greater margin of contraceptive efficacy and fewer withdrawal symptoms than standard 21/7 COC regimens.

Compliance

High rates of compliance have been reported when basing compliance on tablet intake or tablets remaining in packs (95.1% vs 91.8% for NOMAC/EE and DRSP/EE respectively).[8,10]

What are the advantages of Zoely®?

Acceptability

NOMAC/E2 has been to shown to produce fewer withdrawals from study due to adverse effects compared to estradiol valerate/dienogest (0% vs 3,3%)[10], but more withdrawals from study than DRSP/EE (14.6% v. 0%).[4] The most common reasons for withdrawal in the NOMAC/E2 group were acne (3.3% for NOMAC/E2 vs 0.2%% for DRSP/EE), weight gain (1.4% vs. 0.7%) and irregular withdrawal bleeding (4.0% vs. 0.7%).[5]

Cycle control is acceptable for Zoely®[10] but absence of withdrawal bleeds has been shown to be significant and seen as disadvantageous by some. An RCT[9] found consistently shorter and lighter withdrawal bleeds for NOMAC/E2 compared to DRSP/EE, with a significantly greater number of absent withdrawal bleeds (30% in NOMAC/E2 vs. 6% in DRSP/EE, p=<0.05). NOMAC/E2 was shown in this trial to have similar breakthrough bleeding (BTB) patterns as DRSP/EE, with 11-20% of women reporting BTB. This number decreased over time and 75% of episodes were reported as "spotting" only.[10]

The same trial[10] reported one or more treatment-related adverse event (AE) in 51.2% of participants during the 52 week treatment period. The commonest adverse events reported for NOMAC/E2 were acne (15.3%), irregular withdrawal bleeding (11.7%), weight increase (7.9%) and headache (6.6%) but these did not differ significantly in frequency to those reported by the DRSP/EE control group.

Safety

Pharmacokinetic data show that NOMAC/E2 is associated with lower mean estrogen levels than those observed during the normal menstrual cycle.[11] A randomised study of 121 women aged 18-50[12] receiving NOMAC/E2 or LNG/EE over six cycles reported that NOMAC/E2 had:

- less effect on haemostatic indices than LNG/E2
- no effect on LDL cholesterol and triglycerides (which were increased by LNG/EE)
- negligible effect on glucose and insulin parameters
- significantly smaller increase in CRP than LNG/EE
- a significantly greater increase in SHBG than LNG/EE

Similar favourable effects on haemostasis have been reported in a further RCT.[13] The clinical relevance of these findings is uncertain and merits further investigation.

NOMAC has been shown to have an inhibitory effect on estrogen biosynthesis in the breast.[14] Further study is required to determine what effect if any this has on breast cancer risk compared to other COCs.

Risks

As epidemiological data is lacking, the risks associated with NOMAC/E2 are assumed to be those of other forms of CHC; guidance for its use, including in women with specific medical conditions, can be found in UK Medical Eligibility for Contraceptive Use (UKMEC) 2009.[15] Restrictions to use are those applying to COC, the combined patch and the vaginal ring.

Does Zoely© interact with other drugs?

In common with other forms of hormonal contraception, interaction with liver enzyme-inducing drugs (including, among others, anticonvulsants, rifampicin, St John's Wort, and reverse transcriptase and protease inhibitors used in HIV) may lead to decreased plasma levels of contraceptive hormones and breakthrough bleeding or contraceptive failure. Additional precautions should be used during administration of these drugs and for 28 days after stopping treatment, or an alternative method considered.

The FSRH no longer advises the need for additional precautions when using antibiotics other than enzyme inducers (rifamycins) in conjunction with combined oral contraceptives.[16]

How does Zoely compare to other CHCs in terms of cost?

The cost per month to the NHS is £5.50.[17] The other COCs currently available in the UK range in price from £0.63 to £8.39 per month.[18]

What does Zoely® add to the current contraceptive choice for women?

Availability of Zoely® will enhance contraceptive choice for women in the UK. Wider availability of extended regimens and of COCs which contain hormones similar to endogenous hormones may appeal to some women. Current evidence suggests that Zoely® is acceptable and safe, with fewer effects on lipid and glucose metabolism and haemostatic parameters than established COCs. However, until further data emerge the indications and contraindications to use of Zoely® must be assumed to be the same as for other combined hormonal contraceptives.

Acknowledgement

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