

Nomegestrol acetate/17-beta estradiol: a review of efficacy, safety, and patient acceptability

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Abstract: Nomegestrol acetate (NOMAC) 2.5 mg with 17-beta estradiol (E2) 1.5 mg is a new combined oral contraceptive (COC) formulation and is the first monophasic E2 pill to be marketed, having been licensed for use in Europe in 2011. It is available to be taken daily in a regimen of 24 active pills followed by four placebo pills. NOMAC is a highly selective 19-nor progestogen derivative with specific binding to progesterone receptors, anti-estrogenic activity and no androgenic, mineralocorticoid nor glucocorticoid effects. E2 is an estrogen that is identical to endogenous estrogen. While it has been in use for only a short period of time, current evidence suggests that NOMAC/E2 is just as effective, safe, and acceptable as existing COC preparations. Two large Phase III trials conducted in the Americas and across Europe, Australia, and Asia showed lower cumulative pregnancy rates in the NOMAC/E2 groups compared to the drospirenone (DRSP) 3 mg in combination with ethinyl estradiol (EE) 30 µg (DRSP/EE) groups but this difference was not statistically significant. NOMAC/E2 exhibits a good safety profile and has less effects on cardiovascular risk, hemostatic, metabolic, and endocrine factors in comparison to COCs containing EE in combination with levonorgestrel (LNG) or DRSP. NOMAC/E2 has also been found to cause less breast cell proliferation when compared to E2 alone and has some anti-proliferative effect on human breast cancer cells. NOMAC/E2 is considered acceptable as its compliance, continuation rates, and bleeding patterns were similar to COCs containing DRSP/EE and LNG 150 µg combined with EE 30 µg or LNG 100 µg combined with EE 20 µg (LNG/EE). However, discontinuation was found to be slightly higher in the NOMAC/E2 groups in the two large Phase III trials comparing NOMAC/E2 use with DRSP/EE. As the scientific literature has limited information on NOMAC/E2, further experience with NOMAC/E2 is required.

Keywords: nomegestrol acetate, estradiol, efficacy, safety, acceptability

Introduction

As the use of contraception world-wide expands, research into newer and better contraceptives continues. The latest addition to the contraceptive repertoire is a combined oral contraceptive (COC) containing nomegestrol acetate (NOMAC, 2.5 mg) and 17-beta estradiol (E2, 1.5 mg) marketed under the trade name Zoely® (Merck Sharp and Dohme Limited, Hertfordshire, UK). It is the first monophasic E2 pill to be marketed and comes in blister packs containing 28 pills, with 24 white active pills and four yellow placebo pills (24/4 regimen). The pills are taken in sequence one a day as long as contraception is required, starting with the first active pill on the first day of the menstrual cycle.¹ NOMAC/E2 has been licensed for contraceptive use in Europe since 2011 and in Australia since 2012, and is yet to be approved for use in the USA.

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This review examines the use of the product combination of NOMAC/E2 for contraception, for which it is currently available only as an oral preparation.

Pharmacology

NOMAC/E2 is a product which belongs to the pharmacological group of sex hormones and modulators of the genital system.² Its main effect is contraceptive, by inhibiting ovulation and affecting cervical secretions.^{3,4} While E2 is an estrogen that is identical to the endogenous estrogen produced by ovaries, NOMAC is a highly selective 19-nor progestogen derivative with specific binding to progesterone (P) receptors, high anti-estrogenic activity and no androgenic effects.^{4,5} These attributes were predicted by an early study⁶ which found that NOMAC did not exhibit the estrogenic activity seen in other 19-norprogestins which were derived from testosterone. The authors hypothesized that the estrogenic activity was due to the 17-hydroxyl group associated with estrogenic progestins, and not the absence of the 19-methyl group as was previously believed.⁶

NOMAC peak plasma levels are attained within 2 hours and steady state concentration is reached 5 days after ingestion of NOMAC/E2.⁷ NOMAC's calculated bioavailability (F_{abs}) is 63.4%, with a half-life of 41.9 ± 16.2 hours (mean \pm standard deviation terminal $t_{1/2}$) after single dosing and 45.9 ± 15.3 hours (mean \pm standard deviation $t_{1/2}$) after multiple dosing of NOMAC/E2.⁸ E2 is well absorbed after oral administration but rapidly metabolized, its bioavailability estimated to be 1%.^{3,9} Serum concentration of E2, which is influenced by endogenous E2, peaks on day 6 during multiple dosing then slowly declines but increases again after 10 days of no NOMAC/E2 pill intake, suggesting endogenous E2 synthesis has resumed. Estrone, E2's main metabolite, increases from trough concentration from baseline to peak on day 6, and remains constant during multiple dosing. Lower concentrations of E2 were observed after a single dose of NOMAC/E2.⁸

After its rapid absorption, NOMAC is extensively bound to albumin (ALB) (97%) but does not bind to sex hormone binding globulin (SHBG) or corticoid binding globulin (CBG).⁹ It is metabolized by the liver's cytochrome P450 (CYP) enzymes and excreted in the urine and feces. Four-fifths of the NOMAC dose is eliminated in 4 days, and almost completely after 10 days.³ E2 undergoes considerable first-pass effect after its absorption. In the circulation E2 binds to SHBG (37%) as well as ALB (61%) after its absorption.³ After rapid transformation by the liver's CYP enzymes and

partly in the gut, E2's metabolites (mainly estrone) undergo conjugation and entero-hepatic circulation. E2's elimination is mainly via urine and determined by the dynamic equilibrium maintained between its metabolites and endogenous E2.^{3,10}

Food was not observed to have any clinically relevant effect on the bioavailabilities of either NOMAC or E2.³ Maximum and average plasma concentrations of NOMAC were about 12 ng/mL and 4 ng/mL respectively. Maximum and average plasma concentrations of E2 are about 90 pg/mL and 50 pg/mL respectively, the latter as seen in early and late phases of the menstrual cycle.³

NOMAC's anti-gonadotropin effect is exerted at the levels of the hypothalamus and pituitary gland, not at the androgen receptor.¹¹ It inhibits ovulation in women at an oral dose of 1.25 mg/day, and at higher doses will suppress follicular development, luteinizing hormone (LH), follicle stimulating hormone, and P.^{11,12} E2 acts at the estrogen receptor but is up to 100 times less potent than ethinyl estradiol (EE).¹³ A combination of E2's rapid metabolism and poor oral bioavailability and potency are related to its weak uterine endometrial effect, which is thought to have contributed to unacceptable bleeding patterns seen with previously developed E2-containing oral contraceptives.¹⁴

Efficacy

Anovulation, follicular activity, and cervical mucus and endometrial effects

The optimal dose of NOMAC in combination with 1.5 mg of E2 to suppress ovarian function was found to be 2.5 mg in a double-blind, randomized, dose-finding study.¹⁵ Inhibition of ovulation was confirmed by P and LH assays and was defined as suppression of both the mid-cycle LH peak (<10 mIU/mL) and P secretion (<3 ng/mL) during the luteal phase. This was a small study that recruited 41 women. Although ovulation was inhibited in all subjects in all arms of the study – receiving monophasic combinations of 0.625, 1.25 and 2.5 mg NOMAC and 1.5 mg E2 orally for 21 out of 28 days – it was noted that administering NOMAC in a 2.5 mg dosage in combination with E2 resulted in lower mean plasma levels of P, LH, and E2 than the other lower NOMAC doses. Moreover, the 2.5 mg NOMAC/E2 combination induced significantly higher levels of E2 and significantly lower levels of P, LH, and follicular stimulating hormone as opposed to the use of 2.5 mg NOMAC alone, suggesting a synergistic anti-gonadotropic action of E2 in addition to compensating for the suppression of endogenous estrogen secretion by 2.5 mg NOMAC alone.¹⁵

Table 1 Summary of published studies relevant to NOMAC/E2's efficacy and safety

Study	Study aim	Number of 28-day NOMAC/E2 treatment cycles	Total duration of NOMAC/E2 treatment in study (woman-years)	Pregnancies reported during NOMAC/E2 treatment	Reported in-treatment serious adverse events (no of subjects)	Frequently* reported in-treatment adverse events
Duijkers et al ^{17,†}	Effects of NOMAC/E2 on ovarian function in comparison to DRSP/EE	6	12 [^]	–	–	Headache Acne Diarrhea Nausea Weight gain
Agren et al ^{23,34}	Effects of NOMAC/E2 on hemostasis, lipid and carbohydrate metabolism, and endocrine function in comparison to LNG 150 µg/EE 30 µg	6	24.5 [^]	–	Worsening of a congenital mitral valve leak (1)	Upper respiratory tract infection Headache Metrorrhagia vaginal candidiasis
Christin-Maitre et al ¹⁶	Comparison of 24-day ^a and 21-day ^b NOMAC/E2 pill regimens	3	^a 8.5 [^] ^b 8.1 [^]	–	–	Headache Acne Pelvic pain Breast pain
Gaussem et al ²⁴	Effects of NOMAC/E2 on hemostasis in comparison to LNG 100 µg/EE 20 µg	3	10.4 [^]	–	–	Headache Dysmenorrhea
Mansour et al ²⁰	Comparison of efficacy and tolerability of NOMAC/E2 to DRSP/EE	13	1,292.5	4	Severe menorrhagia (1)	Acne Irregular withdrawal bleeding Weight gain Headache
Sørdal et al ³⁵	Effects of NOMAC/E2 on bone mineral density in comparison to LNG 150 µg/EE 30 µg	26	86 [^]	–	–	Not reported
Westhoff et al ¹⁹	Comparison of efficacy, safety, and tolerability of NOMAC/E2 to DRSP/EE	13	1,146	13	Cholelithiasis (2) Cholecystitis (1) Optic neuritis (1) Migraine (1)	Acne Weight gain Irregular withdrawal bleeding Metrorrhagia

Notes: *Incidence of adverse event in $\geq 5\%$ of subjects treated with NOMAC/E2 in the study except where stated; [†]incidence of adverse event in $> 10\%$ of subjects treated with NOMAC/E2 was reported as frequent in this study; [^]not specifically stated in publication but calculated from study data based on subjects who completed study; ^arefers to 8.5, the woman-years calculated for the 24-day group in this study; ^brefers to 8.1, the woman-years calculated for the 21-day group in this study.

Abbreviations: EE, ethinyl estradiol; E2, 17-beta estradiol; DRSP, drospirenone; LNG, levonorgestrel; NOMAC, nomegestrol acetate.

A double-blind randomized study¹⁶ on suppression of follicular growth by the combination of NOMAC/E2 (2.5 mg/1.5 mg) compared the effects of two dose regimens on ovarian activity over three 28-day cycles. Subjects were randomized to either NOMAC/E2 for 24 days with a 4-day placebo interval per cycle or NOMAC/E2 for 21 days with a 7-day placebo interval per cycle. No pregnancies occurred in the 72 women who completed the study, and there was no evidence of ovulation in either group. However the mean diameter of the largest follicle was significantly smaller in the 24-day group. This greater inhibition of follicular growth with the 24-day NOMAC/E2 regimen than the 21-day NOMAC/E2 regimen suggested that the shorter pill-free interval results

in greater suppression of ovarian activity and hence better contraceptive efficacy.¹⁶

An earlier open-label randomized study¹⁷ showed no ovulation in the 32 women treated with NOMAC/E2 (24/4-day regimen) over six 28-day treatment cycles, as with the 16 women treated with drospirenone (DRSP) 3 mg in combination with EE 30 µg (DRSP/EE, 21/7-day regimen) with whom they were compared. Maximum follicular diameters of > 15 mm, a value suggestive of follicular activity associated with ovulation, were observed in two women in the DRSP/EE group but in no women in the NOMAC/E2 group. There was a greater decrease in the likelihood of sperm penetration of the cervical mucus (Insler score)¹⁸ in the NOMAC/E2 group (-74%) in comparison to the

DRSP/EE group (−56%) in cycle 1 of the study. Also, a marginally greater reduction in mean maximum endometrial thickness of women in the NOMAC/E2 group than the DRSP/EE group after six treatment cycles was observed.¹⁷

Incidence of pregnancy

A Phase III trial¹⁹ conducted in the Americas – 89 gynecology and general practitioner clinics in the United States, Canada, Argentina, Brazil, Chile, and Mexico – evaluated the contraceptive efficacy of NOMAC/E2 (n=988) in comparison with a monophasic COC containing DRSP 3 mg and EE 30 µg (DRSP/EE, n=344) in women aged 18–50 over 1 year (thirteen 28-day treatment cycles). In this open-label randomized trial there was a cumulative pregnancy rate of 1.09 (95% confidence interval [CI]: 0.63–1.88) in the NOMAC/E2 group, which was better but not statistically significantly different from the rate of 1.75 (95% CI: 0.83–3.66) observed in the DRSP/EE group.¹⁹

A parallel study²⁰ was conducted in women aged 18–50 across Europe, Australia, and Asia. NOMAC/E2 (n=1,142) was compared with DRSP/EE (n=410) over 1 year or thirteen 28-day treatment cycles as well. The cumulative pregnancy rate in the NOMAC/E2 group (0.33, 95% CI: 0.12–0.87) was lower than in the DRSP/EE group (0.64, 95% CI: 0.21–1.97) but this difference was not statistically significant either.²⁰ See Table 1 for a summary of published studies relevant to NOMAC/E2's efficacy and safety.

Safety

Animal studies that evaluated the steroid receptor selectivity of NOMAC have provided valuable data regarding its improved safety profile in relation to medroxy-progesterone acetate and other synthetic progestins.²¹ Preclinical dose toxicity studies with NOMAC, E2, and NOMAC/E2 showed expected gestagenic and estrogenic effects. Fetotoxicity as seen with E2 exposure was observed in the reproductive toxicity studies. While NOMAC is not genotoxic, no genotoxicity nor carcinogenicity studies were done with NOMAC/E2.³

The absence of androgenicity in NOMAC appears to have a neutral effect on metabolic factors and on blood vessels.²² E2, which is structurally identical to endogenous E2, may also be safer than EE due to a lesser effect on the liver and effectively hemostasis and carbohydrate and lipid metabolism.¹⁰ As NOMAC/E2 is metabolized by the liver, renal impairment is unlikely to affect its metabolism. There are however no studies on NOMAC/E2 use in renal and hepatic impaired individuals.³ No safety concerns were observed with multiple dosing of up to five times the daily

dose nor with single dosing of up to 40 times the daily dose of NOMAC/E2.³ Hypersensitivity to NOMAC/E2 has been reported but its frequency is yet to be determined.³

Adverse events

In an open label randomized study²³ comparing NOMAC/E2 and levonorgestrel (LNG) 150 µg in combination with EE 30 µg, LNG/EE, for six 28-day treatment cycles, NOMAC/E2 was found to have a similar adverse event (AE) profile to LNG/EE. Upper respiratory tract infection (six and five subjects), headache (three and seven subjects), acne (two and four subjects), influenza (one and four subjects), metrorrhagia (three and one subjects), and vaginal candidiasis (two and one subjects) were AEs occurring in the NOMAC/E2 and LNG/EE groups respectively. Four women in the NOMAC/E2 group discontinued treatment due to depression, nausea, and a combination of tachycardia, calf pain and limb weakness. Four women in the LNG/EE group discontinued treatment due to decreased sexual desire, nausea, and headache. The only serious adverse event (SAE) reported was worsening of a congenital mitral valve leak in the NOMAC/E2 group and the subject was withdrawn.²³

During the 1-year comparison of NOMAC/E2 and DRSP/EE in the Americas, five of the 35 SAEs that had occurred were considered attributable to the study treatments, and all of which had occurred in the NOMAC/E2 group.¹⁹ These five SAEs were cholelithiasis (two), cholecystitis (one), optic neuritis (one), and migraine (one). AEs of one or more considered to be treatment-related had been reported in 48.8% of the NOMAC/E2 and 36.3% of the DRSP/EE treatment groups respectively. Frequently reported AEs were more likely in the NOMAC/E2 group than the DRSP/EE group: acne (16.4% compared with 8.7%), weight gain (9.5% compared with 5.2%), irregular withdrawal bleeding (9.1% compared with 0.5%), and metrorrhagia (5.8% compared with 2.7%).¹⁹

In the 1-year comparison of NOMAC/E2 and DRSP/EE in women across Europe, Australia, and Asia, three SAEs were considered treatment-related.²⁰ One SAE, “severe menorrhagia”, had occurred in the NOMAC/E2 group and the other two – “deep vein thrombosis left calf” and “systemic lupus erythematosus with concomitant patellar tendon bearing” – in the DRSP/EE group. AEs of one or more considered to be treatment-related had been reported in 51.2% and 37.0% of the NOMAC/E2 and DRSP/EE groups respectively. Frequently reported AEs in these respective groups were acne (15.3% and 7.1%), irregular withdrawal bleeding (11.7% and 0.4%), weight gain (7.9% and 6.2%), and headache (6.6% and 6.2%).²⁰

In the study comparing 24-day and 21-day regimens of NOMAC/E2 over three 28-day treatment cycles, there was no SAE nor were there any discontinuations due to an AE.¹⁶ Nineteen of the 72 women who completed this study – nine in the 24-day group and ten in the 21-day group – had experienced at least one AE. The AEs most frequently reported were headache, acne, pelvic pain, and breast pain with no significant difference between the two treatment groups.

In a Phase IIa double-blind randomized study of three 28-day treatment cycles of either NOMAC/E2 or LNG 100 µg in combination with EE 20 µg there were no SAEs.²⁴ The most frequently reported AEs in the NOMAC/E2 and LNG/EE groups respectively were also headache (four and five subjects), dysmenorrhea (four and three subjects), and acne (two and five subjects).

No remarkable changes from baseline were observed in the routine laboratory parameters of women treated in the two studies that compared NOMAC/E2 (total – 2,130) with DRSP/EE (total – 754) over 1 year.^{19,20}

Cardiovascular effects

A prolonged QT interval, the time period between start of the heart's ventricular depolarization and the end of ventricular repolarization, can cause arrhythmias. Persistent ventricular tachyarrhythmias (torsades de pointes) can lead to sudden death. The potential of drugs to cause prolonged QT interval is therefore determined as part of their safety profile.²⁵ NOMAC/E2's ability to prolong the QT interval was determined, in both therapeutic (2.5/1.5 mg) and suprathreshold (12.5/7.5 mg) doses, in a thorough QT/QTc study.²⁶ This study's design complied with the E14 guidance of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.²⁷ One hundred and eighty-nine healthy women aged 18–50 were randomized into one of four treatment groups – NOMAC/E2 2.5/1.5 mg (therapeutic dose), NOMAC/E2 12.5/7.5 mg (suprathreshold dose), placebo, or minofloxacin.²⁶ A safety analysis was also done for all participants who received the study drug – any AEs, SAEs or death. One hundred and eighty-two women completed the study (mean age 35±9) with the seven discontinuations in the treatment groups having been due to personal reasons (two minofloxacin, one NOMAC/E2 2.5/1.5 mg), AEs (one minofloxacin, one placebo), and positive urinary drug test (one minofloxacin, one placebo). No clinically relevant prolongation of the mean QTcF interval was observed after daily administration of either therapeutic or suprathreshold doses of NOMAC/E2 over the 2-week study period.

C-Reactive Protein (CRP)

CRP is an inflammation marker that has been found to be a useful risk marker of cardiovascular disease.²⁸ Agren et al reported an increase in serum CRP levels in both NOMAC/E2 (+67%) and LNG/EE (+258%) groups after six 28-day treatment cycles, however significantly smaller ($P<0.001$) in NOMAC/E2 users.²³

Blood pressure and heart rate

A number of factors have been implicated in the pathophysiology of raised blood pressure with hormonal contraceptive use.²⁹ One possible mechanism is by hormonal contraceptives activating the renin-angiotensin-aldosterone pathway in the liver leading to increased circulating mineralocorticoids, increased plasma sodium and subsequent fluid retention thus raising circulating blood pressure. This pathway is activated by EE. The effect of a combined hormonal contraceptive's (CHC's) estrogen component on mineralocorticoid activity and blood pressure can therefore be counteracted by the CHC's progestogen if it has anti-mineralocorticoid properties, as seen in CHC preparations containing DRSP.³⁰ NOMAC was not found to reduce the beneficial effects of E2 on coronary artery responses in non-human primates.³¹ E2's effect on the liver and subsequent mineralocorticoid activity is lesser than that of EE.³²

No remarkable changes in the blood pressure measurements from baseline were observed in the two 1-year comparison studies conducted across Europe, Asia and Australia,²⁰ and the Americas¹⁹ involving a total of 2,130 women who used NOMAC/E2.

No differences were observed in the blood pressure and heart rate measurements of 18 healthy women prior to and after 6 months of using either a quadriphasic formulation of E2 valerate (E2V) in combination with dienogest (DNG) (DNG/E2V, n=11) or monophasic E2 (E2, 1.5 mg) in combination with NOMAC 2.5 mg (NOMAC/E2, n=7).³³ These women had been invited to participate in the study after routine counseling on all contraceptive options and they had spontaneously chosen one of the COC formulations under investigation. Both groups of women who completed the study were similar in age (mean 32.5±7.49), of normal body mass index (mean 22.87±4.08), normotensive and non-smoking. The authors gave a detailed explanation of method used in obtaining the day- and night-time measurements over 24 hours. Although this was not meant to be a comparative study of these two COC formulations, no differences were reported between DNG/E2V and NOMAC/E2 in their effects on the blood pressures and heart rates of the women.

Hemostasis

Agren et al reported on an open-label study where 121 women were randomized to receive either NOMAC/E2 or LNG 150 µg in combination with EE 30 µg (LNG/EE).²³ Various parameters were measured to assess the thrombin turnover/fibrinolysis (prothrombin 1 + 2 and D-dimer), anticoagulatory (endogenous thrombin potential (ETP)-based activated protein C [APC] sensitivity ratio, activated partial prothrombin time [aPTT]-based APC sensitivity ratio, antithrombin III activity, Protein C, Protein S) and procoagulatory (Factor II, Factor VII coagulant activity, activated Factor VII, Factor VIII activity) indices of the women at baseline and after six 28-day treatment cycles of either COC. One-hundred and five women completed the study, of which 53 were in the NOMAC/E2 group. Study discontinuations (n=3) prior to treatment were in the LNG/EE group and due to acne, withdrawn consent or personal reasons (found new job). There were 13 women who discontinued after commencement of treatment due to AEs (n=8, four in each COC treatment group), pregnancy wish (one), moved to another city (one), and loss to follow up (three). Of these discontinuations, seven had been in the NOMAC/E2 group while six had been in the LNG/EE group. For fibrinolysis indices, there was essentially no change in prothrombin 1 + 2 in the NOMAC/E2 group while there was an insignificant increase ($P=0.085$) in the LNG/EE group; D-dimer results were inconclusive for both groups because over half of values were undetectable. For anticoagulatory indices, there was a statistically significant increase in endogenous thrombin potential-based APC sensitivity ratio in both groups, though this was much greater in the LNG/EE group ($P<0.001$); the activated partial prothrombin time-based APC sensitivity ratio was nearly unchanged in both groups; only small changes were observed from baseline in the antithrombin III, Protein C, and Protein S parameters in both groups. However, these parameters were statistically significantly different between the treatment groups ($P<0.001$) except for free Protein S.

A Phase IIa, double-blind randomized parallel group study²⁴ determined hemostatic effects of NOMAC/E2 compared to LNG 100 µg in combination with EE 20 µg (LNG/EE) after three 28-day treatment cycles. Ninety women aged 18–38 and body mass index of 17–30 kg/m² were randomized and completed the study. The primary endpoint was change in prothrombin fragment 1 + 2 levels but other fibrinolysis, anticoagulatory, and procoagulatory indices were also determined. There was an increase in prothrombin fragment 1 + 2 levels in the LNG/EE group but not in the NOMAC/E2 group (−0.02 versus +0.08 nM, $P<0.01$). There was also a

significantly higher increase in Factor II and free Protein S levels in the LNG/EE group as well as greater increases in D-dimer, plasminogen, Factor VIII, and Protein S activity in comparison to the NOMAC/E2 group. Antithrombin levels were reduced with LNG/EE treatment but not with NOMAC/E2. For platelet aggregation there were no significant differences between the two groups.

Lipids

Serum total cholesterol and triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), lipoprotein (a) and apolipoprotein A1 + apolipoprotein B levels were determined before and after six 28-day treatment cycles of NOMAC/E2 and LNG/EE (150 µg/30 µg).²³ Of the 105 women who completed this study, 53 had been randomized to the NOMAC/E2 group. No relevant changes were seen in the total cholesterol, HDL-C, LDL-C, total triglycerides or lipoprotein (a) of women in the NOMAC/E2 group. Women in the LNG/EE group had no change in total cholesterol, but had decreased HDL-C, increased LDL-C, increased total triglycerides and small changes in lipoprotein (a). These differences in the LNG/EE group compared to the NOMAC/E2 group were statistically significant. For apolipoprotein A1 and apolipoprotein B, women in the NOMAC/E2 group had a significantly greater increase ($P=0.006$) and significantly smaller increase ($P<0.001$) respectively in the NOMAC/E2 group compared to those women in the LNG/EE group.

Carbohydrate metabolism

Oral glucose tolerance test, glucose, and insulin levels were measured before (t=0) and at 30, 60, 90, 120, and 180 minutes after drinking a glucose solution (75 g/100 mL) in the same open-label randomized study reported by Agren et al.²³ While there were negligible changes to these parameters in women in the NOMAC/E2 group, women in the LNG/EE group had increases in all the measured parameters with statistically significant differences observed ($P\leq 0.002$) between the NOMAC/E2 and LNG/EE groups. No changes in HbA_{1c} were observed in either NOMAC/E2 or LNG/EE groups.

SHBG

Both groups of women in the open-label randomized study mentioned earlier (Agren et al)²³ had increased SHBG after six 28-day treatment cycles. However this was significantly greater ($P=0.019$) in the NOMAC/E2 group (44%) than the LNG/EE (150 µg/30 µg) group (22%).

Endocrine function

NOMAC/E2 appears to have less of an effect on endocrine function than LNG/EE (150 µg/30 µg). Agren et al³⁴ also reported on the changes in the markers of endocrine function with NOMAC/E2 in comparison to LNG/EE after six 28-day treatment cycles. One-hundred and five women completed this study. Total cortisol, CBG, and thyroxine binding globulin increased from baseline in both groups, however this increase from baseline to cycle 6 was significantly higher in the LNG/EE group ($P < 0.001$). There were only small changes observed in the thyroid stimulating hormone and free thyroxine (T4) levels from baseline with no statistically significant differences between the two groups. Androgens and their precursors decreased, with a significantly greater reduction in the LNG/EE group than the NOMAC/E2 group except for free testosterone. There was a greater decrease in free testosterone relative to total testosterone in the NOMAC/E2 group.³⁴

Bone mineral density

The effects of NOMAC/E2 and LNG/EE (150 µg/30 µg) on bone mineral density (BMD) after 26 28-day treatment cycles were compared in an open-label prospective randomized study.³⁵ Seventy-five women of reproductive age (20–35 years) completed this 2-year study in Norway. Differences seen in BMD from baseline for lumbar spine and femoral neck between the treatment groups were not significant ($P = 0.19$ and $P = 0.57$ respectively). There were also no significant changes in BMD from baseline or between the treatment groups for total hip and trochanter.

Breast cancer risk

There is currently no clinical data to demonstrate the risk of breast cancer with NOMAC/E2 use however available evidence suggests its possible effect on human breast tissue. E2 shows similar proliferative effects on human breast cancer cells compared to EE.³⁶ NOMAC on the other hand does not cause increased proliferation in normal or human breast cancer cells.^{37–39} NOMAC/E2 was found to cause less breast cell proliferation when compared to E2 alone³⁶ and has some anti-proliferative effect on human breast cancer cells.⁴⁰ Intermittent compared to continuous use of NOMAC/E2 is also associated with less breast cell proliferation and estrogen α receptor expression.³⁶ Also, recent data on CHCs and breast cancer have demonstrated no increased risk of breast cancer,^{41,42} with lower estrogen content and non-androgenic progestogens being responsible for this effect.^{43,44} E2 is a natural estrogen and considered no more estrogenic than 20 µg

of EE while NOMAC is a non-androgenic progestogen. This in theory suggests that NOMAC/E2 should have no higher breast cancer risk than the low dose COCs that are currently in use. See Table 1 for a summary of published studies relevant to NOMAC/E2's efficacy and safety.

Patient acceptability

Patient acceptability of NOMAC/E2 on its own has not been studied however this may be suggested by tolerability, compliance, and continuation that has been reported. NOMAC/E2 has been shown to be as well tolerated as other COCs in the randomized studies that have been discussed so far.

Compliance

High compliance rates – defined by most studies as one tablet taken daily on at least 95% of treatment days – have been reported with NOMAC/E2, and similar for its study comparators.^{17,20,23,35} For example, in the largest study where 2,152 women were randomized to either NOMAC/E2 (n=1,613) or to DRSP/EE (n=539), 2,126 were treated and 1,552 completed the trial, with a high compliance rate of 94.9% for NOMAC/E2 users and 91.4% for DRSP/EE users.²⁰

Continuation rates

Continuation is a possible indication of a patient's acceptability of a contraceptive method. In the randomized study reported by Agren et al,²³ 105 women completed of the 118 women who had begun treatment following randomization to either NOMAC/E2 or LNG/EE (150 µg/30 µg), with continuation rates of 88.3% and 89.7% respectively. Gaussem et al also concluded that NOMAC/E2 was just as acceptable as LNG/EE (100 µg/20 µg) after three 28-day treatment cycles in a double-blind randomized study as there were no discontinuations in either group due to AEs.²⁴

However in the 1-year open label randomized study of NOMAC/E2 in comparison to DRSP/EE in the Americas, 41% and 38% respectively discontinued treatment.¹⁹ The main reason for discontinuation in both groups was AEs, which was significantly higher in the NOMAC/E2 (17.3%) group than the DRSP/EE group (10.1%). The most frequently reported treatment-related AEs in the NOMAC/E2 and DRSP/EE groups were acne (16% compared to 8.7%), weight gain (9.5% compared with 5.2%), and irregular withdrawal bleeding (9.1% compared with 0.5%).

Discontinuation of NOMAC/E2 and DRSP/EE treatments was 28.2% and 23.4% respectively in the 1-year comparison study reported by Mansour et al.²⁰ Discontinuation mainly

due to AEs was again higher in the NOMAC/E2 group (18.2%) compared to the DRSP/EE group (10.5%). The most frequently reported treatment-related AEs in the NOMAC/E2 and DRSP/EE groups were acne (15.3% compared to 7.1%), irregular withdrawal bleeding (11.7% compared 0.4%), and weight gain (7.9% compared to 6.2%).

Acne

NOMAC may be expected to reduce the incidence of acne and seborrhea because of its anti-androgenic effects. About a third of women in the NOMAC/E2 group (32.7%) and DRSP/EE group (32.5%) had acne prior to treatment in the 1-year study reported by Mansour et al.²⁰ In some of these women, acne improved (NOMAC/E2 – 48.4%; DRSP/EE – 61.4%) while in a few their acne worsened (NOMAC/E2 – 7.2%; DRSP/EE – 1.8%). Overall, about 75% of women in both groups saw no change, with acne occurring or worsening in 9.9% and 4.0% of women in the NOMAC/E2 and DRSP/EE groups respectively.

The women with acne prior to either NOMAC/E2 or DRSP/EE treatment in the 1-year study reported by Westhoff et al¹⁹ was similar at 33.3% and 33.8% respectively, and their acne decreased over time. However the DRSP/EE group were more likely to see improvement in acne ($P<0.001$), and there were more new cases of acne in the NOMAC/E2 group (12.4%) than the DRSP/EE group (4.2%).

Bleeding patterns

A comparison of 24-day and 21-day regimens of NOMAC/E2 in 72 women over three 28-day treatment cycles showed significantly shorter mean duration of withdrawal bleeding with the 24-day regimen.¹⁶ However there was no difference in the frequency of intermenstrual or withdrawal bleeding between the two groups.

Mean total vaginal, intermenstrual, and withdrawal bleeding were all significantly shorter with NOMAC/E2 than with LNG/EE (100 µg/20 µg) over three 28-day treatment cycles in another study.²⁴

For both groups of women that completed 1 year of NOMAC/E2 (n=988) and DRSP/EE (n=344) in the Americas, the median duration of unscheduled bleeding or spotting during the study fluctuated between 2 and 3 days.¹⁹ Although the mean number of bleeding days was significantly lower in the NOMAC/E2 group ($P<0.001$), there was a higher incidence of unscheduled bleeding or spotting as well as absence of withdrawal (scheduled) bleeding in comparison to the DRSP/EE group.

Similarly, the median duration of unscheduled bleeding or spotting was 2–3 days in the NOMAC/E2 group (n=1,142) and 1–4 days in the DRSP/EE group (n=410) in the other 1-year study.²⁰ There was significantly shorter, and sometimes absent, scheduled bleeding in the NOMAC/E2 group in comparison to the DRSP/EE group.

Body weight

In both the NOMAC/E2 and DRSP/EE groups of women there was significant increase in weight from baseline (medians of 1 kg and 0.2 kg respectively) after 1 year ($P=0.001$) in the study reported by Westhoff et al.¹⁹ Mansour et al also reported increase in mean body weight of 1 kg in the NOMAC/E2 group, significantly higher ($P=0.001$) than the increase of 0.3 kg observed in the DRSP/EE group over 1 year.²⁰

Reversibility

Seventy-two percent of women were determined to have ovulated in the post treatment cycle during the comparison study of 24-day and 21-day regimens of NOMAC/E2, as suggested by their P levels.¹⁶ The changes in their cervical mucus scores and endometrial thickness also suggested a return to their normal menstrual cycles. Similarly, 79% of women in the NOMAC/E2 group were observed to have a return of ovulation in the post treatment cycle in comparison to 75% of women in the DRSP/EE group after six 28-day treatment cycles in another comparison study.¹⁷

Limitations

This review presents a compilation of published data on the pharmacological product NOMAC 2.5 mg/E2 1.5 mg (NOMAC/E2). It does not include any information from ongoing or unpublished studies, nor post-marketing surveillance data. Only two randomized trials over 1-year periods have been reported that were purposely to determine NOMAC/E2's efficacy and safety, and both of these trials used DRSP 3 mg/EE 30 µg as the comparator. Existing safety data on NOMAC/E2 is limited, with the information on safety presented in this paper mainly on its impact on physiological parameters or surrogate markers, which may not be predictive of specific adverse clinical outcomes.

Conclusion

Available evidence suggests NOMAC/E2 in a 24/4 regimen is possibly more effective at inhibiting ovulation, safer, and is associated with less withdrawal bleeding than COCs like DRSP/EE and LNG/EE. Studies also suggest a slightly higher incidence of acne, unscheduled bleeding, and weight

gain with NOMAC/E2 compared to DRSP/EE. Compliance, continuation, and adverse effects of NOMAC/E2 are comparable with DRSP/EE and LNG/EE. However, NOMAC/E2 is relatively new to the market, having been introduced in Europe as recently as 2011 and is yet to be approved for use in the USA. Further experience with its use is required to see whether this new COC will gain wider acceptance the world over.

Disclosure

The authors have no conflicts of interest to disclose.

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