



# Combined oral contraception: nomegestrol/estradiol (Zoely)

Evidence summary

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[www.nice.org.uk/guidance/esnm28](http://www.nice.org.uk/guidance/esnm28)

## Key points from the evidence

The content of this evidence summary was up-to-date in December 2013. See [summaries of product characteristics \(SPCs\)](#), [British national formulary \(BNF\)](#) or the [MHRA](#) or [NICE](#) websites for up-to-date information.

## Summary

Nomegestrol/estradiol (Zoely) has similar contraceptive efficacy to drospirenone/ethinylestradiol (Yasmin) with similar numbers of days of unscheduled bleeding, fewer days of withdrawal bleeding and significantly more absence of withdrawal bleeding. Acne and weight gain were reported more frequently in women taking nomegestrol/estradiol than in women taking drospirenone/ethinylestradiol (statistical significance not reported).

Effectiveness	Safety
<ul style="list-style-type: none"><li>• Two randomised controlled trials (RCTs) found that compared with drospirenone/ethinylestradiol, nomegestrol/estradiol:<ul style="list-style-type: none"><li>– had a similar contraceptive efficacy</li><li>– had a statistically significant higher incidence of unscheduled bleeding or spotting in some cycles, but a similar number of days with unscheduled bleeding or spotting (around 2–3 days)</li><li>– gave fewer days of withdrawal bleeding or spotting (3–4 days compared with 5 days, p value reported in 1 study only)</li><li>– was more likely to result in an absence of withdrawal bleeding (more than 30% compared with about 5% in cycle 12; statistically significant).</li></ul></li></ul>	<ul style="list-style-type: none"><li>• The <u>summary of product characteristics</u> advises that the warnings of serious adverse events seen with other combined oral contraceptives (such as venous thromboembolism, other circulatory disorders, breast cancer and cervical cancer) are considered applicable to nomegestrol/estradiol.</li><li>• Adverse events led to about 18% of women stopping nomegestrol/estradiol and 10% of women stopping drospirenone/ethinylestradiol.</li></ul>

User factors	Resource implications
<ul style="list-style-type: none"> <li>• According to the <a href="#">summary of product characteristics</a>, acne and abnormal (mainly absent) withdrawal bleeding have been reported in at least 1 in 10 women taking nomegestrol/estradiol.</li> <li>• In 2 RCTs, acne, irregular withdrawal bleeding and weight gain were reported more often with nomegestrol/estradiol than with drospirenone/ethinylestradiol (p values not reported).</li> <li>• Lighter, shorter withdrawal bleeds may be seen as an advantage by some women. Absence of withdrawal bleeding may be seen as an advantage or disadvantage.</li> </ul>	<ul style="list-style-type: none"> <li>• Costs of combined oral contraceptives range from £1.80 to £29.25 for a 3-month supply.</li> <li>• The cost of a 3-month pack of nomegestrol/estradiol (Zoely) is £16.50 (<a href="#">MIMS</a>, October 2013).</li> </ul>

## Key points

Nomegestrol/estradiol ([Zoely](#)) is a combined oral contraceptive that received a marketing authorisation for oral contraception in July 2011. It was not marketed in the UK until May 2013. Nomegestrol/estradiol is taken as a 24/4 regimen (24 active tablets containing 2.5 mg nomegestrol and 1.5 mg 17 $\beta$ -estradiol, followed by 4 inactive tablets) unlike most other combined oral contraceptives, which are taken as 21/7 regimens. It is 1 of 2 combined oral contraceptives that contain synthetic estradiol that is chemically identical to human estradiol; the other is dienogest/estradiol ([Qlaira](#)), which is taken as a 26/2 regimen.

This evidence summary is based on 2 randomised, open-label multicentre trials of similar size and design, which were conducted in parallel in different countries ([Mansour et al.](#)

2011 [n=2152]; Westhoff et al. 2012 [n=2281]).

Both studies found that, over 13 cycles, there was no statistically significant difference in contraceptive efficacy between nomegestrol/estradiol and drospirenone/ethinylestradiol (Yasmin) in women aged 18–35 years (the primary outcome). In Mansour et al. (2011) the Pearl Index (in-treatment pregnancies per 100 woman-years of exposure; 1 woman-year equals 13 cycles of 28 days) was estimated to be 0.38 in the nomegestrol/estradiol group and 0.81 in the drospirenone/ethinylestradiol group (p value not reported). In Westhoff et al. (2012) the Pearl Index was 1.27 in the nomegestrol/estradiol group and 1.89 in the drospirenone/ethinylestradiol group (p value not reported). In previous trials assessing the efficacy of new oral contraceptives the Pearl Index has ranged between 0.0 and 2.0.

Unscheduled bleeding or spotting decreased over time in the nomegestrol/estradiol groups. However, it was statistically significantly more common in the nomegestrol/estradiol group than in the drospirenone/ethinylestradiol group in cycles 2–4 and 11 ( $p < 0.05$ ) in Mansour et al. (2011), and in cycles 2–6 ( $p < 0.05$ ) in Westhoff et al. (2012). In both studies, in women who experienced unscheduled bleeding or spotting, the median number of days was similar between the groups, fluctuating between about 2 and 3 days (p values not reported).

Absence of withdrawal bleeding was statistically significantly more common in the nomegestrol/estradiol groups than in the drospirenone/ethinylestradiol groups ( $p < 0.05$  in Mansour et al. 2011 and  $p < 0.001$  in Westhoff et al. 2012 in all cycles). A progressive increase in the incidence of absence of withdrawal bleeding was seen in the nomegestrol/estradiol group in both studies, ranging from 22 to 31% in cycles 4–12 in Mansour et al. (2011), and from about 18 to 34% in all cycles in Westhoff et al. (2012).

In both studies, in women who experienced withdrawal bleeding or spotting, the median number of days was lower in women taking nomegestrol/estradiol than in women taking drospirenone/ethinylestradiol (3–4 days compared with 5 days). The difference between the groups was statistically significant in Westhoff et al. (2012) ( $p < 0.001$  in all cycles); the p value was not reported in Mansour et al. (2011).

In the 2 studies, about 50% of women taking nomegestrol/estradiol experienced adverse events related to the contraceptive, compared with about 37% of women taking drospirenone/ethinylestradiol. The most frequently reported adverse events related to the contraceptive in both studies were acne, irregular withdrawal bleeding and weight gain. These adverse events were more common in the nomegestrol/estradiol groups, although

the significance of the differences between the groups was not reported. In both studies adverse events led to about 18% of women stopping nomegestrol/estradiol and 10% of women stopping drospirenone/ethinylestradiol.

A [Faculty of Sexual & Reproductive Healthcare statement on the use of nomegestrol/estradiol](#) notes that combined oral contraceptives that have extended regimens (for example, 24/4 or 26/2) or that contain hormones similar to endogenous hormones may appeal to some women. It states that current evidence suggests that nomegestrol/estradiol is acceptable and safe. However, until more data are available the indications and contraindications for nomegestrol/estradiol must be assumed to be the same as for other combined hormonal contraceptives.

The [summary of product characteristics for Zoely](#) advises that, because no epidemiological data are currently available for combined oral contraceptives containing estradiol, the warnings of serious adverse events seen with other combined oral contraceptives (such as venous thromboembolism, other circulatory disorders, breast cancer and cervical cancer) are considered applicable to nomegestrol/estradiol.

Localities making formulary decisions about nomegestrol/estradiol will need to take this evidence into account, bearing in mind that user preference is an important factor in contraceptive choice. A reduction in or absence of withdrawal bleeding may be attractive to some women, but seen as a disadvantage to others. Acquisition cost may be another important factor: a 3-month pack of nomegestrol/estradiol (Zoely) is £16.50, which is in the middle of the range of combined oral contraceptives (£1.80 to £29.25 for a 3-month supply).

The manufacturer of nomegestrol/estradiol (Zoely, Merck Sharp & Dohme) and the specialists involved in the production of this evidence summary have suggested that nomegestrol/estradiol is likely to be used as a second- or third-line option in only a small subgroup of women who have found alternative combined hormonal contraceptives unsuitable.

### Key evidence

Mansour D, Verhoeven C, Sommer W et al. (2011) Efficacy and tolerability of a monophasic combined oral contraceptive containing nomegestrol acetate and 17 $\beta$ -oestradiol in a 24/4 regimen, in comparison to an oral contraceptive containing ethinylestradiol and drospirenone in a 21/7 regimen. *European Journal of Contraception and Reproductive Health Care* 16: 430–43

Westhoff C, Kaunitz AM, Korver T et al. (2012) Efficacy, safety, and tolerability of a monophasic oral contraceptive containing nomegestrol acetate and 17 $\beta$ -estradiol: a randomized controlled trial. *Obstetrics and Gynecology* 119: 989–99

## About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance**.

## Relevance to NICE guidance programmes

The combined oral contraceptive nomegestrol/estradiol (Zoely) was not considered appropriate for a NICE technology appraisal and is not currently planned into any other work programme.

## Introduction

The combined oral contraceptive pill is one of the most commonly used contraceptive methods in the UK. Most combined oral contraceptives used in the UK are fixed dose (monophasic) pills containing ethinylestradiol (a synthetic oestrogen) in combination with a progestogen. Variable dose (phasic) combined oral contraceptives are also available. Most combined oral contraceptives contain 21 active pills; the first 7 pills inhibit ovulation and the remaining 14 pills maintain anovulation. Traditionally, women have then either had 7 pill-free days or taken 7 placebo tablets before starting the next packet of pills. During this time, most women will have a withdrawal bleed, which is caused by the withdrawal of

hormones rather than physiological menstruation.

The [Faculty of Sexual & Reproductive Healthcare clinical guidance on combined hormonal contraception \(2011\)](#), which has been [accredited by NICE](#), advises that all combined hormonal contraceptives (combined oral contraceptive pills, the combined transdermal patch and the combined vaginal ring) are similarly effective. Healthcare professionals prescribing combined hormonal contraceptives should be guided by the woman's personal preference, risk of venous thromboembolism, any contraindications, possible non-contraceptive benefits and experience with other contraceptive formulations. See the Faculty of Sexual & Reproductive Healthcare's guidance for more information.

## Product overview

### Drug action

The active tablets in nomegestrol/estradiol (Zoely) contain 2.5 mg nomegestrol acetate, a highly selective progestogen that is similar to human progesterone and has no oestrogenic, androgenic, glucocorticoid or mineralocorticoid activity, and 1.5 mg 17 $\beta$ -estradiol (as hemihydrate), a synthetically produced oestrogen that is chemically identical to human 17 $\beta$ -estradiol.

### Licensed therapeutic indication

Nomegestrol/estradiol (Zoely) is a combined oral contraceptive that received a marketing authorisation for oral contraception in July 2011. It was not marketed in the UK until May 2013.

### Course and cost

One tablet is taken daily for 28 consecutive days. Each pack starts with 24 white active tablets, followed by 4 yellow inactive tablets. A subsequent pack is started immediately after finishing the previous pack, with no break in taking a daily tablet and irrespective of the presence or absence of withdrawal bleeding. Withdrawal bleeding usually starts on day 2–3 after taking the last active tablet and may not have finished before the next pack is started.

A 3-month pack of Zoely costs £16.50 excluding VAT, which is equivalent to £5.50 per cycle ([MIMS](#), November 2013).

## Evidence review

This evidence summary is based on 2 [randomised](#), [open-label](#) multicentre trials of similar size and design, which were conducted in parallel in different countries ([Mansour et al. 2011](#) and [Westhoff et al. 2012](#)). These were the 2 key studies assessed by the European Medicines Agency when a licence application was submitted for norgestrel/estradiol (see the [European public assessment report for Zoely](#)).

- Design: both studies were randomised and open-label. [Mansour et al. \(2011\)](#) was conducted in 95 gynaecological or general practices in Europe, Asia and Australia; [Westhoff et al. \(2012\)](#) was conducted in 89 gynaecological or general practices in the United States, Canada, Argentina, Brazil, Chile and Mexico.
- Population: the studies included healthy, sexually active women aged 18–50 years with a body mass index (BMI) between 17 and 35 kg/m<sup>2</sup> who needed contraception and did not plan to use condoms. [Mansour et al. \(2011\)](#) included 2152 women with a mean age of 28 years and a mean BMI of 23 kg/m<sup>2</sup>. [Westhoff et al. \(2012\)](#) included 2281 women with a mean age of 28 years and a mean BMI of 24.5 kg/m<sup>2</sup>. In both studies, baseline characteristics were reported to be similar between the groups.
- Intervention and comparison: participants were randomly allocated in a 3:1 ratio to either norgestrel acetate 2.5 mg plus 17 $\beta$ -estradiol 1.5 mg in a 24/4 regimen ([Mansour et al. 2011](#) n=1613, [Westhoff et al 2012](#) n=1710) or drospirenone 3 mg plus ethinylestradiol 30 micrograms in a 21/7 regimen ([Mansour et al. 2011](#) n=539, [Westhoff et al 2012](#) n=571) for 13 consecutive 28-day cycles. Electronic diaries were used to record pill intake and document vaginal bleeding, condom use and vaginal intercourse.



- Outcomes: the primary outcome in both studies was contraceptive efficacy in women aged 18–35 years, assessed by recording in-treatment pregnancies between the first and the last day of taking the trial drug plus an extension window (2 days in [Mansour et al. 2011](#), 7 days in [Westhoff et al 2012](#)). Contraceptive efficacy was expressed as the Pearl Index (in-treatment pregnancies per 100 woman-years of exposure; 1 woman-year equals 13 cycles of 28 days). Cycles during which condoms were consistently used as a barrier back-up method were excluded. Secondary outcomes included:
  - Contraceptive efficacy in the overall age group (18–50 years).
  - The number of days of bleeding or spotting per 91-day reference period. Vaginal bleeding was classified as spotting if no or 1 pad or tampon was needed per day, or bleeding if more than 1 pad or tampon was needed per day.
  - Incidence and duration of unscheduled bleeding or spotting. Unscheduled bleeding or spotting was classified as any bleeding or spotting episode that occurred during the expected non-bleeding period.
  - Incidence of absence of withdrawal bleeding. Withdrawal bleeding was classified as any bleeding or spotting episode that began during or continued into the expected bleeding period.
  - Safety and tolerability. Data were obtained by monitoring adverse events and routine laboratory parameters, and by physical and gynaecological examinations.

The key efficacy results for both studies are reported in [table 1](#) and key safety results for both studies are reported in [table 2](#).

## Table 1 Summary of efficacy

[Mansour et al. \(2011\)](#) and [Westhoff et al. \(2012\)](#)

		<b>Nomegestrol/ estradiol</b>	<b>Drospirenone/ ethinylestradiol</b>	<b>Analysis</b>
Randomised	<a href="#">Mansour et al.</a>	n=1613	n=539	

	<u>Westhoff et al.</u>	n=1710	n=571	
Efficacy	<u>Mansour et al.</u>	n=1591 <sup>1</sup>	n=535 <sup>1</sup>	
	<u>Westhoff et al.</u>	n=1666 <sup>2</sup>	n=554 <sup>2</sup>	
Primary outcome: contraceptive efficacy in women aged 18–35 years	<u>Mansour et al.</u>	n=1315 <sup>3</sup> 4 pregnancies PI 0.38 (95% CI 0.10 to 0.97)	n=442 <sup>3</sup> 3 pregnancies PI 0.81 (95% CI 0.17 to 2.35)	No statistically significant difference between groups <u>p value</u> not reported
	<u>Westhoff et al.</u>	n=1375 <sup>3</sup> 12 pregnancies PI 1.27 (95% CI 0.66 to 2.22)	n=463 <sup>3</sup> 6 pregnancies PI 1.89 (95% CI 0.69 to 4.11)	No statistically significant difference between groups <u>p value</u> not reported
Selected secondary outcomes:				
Contraceptive efficacy in women aged 18–50 years	<u>Mansour et al.</u>	PI 0.31 (95% CI 0.08 to 0.79)	PI 0.66 (95% CI 0.14 to 1.94)	No statistically significant difference between groups <u>p value</u> not reported
	<u>Westhoff et al.</u>	PI 1.13 (95% CI 0.60 to 1.94)	PI 1.83 (95% CI 0.74 to 3.77)	No statistically significant difference between groups <u>p value</u> not reported

Mean number of days bleeding and/or spotting per 91-day reference period	<u>Mansour et al.</u> Bleeding and spotting	1st 91-day period: 14.9 4th 91-day period: 10.6	1st 91-day period: 18.5 4th 91-day period: 19.2	Statistical significance of differences and p values not reported
	<u>Westhoff et al.</u> Bleeding	1st 91-day period: 5.9 4th 91-day period: 4.1	1st 91-day period: 9.8 4th 91-day period: 11.6	Statistically significantly lower in the nomegestrol/ estradiol group in all 4 91-day periods, p<0.001
	Spotting	1st 91-day period: 8.9 4th 91-day period: 5.4	1st 91-day period: 7.9 4th 91-day period: 7.7	Statistically significantly lower in the nomegestrol/ estradiol group in 91-day periods 3 (p=0.031) and 4 (p<0.001)
Incidence of unscheduled bleeding or spotting	<u>Mansour et al.</u>	Range 20 to 14% in cycles 4–13	Range 17 to 11% in cycles 4–13	Statistically significantly higher in the nomegestrol/ estradiol group in cycles 2–4 and 11, p<0.05
	<u>Westhoff et al.</u>	Range about 30 to 16% in all 13 cycles <sup>4</sup>	Range about 21 to 8% in all 13 cycles <sup>4</sup>	Statistically significantly higher in the nomegestrol/ estradiol group in cycles 2–6, p<0.05
Incidence of absence of withdrawal bleeding	<u>Mansour et al.</u>	Range 22 to 31% in cycles 4–12	Range 3 to 6% in cycles 4–12	Statistically significantly higher in the nomegestrol/ estradiol group in cycles 2–12, p<0.05

	<u>Westhoff et al.</u>	Range about 18 to 34% in cycles 1–12 <sup>4</sup>	Range about 3 to 9% in cycles 1–12 <sup>4</sup>	Statistically significantly higher in the nomegestrol/ estradiol group in cycles 2–12, p<0.001
<p>Abbreviations: CI, <u>confidence interval</u>; PI, Pearl Index; ITT, <u>intention-to-treat</u></p> <p><sup>1</sup> Efficacy analyses were based on the modified ITT group, which included all randomised women who took at least 1 dose of trial medication.</p> <p><sup>2</sup> For contraceptive efficacy, analyses were based on the modified ITT group, which included all women who completed at least 1 cycle. It is unclear whether this applies to all other efficacy analyses.</p> <p><sup>3</sup> The PI was based on all women in the modified ITT group, excluding any cycles in which condoms were always used.</p> <p><sup>4</sup> Exact data not supplied. Estimated from figures in the paper.</p>				

## Table 2 Summary of safety

Mansour et al. (2011) and Westhoff et al. (2012)

		<b>Nomegestrol/ estradiol</b>	<b>Drospirenone/ ethinylestradiol</b>	<b>Analysis</b>
Randomised	<u>Mansour et al.</u>	n=1613	n=539	
	<u>Westhoff et al.</u>	n=1710	n=571	
Safety <sup>1</sup>	<u>Mansour et al.</u>	n=1591	n=535	
	<u>Westhoff et al.</u>	n=1666	n=554	
Discontinuation rate	<u>Mansour et al.</u>	28.2%	23.4%	<u>p value</u> not reported
	<u>Westhoff et al.</u>	40.7%	37.9%	p value not reported

Incidence of treatment-related adverse events	<u>Mansour et al.</u>	51.2%	37.0%	p value not reported
	<u>Westhoff et al.</u>	48.8%	36.3%	p value not reported
Discontinuation rate due to adverse events	<u>Mansour et al.</u>	18.2%	10.5%	p value not reported
	<u>Westhoff et al.</u>	17.3%	10.1%	p value not reported
Incidence of acne as a treatment-related adverse event (discontinuation rate)	<u>Mansour et al.</u>	15.3% (3.3%)	7.1% (0.2%)	p values not reported
	<u>Westhoff et al.</u>	16.4% (13.5%)	8.7% (not reported)	p value not reported
Incidence of irregular withdrawal bleeding as a treatment-related adverse event (discontinuation rate)	<u>Mansour et al.</u>	11.7% (4.0%)	0.4% (0.7%)	p values not reported
	<u>Westhoff et al.</u>	9.1% (3.8%)	0.5% (1.8%)	p value not reported for incidence. Discontinuation rate statistically significantly higher in the norgestrel/estradiol group, p<0.023
Incidence of weight increase as a treatment-related adverse event (discontinuation rate)	<u>Mansour et al.</u>	7.9% (1.4%)	6.2% (0.7%)	p values not reported
	<u>Westhoff et al.</u>	9.5% (8.3%)	5.2% (not reported)	p values not reported

Increase in body weight from baseline	<a href="#">Mansour et al.</a>	Mean 1.00 kg	Mean 0.35 kg	Statistically significantly higher in the nomegestrol/estradiol group, p=0.001
	<a href="#">Westhoff et al.</a>	Median 1.00 kg	Median 0.2 kg	p value not reported

Abbreviations: CI, confidence interval; PI, Pearl Index

<sup>1</sup> Safety analyses included all randomised women who received at least 1 dose of trial medication.

## Clinical effectiveness

### Contraceptive efficacy

Both studies found that there was no statistically significant difference in contraceptive efficacy between nomegestrol/estradiol and drospirenone/ethinylestradiol in women aged 18–35 years (the primary outcome). In [Mansour et al. \(2011\)](#) the Pearl Index was estimated to be 0.38 (95% confidence interval [CI] 0.10 to 0.97) in the nomegestrol/estradiol group and 0.81 (95% CI 0.17 to 2.35) in the drospirenone/ethinylestradiol group (p value not reported) in women aged 18–35 years. In [Westhoff et al. \(2012\)](#) the Pearl Index in women aged 18–35 years was 1.27 (95% CI 0.66 to 2.22) in the nomegestrol/estradiol group and 1.89 (95% CI 0.69 to 4.11) in the drospirenone/ethinylestradiol group (p value not reported). Similar results were seen for the overall age group (18–50 years) in both studies. In previous trials assessing the efficacy of new oral contraceptives the Pearl Index has ranged between 0.0 and 2.0.

### All bleeding and spotting

In both studies, the mean number of days on which women experienced bleeding or spotting was lower in woman taking nomegestrol/estradiol than in women taking drospirenone/ethinylestradiol. The number of bleeding or spotting days decreased over the course of the study (13 cycles) in women taking nomegestrol/estradiol, but not in women taking drospirenone/ethinylestradiol. See [table 1](#) for details.

## Unscheduled bleeding or spotting

As with overall bleeding, in both studies unscheduled bleeding or spotting decreased over time in the nomegestrol/estradiol group. In comparison, after the first few cycles, there was no obvious trend in the drospirenone/ethinylestradiol group. However, in some cycles, particularly early cycles, unscheduled bleeding or spotting was statistically significantly more common with nomegestrol/estradiol than with drospirenone/ethinylestradiol.

In [Mansour et al. \(2011\)](#) in cycles 4–13 the incidences of unscheduled bleeding or spotting ranged from 20 to 14% in women taking nomegestrol/estradiol and from 17 to 11% in women taking drospirenone/ethinylestradiol. Bleeding or spotting was statistically significantly more common in the nomegestrol/estradiol group in cycles 2–4 and 11 ( $p < 0.05$ ) than in the drospirenone/ethinylestradiol group.

In women who experienced unscheduled bleeding or spotting, the median number of days per cycle was similar between the groups (2–3 days in the nomegestrol/estradiol group and 1–4 days in the drospirenone/ethinylestradiol group;  $p$  value not reported).

In [Westhoff et al. \(2012\)](#), over all cycles, the incidence of unscheduled bleeding or spotting was around 30 to 16% in women taking nomegestrol/estradiol, and around 21 to 8% in women taking drospirenone/ethinylestradiol. Bleeding or spotting was statistically significantly more common in the nomegestrol/estradiol group in cycles 2–6 ( $p < 0.05$ ) than in the drospirenone/ethinylestradiol group.

In women who experienced unscheduled bleeding or spotting the median number of days was similar between the groups, fluctuating between 2 and 3 days in both groups ( $p$  value not reported).

## Withdrawal bleeding

In both studies, the absence of withdrawal bleeding was statistically significantly more common in the nomegestrol/estradiol group in all cycles, than in the drospirenone/ethinylestradiol group. Withdrawal bleeds, in women who experienced them, were shorter and lighter in the group taking nomegestrol/estradiol.

In [Mansour et al. \(2011\)](#) absence of withdrawal bleeding increased progressively in the nomegestrol/estradiol group, with the incidence ranging from 22% in cycle 4 to 31% in cycle 12. In comparison, the incidence varied between 3 and 6% in the drospirenone/

ethinylestradiol group with no obvious trend. The difference between the groups was statistically significant in all cycles ( $p < 0.05$ ).

In women who experienced withdrawal bleeding, the median number of withdrawal bleeding or spotting days was lower in the group taking nomegestrol/estradiol than in the group taking drospirenone/ethinylestradiol (3–4 days compared with 5 days;  $p$  value not reported). The difference was due to a difference in bleeding rather than spotting days (2 days of bleeding with nomegestrol/estradiol and 3 days with drospirenone/ethinylestradiol;  $p$  value not reported).

A progressive increase in the incidence of absence of withdrawal bleeding was also seen in the nomegestrol/estradiol group in [Westhoff et al. \(2012\)](#), ranging from about 18 to 34% over the course of the study. In comparison, the incidence fluctuated between around 3 and 9% in the drospirenone/ethinylestradiol group. The difference between the groups was statistically significant in all cycles ( $p < 0.001$ ).

In women who experienced withdrawal bleeding or spotting, the median number of days was statistically significantly lower in women taking nomegestrol/estradiol than in women taking drospirenone/ethinylestradiol (3–4 days compared with 5 days;  $p < 0.001$  in all cycles).

## Safety and tolerability

The [summary of product characteristics](#) advises that, because no epidemiological data are currently available for combined oral contraceptives containing estradiol, the warnings of serious adverse events seen with other combined oral contraceptives (such as venous thromboembolism, other circulatory disorders, breast cancer and cervical cancer) are considered applicable to nomegestrol/estradiol.

According to the [summary of product characteristics for Zoely](#), the most frequently reported adverse events in studies of nomegestrol/estradiol were acne and abnormal withdrawal bleeding (predominantly absence of withdrawal bleeding), which affected at least 1 in 10 women. Other common adverse events, affecting between 1 in 100 and 1 in 10 women, were decreased libido, depression or mood changes, headache or migraine, nausea, unscheduled bleeding or spotting, menorrhagia, breast or pelvic pain and weight increase.

In [Mansour et al. \(2011\)](#) and [Westhoff et al. \(2012\)](#) about 50% of women taking



nomegestrol/estradiol had adverse events that were considered to be related to the contraceptive, compared with about 37% of women taking drospirenone/ethinylestradiol. The most frequently reported related adverse events (occurring in 5% or more women) were acne, irregular withdrawal bleeding and weight gain in both studies. According to the [summary of product characteristics](#), in these 2 studies combined, acne was reported by 15.4% of women taking nomegestrol/estradiol compared with 7.9% of women taking drospirenone/ethinylestradiol; weight gain was reported by 8.6% of women taking nomegestrol/estradiol compared with 5.7% of women taking drospirenone/ethinylestradiol; and abnormal withdrawal bleeding (predominantly absence of withdrawal bleeding) was reported by 10.5% of women taking nomegestrol/estradiol compared with 0.5% of women taking drospirenone/ethinylestradiol. The significance of the differences between the groups was not reported. (See [table 2](#) for data on adverse events in the individual studies.)

In both studies adverse events led to about 18% of women stopping nomegestrol/estradiol and 10% of women stopping drospirenone/ethinylestradiol. In [Mansour et al. \(2011\)](#) acne, irregular withdrawal bleeding and weight gain accounted for most of the differences in discontinuation rates between the 2 groups (see [table 2](#) for more details). In [Westhoff et al. \(2012\)](#) statistically significantly more women taking nomegestrol/estradiol stopped treatment because of irregular withdrawal bleeding (3.8%, compared with 1.8% with drospirenone/ethinylestradiol;  $p < 0.023$ ). Differences between the contraceptives are not reported for acne and weight gain.

In both studies the presence of acne decreased over time with both contraceptives. The authors suggest that nomegestrol/estradiol may not cause acne, but acne may have been frequently reported because assessment for acne at each clinic visit had raised awareness. Also, differences between the 2 groups might be because drospirenone/ethinylestradiol has a positive effect on acne, rather than nomegestrol/estradiol having a negative effect.

The authors also suggest that reports of adverse effects and discontinuation because of irregular withdrawal bleeding in women taking nomegestrol/estradiol might have been reduced if healthcare professionals and women had been counselled that withdrawal bleeding might not occur.

In both studies the body weight of women taking nomegestrol/estradiol increased by 1 kg on average over 13 cycles. In comparison, women taking drospirenone/ethinylestradiol gained 0.35 kg in [Mansour et al. \(2011\)](#) ( $p < 0.001$ ) and 0.2 kg in [Westhoff et al. \(2012\)](#) ( $p$  value not reported). These results are consistent with a [Cochrane review](#) that

concluded that combined hormonal contraceptives do not have a large effect on weight.

Venous thromboembolism was not reported by any women taking nomegestrol/estradiol in the studies. However, according to the [summary of product characteristics](#), venous thromboembolic events have been reported during post-marketing use. A [European Medicines Agency review of the risk of venous thromboembolism with combined hormonal contraceptives](#) reports that available data for nomegestrol are insufficient for comparison with other progestogens, but further studies are ongoing or planned.

## Evidence strengths and limitations

The 2 studies were well designed. However, although they were randomised, [controlled](#) and [allocation was concealed](#), they do have limitations. Neither of the studies was [blinded](#), which is a potential source of [bias](#). An [open-label](#) design was chosen because the differences in the nomegestrol/estradiol and drospirenone/ethinylestradiol regimens (24/4 compared with 21/7) would lead to obvious differences in the timing of withdrawal bleeding and in the missed pill guidance given to the 2 groups. Both studies were funded by Merck Sharp & Dohme.

The inclusion and exclusion criteria of the studies were generally representative of the standard population used for evaluating contraceptives in healthy women of childbearing potential. However, no young women aged 12–17 years were included: both studies included women aged 18–50 years. The [summary of product characteristics for Zoely](#) states that no data on efficacy and safety are available for young women under 18.

The definition used for in-treatment pregnancies for the licensing of contraceptives in Europe is pregnancies with an estimated date of conception from the day of first intake of trial medication up to and including the day of last intake of trial medication, extended with a maximum of 2 days. In [Westhoff et al. \(2012\)](#) the extension period was 7 days rather than 2 days. However, in the [European public assessment report for Zoely](#), the analyses for this study are based on a 2-day extension period and the results seen are similar to those reported in [Westhoff et al. \(2012\)](#).

The baseline characteristics of the women appear to be well balanced between the 2 groups in both studies. However, no statistical analysis was performed to determine the significance of any differences.

According to the [European public assessment report for Zoely](#), baseline characteristics

differed between the 2 studies with regards to race, ethnicity, weight, gynaecological and contraceptive history and socioeconomic background. This may be the reason for some of the differences between the study results, such as the Pearl Index (0.38 for nomegestrol/estradiol and 0.81 for drospirenone/ethinylestradiol in [Mansour et al. 2011](#); 1.27 for nomegestrol/estradiol and 1.89 for drospirenone/ethinylestradiol in [Westhoff et al. 2012](#)) and discontinuation rates (28.2% for nomegestrol/estradiol and 23.4% for drospirenone/ethinylestradiol in [Mansour et al. 2011](#); 40.7% for nomegestrol/estradiol and 37.9% for drospirenone/ethinylestradiol in [Westhoff et al. 2012](#)).

The total number of women who stopped taking the contraceptive was high in both groups in both studies. However, the [European public assessment report for Zoely](#) notes that the discontinuation rates are lower than planned in the sample size calculations. The difference between the discontinuation rates in the studies is mainly because of a higher percentage of 'withdrawal of informed consent' and 'lost to follow up' in [Westhoff et al. \(2012\)](#) than in [Mansour et al. \(2011\)](#).

The [European public assessment report for Zoely](#) suggests that women in [Westhoff et al. \(2012\)](#) adhered less to the contraceptive regimen than women in [Mansour et al. \(2011\)](#). In [Westhoff et al. \(2012\)](#) 27 women were excluded from the intention-to-treat analysis because of the limited credibility of their electronic data; in [Mansour et al. \(2011\)](#) only 2 women were excluded for this reason.

[Mansour et al. \(2011\)](#) was conducted in Europe, Asia and Australia and may be more relevant to UK practice than [Westhoff et al. \(2012\)](#), which was conducted in the United States, Canada, Argentina, Brazil, Chile and Mexico.

## Context

### Alternative oral contraceptives

A wide variety of combined oral contraceptives are available in the UK, using different oestrogens, progestogens, doses and regimens. See the [British national formulary](#) and the Cost of alternative contraceptives section of this evidence summary for more information.

## Costs of alternative contraceptives

Preparation	Oestrogen (micrograms)/progestogen (micrograms)	Cost per 3 months <sup>1</sup>
<b>Fixed dose</b>		
<b>Estradiol/nomegestrol</b>		
Zoely	1500/2500	£16.50
<b>Ethinylestradiol/desogestrel</b>		
Cimizt	30/150	£4.53
Gedarel 20/150	20/150	£5.98
Gedarel 30/150	30/150	£4.93
Marvelon	30/150	£6.45
Mercilon	20/150	£7.67
<b>Ethinylestradiol/drospirenone</b>		
Yasmin	30/3000	£14.70
<b>Ethinylestradiol/gestodene</b>		
Femodene (also ED)	30/75	£6.73 £7.10 (ED)
Femodette	20/75	£8.85
Katya	30/75	£5.03
Millinette 20/75	20/75	£6.37
Millinette 30/75	30/75	£4.85
Sunya	20/75	£6.62
<b>Ethinylestradiol/levonorgestrel</b>		
Elevin	30/150	£29.25
Levest	30/150	£1.80

Microgynon 30 (also ED)	30/150	£2.82 £2.99 (ED)
Ovranette	30/150	£2.20
Rigevidon	30/150	£1.89
<b>Ethinylestradiol/norethisterone</b>		
Brevinor	35/500	£1.99
Loestrin 20	20/1000	£2.70
Loestrin 30	30/1500	£3.90
Norimin	35/1000	£2.28
Ovysmen	35/500	£1.89
<b>Ethinylestradiol/norgestimate</b>		
Cilest	35/250	£7.16
Lizinna	35/250	£5.37
<b>Mestranol/norethisterone</b>		
Norinyl-1	50/1000	£2.19
<b>Variable dose</b>		
<b>Estradiol/dienogest</b>		
Qlaira	3000/0 (2 tabs) 2000/2000 (5 tabs) 2000/3000 (17 tabs) 1000/0 (2 tabs)	£25.18
<b>Ethinylestradiol/gestodene</b>		
Triadene	30/50 (6 tabs) 40/70 (5 tabs) 30/100 (10 tabs)	£10.40
<b>Ethinylestradiol/levonorgestrel</b>		

Logynon (also ED)	30/50 (6 tabs)	£3.82
	40/75 (5 tabs)	£4.00 (ED)
	30/125 (10 tabs)	
TriRegol	30/50 (6 tabs)	£2.87
	40/75 (5 tabs)	
	30/125 (10 tabs)	
<b>Ethinylestradiol/norethisterone</b>		
BiNovum	35/500 (7 tabs)	£2.49
	35/1000 (14 tabs)	
Synphase	35/500 (7 tabs)	£3.60
	35/1000 (9 tabs)	
	35/500 (5 tabs)	
TriNovum	35/500 (7 tabs)	£3.46
	35/750 (7 tabs)	
	35/1000 (7 tabs)	
Abbreviations: ED, every day		
<sup>1</sup> Costs taken from <a href="#">MIMS</a> , November 2013		

## Estimated impact for the NHS

### Likely place in contraceptive choice

The [Faculty of Sexual & Reproductive Healthcare clinical guidance on combined hormonal contraception \(2011\)](#) advises that healthcare professionals prescribing combined hormonal contraceptives should be guided by the woman's personal preference, risk of venous thromboembolism, any contraindications, possible non-contraceptive benefits, and experience with other contraceptive formulations. See the Faculty of Sexual & Reproductive Healthcare guidance for more information.

In [Mansour et al. \(2011\)](#) and [Westhoff et al. \(2012\)](#) acne, irregular withdrawal bleeding and weight gain were reported more often with nomegestrol/estradiol than with drospirenone/

ethinylestradiol. However, withdrawal bleeds were lighter and shorter with nomegestrol/estradiol than with drospirenone/ethinylestradiol, which may be seen as an advantage by some women. The more common absence of withdrawal bleeding with nomegestrol/estradiol may be seen as an advantage or disadvantage.

A [Faculty of Sexual & Reproductive Healthcare statement on the use of nomegestrol/estradiol](#) notes that combined oral contraceptives that have extended regimens (for example, 24/4 or 26/2) or that contain hormones similar to endogenous hormones may appeal to some women. It states that current evidence suggests that nomegestrol/estradiol is acceptable and safe. However, until more data are available the indications and contraindications for nomegestrol/estradiol must be assumed to be the same as for other combined hormonal contraceptives.

Localities making formulary decisions about nomegestrol/estradiol will need to take this evidence into account, bearing in mind that user preference is an important factor in contraceptive choice. A reduction in or absence of withdrawal bleeding may be attractive to some women, but seen as a disadvantage to others. Acquisition cost may be another important factor: a 3-month pack of nomegestrol/estradiol (Zoely) is £16.50, which is in the middle of the range of combined oral contraceptives (£1.80 to £29.25 for a 3-month supply).

The manufacturer of nomegestrol/estradiol ([Zoely](#), Merck Sharp & Dohme) has suggested that, in the UK, nomegestrol/estradiol will usually be prescribed as a second- or third-line option, as an alternative to products such as drospirenone/ethinylestradiol ([Yasmin](#), the fixed-dose combined oral contraceptive used as a comparator in the studies assessed in this evidence summary) or dienogest/estradiol ([Qlaira](#), currently the only other combined oral contraceptive that contains estradiol and has a pill-free interval of less than 7 days).

## Estimated usage

The manufacturer of nomegestrol/estradiol (Zoely, Merck Sharp & Dohme) and the specialists involved in the production of this evidence summary have suggested that nomegestrol/estradiol is likely to be used as a second- or third-line option in only a small subgroup of women who have found alternative combined hormonal contraceptives unsuitable.

Costs of combined oral contraceptives range from £1.80 to £29.25 for a 3-month supply. Possible alternatives to nomegestrol/estradiol (Zoely) include drospirenone/

ethinylestradiol ([Yasmin](#)) and dienogest/estradiol ([Qlaira](#)). The cost of a 3-month pack is £16.50 for Zoely, £14.70 for Yasmin and £25.18 for Qlaira ([MIMS](#), October 2013).

## References

[British national formulary](#) (April 2013) [online; accessed 4 October 2013]

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# About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance.**

For information about the process used to develop this evidence summary, see [Evidence summaries: new medicines – integrated process statement](#).

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