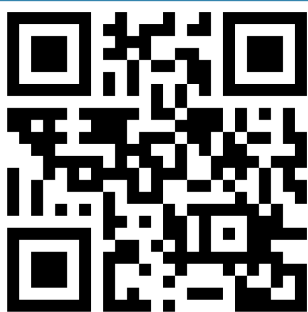


New developments in oral contraception: clinical utility of estradiol valerate/dienogest (Natazia[®]) for contraception and for treatment of heavy menstrual bleeding: patient considerations

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Abstract: Natazia[®] is a new oral contraceptive with estradiol valerate and dienogest in a unique multiphasic formulation that includes a shortened hormone-free interval. This new formulation has been approved for both contraception and also as a treatment for heavy menstrual bleeding in women who desire to use oral contraceptives as their method of birth control. It is marketed in the US as Natazia[®] and elsewhere as Qlaira[®]. This article will review the properties of each of the major new features of this pill: estradiol used in place of ethinyl estradiol, dienogest as the progestin, and the unique dosing pattern of this product. It will also summarize the results of the pivotal clinical trials of contraceptive effectiveness, bleeding patterns, safety and tolerability. The lessons learned from the clinical trials about the effectiveness of this formulation in the treatment of excessive menstrual bleeding will be summarized. Also, results of trials comparing this new pill to other popular formulations for “menstrually-related” symptoms and for potential female sexual dysfunction related to use of oral contraceptives will be presented. This review will suggest how all this information might be used to counsel women about how to use this pill most successfully.

Keywords: oral contraceptives, estradiol valerate, dienogest, heavy menstrual bleeding, menorrhagia, dynamic dosing

Introduction

Oral contraceptives have evolved dramatically over the last half century to achieve two important objectives: (1) to enhance safety and (2) to increase patient satisfaction by reducing side effects and by providing noncontraceptive benefits. Safety has been improved primarily by reducing the estrogen content of pills from the 150 mcg mestranol found in the Enovid-10 formulation to the sub-50 mcg ethinyl estradiol (EE) doses found in modern birth control pills. Progestin doses were reduced in parallel with estrogen doses and new progestins were introduced to reduce unscheduled bleeding and to reduce side effects, such as acne, facial hair growth, and oily skin. No further reduction in EE doses is anticipated because existing low-dose EE pills have been found to be associated with more unscheduled bleeding and spotting.¹ Multiphasic formulations provided different dosing options to increase endometrial support throughout a cycle while reducing total progesterone exposure over the cycle. Hormone-free intervals were shortened in low-dose formulations to obtain better control of bleeding in subsequent cycles. The numbers of hormone-free intervals were reduced to minimize the number of scheduled bleeds that women experience with oral contraceptive use.

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The newest oral contraceptive (Natazia[®], [Bayer Healthcare, Berlin, Germany], Qlaira[®] [Bayer Healthcare, Berlin, Germany]) represents innovation in all of these aspects. The estrogen used is estradiol valerate, an estrogen with weaker metabolic impacts than ethinyl estradiol. The progestin is dienogest (DNG), which is known to profoundly suppress the endometrium for cycle control and to impact directly on ovarian function for ovulation inhibition. These hormones are arranged in a very pragmatic dosing pattern that builds on the features of each hormone to provide desirable cycle control and also shortens the hormone-free interval. A brief history helps to put these new developments into context.

Estrogen and progestins in combined oral contraceptives (COCs)

In every oral contraceptive, the progestin provides the lion's share of contraceptive activity – suppressing ovulation and thickening cervical mucus. All oral contraceptives utilize synthetic progestins because natural progesterone is poorly absorbed orally, has a short half-life, and is sedating. The progestins used in the first three so-called generations of birth control pills were all derived from 19-nortestosterone. Estrogen has routinely been relied upon to provide endometrial stability and to potentiate the activity of the progestin by increasing concentrations of progestin receptors in the endometrium in order to make scheduled bleeding predictable and to minimize unscheduled bleeding.² Synthetic estrogens have been used in all of the first four generations of pills because the natural compound – estradiol – is both poorly absorbed when administered orally and is rapidly metabolized by the liver;³ when used in a pill with norethindrone estradiol resulted in an unacceptable bleeding profile.^{4–9} However, the synthetic ethinyl estradiol (EE) is highly resistant to such degradation¹⁰ and can be used in a once-a-day dosing but induces greater metabolic impacts compared to estradiol.^{11,12}

DNG

DNG is a progestin that is relatively new to US clinicians, but it has been used by European prescribers in several reproductive health products. In combination with ethinyl estradiol, DNG has been used in oral contraceptives (Valette[®], Jeanine[®], Celimona[®]).^{13–15} In combination with E₂V in 1 mg and 2 mg doses, DNG has been used in postmenopausal hormone therapies (Climodien[®], Lafamme[®]). As a single agent therapy for endometriosis (Visanne[®]), DNG has been shown

to be as effective in reducing the pain associated with that condition as GnRH agonists without the profound side effects of those agonists.^{16–20} DNG has profound impacts on the endometrium. DNG has good specificity to the progesterone receptor in the endometrium compared with other progestins. Administered orally, DNG showed the strongest endometrial activity (ED₅₀ = 0.0042 mg/kg) in McPhail test. DNG showed higher plasma concentrations than those of the other progestins.²¹ It has been shown to suppress angiogenesis in endometrial autografts treated with DNG, as demonstrated by reduced size of microvasculature network and decreased microvascular density.²² DNG also inhibits aromatase and cyclooxygenase expression and estradiol production in endometriotic stromal cells.²³

Estradiol in oral contraceptives

There is ongoing interest worldwide in using E₂ in oral contraceptives, but to date there are only three oral contraceptives that have successfully replaced ethinyl estradiol with estradiol. The first is Femilar[®], which contains E₂V/CPA, and which is available in Finland; its use is restricted to perimenopausal women or women age 35–40 years in whom a COC containing EE is not appropriate.²⁴ A second is a monophasic 17β-E₂/norgestrel acetate formulation available in Europe for contraception.²⁵ The third is this E₂V/DNG formulation discussed in this paper. In the US, and in European countries, E₂V/DNG is approved not only for pregnancy protection, but also as treatment of idiopathic heavy menstrual bleeding (HMB) in women who choose to use oral contraceptives as their method of birth control.

This paper will discuss in detail each of the unique components of this E₂V/DNG pill, its mechanisms of action, and the benefits and the risks of this formulation, with an emphasis on information that will be most helpful in patient counseling.

Description of the product

Natazia[®] is a 4-phasic formulation with a unique estrogen step-down, progestin step-up dosing that was empirically developed to inhibit ovulation with the lowest dose hormone while maintaining acceptable cycle control. Effective inhibition of ovulation with DNG is seen at the 2 mg dose.²⁶ However, DNG also exerts a potent suppressive effect on the endometrium, so much so that if administered alone or simultaneously with a weak estrogen, unacceptable unscheduled spotting and bleeding result. Understanding that it would function best if the endometrium had slight unopposed estrogen stimulation exposure to proliferate and

sensitize it to the action of the DNG, several different dosing regimens were tested. Many provided good ovulation control but produced unacceptable bleeding.²⁷ A 2 mg DNG multiphasic combination was found to solve the problem of poor cycle control with E,²⁷ but it was discovered that in combination with estrogen, higher doses of DNG would be needed to suppress ovulation. The “dynamic dosing” outlined in Figure 1 was most successful in producing low Hoogland scores (low ovarian activity) and good cycle control.²⁸ The first two tablets each contain 3 mg estradiol valerate. On day 3, the estrogen dose is decreased to 2 mg and 2 mg DNG is added. This combination is continued through the end of the first week (pill days 3–7). The next 17 pills each contain the same 2 mg estradiol valerate, but the DNG dose is increased to 3 mg to ensure sustainability of endometrial stroma and to enhance ovulation inhibition. In the pills for days 25 and 26, the DNG is removed and the estradiol valerate levels are dropped to 1 mg. The final two pills in the packet are placebos. Estrogen dominance provided early in the cycle increases receptors for progestin, promotes the initial proliferation of the endometrium, and renders the endometrium more responsive to increased progestin doses later in the cycle. This enhances endometrial stromal stability and improves cycle control.² Extending estrogen at the end of the cycle may prevent fluctuations in estrogen serum level and increases endometrial stability in the subsequent cycle.

Pharmacodynamics

Components

Estradiol valerate is a synthetic prodrug of 17 β -estradiol. Its chemical name is estra-1,2,5(10)-triene-3,17-diol (17 β) 17-pentanoate and its empirical formula is C₂₃H₃₂O₃. The valerate side chain is rapidly cleaved in the intestinal wall and in the liver to form 17 β -estradiol and valeric acid. Estradiol valerate 2 mg is bioequivalent to 1.5 mg micronized estradiol.^{29,30} The estradiol is further metabolized into estrone and estrone sulfate following the same hepatic metabolic pathways observed during metabolism of ovarian-produced estradiol.

A 2 mg daily dose of E₂V has the same impacts on the hypothalamic-pituitary-ovarian axis, ovarian activity, endometrial stimulation, and vaginal surface cell maturation as a 20 mcg dose of ethinyl estradiol.^{29,31} However, estradiol is considered weaker than EE in several metabolic dimensions.³² Estradiol has lower bioavailability than EE;³³ it has less sustained biological activity because it is rapidly metabolized to estrone. Functionally, estradiol results in less induction of hepatic protein synthesis, especially of less sex hormone-binding globulin (SHBG), angiotensinogen, and clotting factors.^{10–12}

DNG is chemically described as (17 α)-17-hydroxy-3-oxo-19-norpregna-4,9-diene-21-nitrile. Its empirical formula is C₂₀H₂₅NO₂. DNG is a progestin that manifests properties of both 19-nortestosterone derivatives as well as those associated with progesterone. The 17 α -ethinyl group, typical of many 19-nortestosterone progestin derivatives, is replaced by a 17 α -cyanomethyl group. Clinically, DNG is similar to 19-nortestosterone derivatives in that it has a short plasma half-life, strong progestational effect in the endometrium, and high oral bioavailability.^{21,26,34} DNG is similar to progesterone derivatives in that it demonstrates both a relatively low inhibition of gonadotropin secretion^{35,36} and anti-androgenic activity³⁷ (about 40% of cyproterone acetate).³⁸ DNG has no interaction with specific transport proteins, such as SHBG or cortisol-binding globulin (CBG). DNG activates progesterone receptors and has antiandrogenic activity in androgen receptors but is neutral on glucocorticoids, mineralocorticoid, and estrogen receptors alpha or beta.²¹ DNG, therefore, is devoid of estrogenic, glucocorticoid, and mineralocorticoid activities. It does bind to albumin (90%), but a relatively high 10% of the drug circulates unbound. DNG does not impact lipid metabolism, liver enzymes, hemostatic parameters, or thyroid production.³⁹

Absorption and distribution

Estradiol valerate is completely absorbed by the intestinal mucosa and is cleaved to release 17 β -estradiol and valeric acid during absorption through the intestinal mucosa and first-

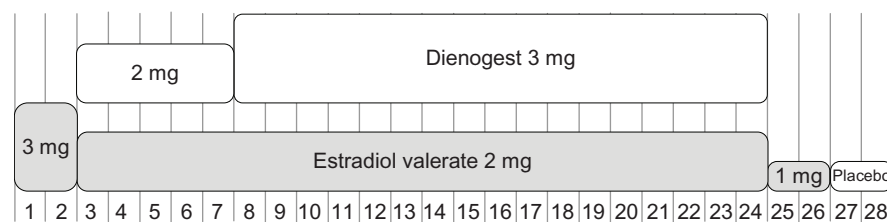


Figure 1 Hormonal components of Natazia® (estradiol valerate/dienogest) administered using an estrogen step-down and a progestin step-up regimen over a 28-day treatment cycle (with 26 days of active tablets).

pass metabolism in the liver.⁴⁰ Estradiol undergoes a profound hepatic first-pass metabolism; before entering the systemic circulation, 95% of the dose is metabolized by cytochrome P450-3A enzymes into estrone, estrone sulfate, and estrone glucuronides.⁴¹ Serum E_2 C_{max} values of 0.0706 ng/mL on day 1 and 0.0660 ng/mL on day 24 were achieved at a median time of 6 hours on day 1 and 3 hours earlier on day 24. This dosing regimen maintains rather constant estrogen levels throughout the cycle for both total exposure and trough levels. The mean area-under-the-curve (AUC)₀₋₂₄ of estradiol was similar on days 1 and 24 (1.246 ng-h/mL and 1.239 ng-h/mL). Trough concentrations were stable, ranging from 0.0336 to 0.0647 ng/mL.

Following the usual pattern of metabolism of endogenous estradiol, day 1 serum estrone values at 4 hours were 0.416 ng/mL and serum estrone sulfate at 3 hours rose to 16.384 ng/mL. Similar values on day 24 were 0.444 ng/mL and 13.478 ng/mL. The corresponding AUC₀₋₂₄ for estrone were 5.750 ng-h/mL (day 1) and 6.814 ng-h/mL (day 24) and for estrone sulfate 177.489 ng-h/mL (day 1) and 163.820 ng-h/mL (day 24). The estrone to estradiol ratio was 5:1, suggesting that ovarian E_2 production is inhibited by lack of follicular growth.⁴² Concentrations of E_2 were within normal ranges of the early follicular phase of a spontaneous menstrual cycle (median 31 pg/mL).

Food increases peak concentration (C_{max}) of estradiol by 23%, but the AUC concentration is not affected. The steady state is reached after 3 days and is not influenced by SHBG levels. Estradiol is 38% bound to SHBG and 60% bound to albumin, leaving 2%–3% circulating in free form.⁴² There is no accumulation of any estrogen compounds.

During the 28 days of E_2 V/DNG administration, no statistically significant changes were seen in serum levels of CBG, and SHBG levels increased by only 40%.⁴³ Intravenous administration of E_2 V/DNG resulted in an apparent volume of distribution for E_2 of 1.2 L/kg.⁴²

DNG is rapidly and almost completely absorbed, with a bioavailability of about 90%.⁴⁴ Food decreases C_{max} of DNG by 28%, but does not affect AUC.⁴⁵ The pharmacokinetics of DNG are dose proportional within this dosing range. C_{max} of DNG on day 24 was 82.9 ng/mL, with minimum concentrations that ranged from 6.8 to 15.1 ng/mL. Steady state was reached after 3 days. The AUC₀₋₂₄ value on day 24 was 80.9 ng-h/mL; the mean accumulation ratio for AUC₀₋₂₄ was 1.24.⁴² DNG is 90% bound to albumin, with 10% circulating in free form. DNG does not bind to SHBG or CBG. Volume of distribution at steady state after intravenous administration of 85 mcg of 3H-DNG is 46 L.

Metabolism and elimination

Approximately 95% of the estradiol is metabolized via the cytochrome P450-3A system, during the first-pass metabolism into the usual metabolites of endogenous estradiol – estrone, estrone sulfate, and estrone glucuronide⁴² – before entering the systemic circulation. Estradiol and its metabolites are predominantly renally excreted, with only 10% fecal excretion. Although the plasma half-life of circulating estradiol is about 90 minutes, the terminal half-life of estradiol is about 14 hours (13–20 hours), due to enterohepatic recirculation and a large pool of estrogen sulfates and glucuronides.

DNG is specifically metabolized by cytochrome P450-3A4 hydroxylation and conjugation mostly into inactive metabolites. In the plasma, DNG levels remain unchanged primarily because of rapid renal excretion of its metabolites. The terminal half-life of DNG is about 11 hours. Urinary to fecal excretion ratio is 3:1. In the first 24 hours, 42% of an oral dose is excreted renally; by 6 days, 63% is excreted.

Mechanisms of action

At the dose of 2 mg/day, DNG effectively inhibited ovulation in all but 3.13% of women. At this dose, DNG exerts only a moderate antigonadotropic activity, but its induction of granulosa cell apoptosis in the follicle also contributes to the effective ovulation inhibition provided by DNG.^{35,46} In combination with E_2 V, however, the 3 mg dose was found to be needed for ovulation suppression.²⁸ At those doses, the anti-estrogenic effect thickens the cervical mucus to block sperm transport into the upper genital tract.⁹ DNG exerts specific activity on the endometrium that is ten times more potent than levonorgestrel.⁴⁷ on endometriotic implants. The estradiol valerate contributes only slightly to suppression of the follicle stimulating hormone.

Candidates for E_2 V/DNG

Reproductive-age women who are at risk for unwanted pregnancy are the prime target population for this product. Even though the metabolic impacts of this estradiol-containing pill may be less profound than ethinyl estradiol containing birth control pills, the contraindications to use of E_2 V/DNG pills are identical to those for all other combination hormonal contraceptives. The US Medical Eligibility Criteria for the CDC makes no recommendations for individual COC formulations.

Administration

The recommendations for starting E_2 V/DNG differ slightly from those of other pills. For one thing, 9 days of non-hormonal backup method use is recommended with initiation

of E₂V/DNG pills. The prescribing information provided by the FDA also advises that a woman should begin taking E₂V/DNG on the first day of her menstrual bleeding. Women switching from another formulation are told to start E₂V/DNG on the first day of scheduled bleeding.⁴⁸ Women switching from patches, vaginal rings, implants or IUDs are told to start the E₂V/DNG the day that they have those other methods removed. Women using progestin-only pills or injections should start E₂V/DNG on the day they would re-dose with their prior method.

Missed-pill instructions

Because of the unique dosing pattern of pills, the instructions in the prescribing information to be provided to women who miss pills are extremely detailed and vary depending upon which particular pill is missed.⁴⁸ The product instructions recommend action if the woman is more than 12 hours late in taking her daily pill. Before that time, the woman is told just to take the pill as soon as she remembers and to take her next pill at the usual time; no backup method or emergency contraception (EC) is needed. The detailed instructions for missed pills are displayed in Table 1.

These instructions may increase urgent consultations from users. In addition, these FDA instructions have two other significant shortcomings. The first shortcoming is that there is no guidance for EC. The second shortcoming is that in some instances, the guidelines are not feasible for US women. For example, the recommendation that a woman who misses 2 days of the pills between days 18–24 should throw her current pack away and take the day 1 pill from a new pill pack ignores the fact that, in the US, a woman who misses a pill on day 18 might not be able to get her next pack from the pharmacy for several more days without having to pay full price for it.

Others have reformatted the missed-pill instructions so they do not appear to be so complicated, but those recommendations suffer from the same shortcomings.⁴⁹ A much more prudent approach would be to advise the woman to take two pills the day she realizes she has missed any pills for longer than 12 hours, and to continue taking one pill a day and use backup for at least 9 days. The only remaining question is if she needs to also use levonorgestrel EC. In general, if a woman has had sex and misses any early (first nine) pills without using any other method, or if she has missed more than five pills later in the pack, she should consider using levonorgestrel EC. This simplified approach may increase unscheduled spotting/bleeding, since the hormonal balance

offered by the dynamic dosing will be disrupted, but this approach should provide pregnancy protection and may reduce questions from patients.

Drug–drug interactions

Prescribing information for E₂V/DNG pills advises that women who are using concomitant medications that are strong inducers of cytochrome P450-3A14 (such as carbamazepine, phenytoin, rifampin, and St John's wort) should not rely on E₂V/DNG alone for contraception while they are using those drugs or for at least 4 weeks after discontinuing use of these inducers. In a study of rifampicin for 4 days, the geometric mean ratios of E₂ AUC and C_{max} were 56% and 75%, while those values for DNG were 17% and 48%.⁵⁰ It should be noted though, that virtually all other antibiotics have no clinically significant impact on plasma concentrations of these synthetic steroids.

Concomitant use of other, weaker CYP3A4 inducers (such as barbiturates, bosentan, felbamate, griseofulvin, oxcarbazepine, or topiramate), may reduce the efficacy and/or increase the likelihood of unscheduled spotting or bleeding. In this situation too, the FDA recommends use of a backup method during use of these drugs and for at least 4 weeks after their cessation.

Use of strong CYP3A4 inhibitors (such as ketoconazole) increases serum AUC levels of E₂V and DNG by 57% and 186%.⁵⁰ Moderate CYP3A4 inhibitors (such as high-dose erythromycin) increase the AUC (0–24 hr) for E₂V by 33% and for DNG by 62%. Long-term use of these agents may increase estrogen-related side effects, but the impact on the risk of venous thromboembolism is unknown. Use of other CYP3A4 inhibitors (such as azole antifungals, cimetidine, verapamil, macrolide, diltiazem, antidepressants, and grapefruit juice) may also increase plasma concentration of these sex steroids, especially if those inhibitors are used on a prolonged basis.

HIV/HCV protein inhibitors and non-nucleoside reverse transcriptase inhibitors have variable effects on cytochrome P450 activity. Some function as inhibitors, while others induce enzyme activity. When these agents are combined in therapy, their net effect must be calculated.

Clinical application: contraception

The contraceptive efficacy of E₂V/DNG has been evaluated in four Phase III clinical trials cited below. The first trial was an open-label, non-comparative study conducted in 50 European centers, in which a total of 1377 healthy women aged 18–50 contributed 23,368 cycles, where “healthy” excluded

Table 1 Missed pill instructions for patients from prescribing information**What should you do if you miss any pills?**

If you forgot to start your new pack of pills on time, **you may already be pregnant**. Use backup contraception (such as condoms and spermicides) every time you have sex. Get a pregnancy test if you have any questions.

- Do not take more than 2 pills in one day. On the days you take 2 pills to make up for missed pills, you may feel a little sick in your stomach (nauseous).
- If you start vomiting or have diarrhea within 4 hours of taking your pill, take another pill of the same color from your pack.

If you are less than 12 hours late taking your pill

- Take your pill as soon as you remember.
- Take the next pill at the usual time.
- You do not need to use backup contraception.

If you miss **ONE PILL for more than 12 hours**

Days 1–17

- Take your missed pill immediately.
- Take your next pill at the usual time (you may have to take two pills that day).
- Use backup contraception for the next 9 days.
- Continue taking one pill each day at the same time for the rest of your cycle.

Days 18–24

- Do not take any pills from your current blister pack and throw the pack away.
- Take Day 1 pill from a new blister pack.
- Use backup contraception for the next 9 days.
- Continue taking one pill from the new blister pack at the same time each day.

Days 25–28

- Take your missed pill immediately.
- Take your next pill at the usual time (you may have to take two pills that day).
- No backup contraception is needed.
- Continue taking one pill each day at the same time for the rest of your cycle.

If you miss **TWO PILLS in a row**

Days 1–17 (if you miss the pills for Days 17 and 18, follow the instructions for Days 17–25 instead)

- Do not take the missed pills. Instead, take the pill for the day on which you first noticed you had missed pills.
- Use backup contraception for the next 9 days.
- Continue taking one pill each day at the same time for the rest of your cycle.

Days 17–25 (if you miss the pills for Days 25 and 26, follow the instructions for Days 25–28 instead)

- Do not take any pills from your current blister pack and throw the pack away.
- Take Day 3 pill from a new blister pack.
- Use backup contraception for the next 9 days.
- Continue taking one pill from the new blister pack at the same time each day.

Days 25–28

- Do not take any pills from your current blister pack and throw the pack away.
- Start a new pack on the same day or start a new pack on the day you usually start a new pack.
- No backup contraception is needed.
- Continue taking one pill from the new pack at the same time each day, for the rest of your cycle.

If you are still not sure of what to do about the pills you have missed:

- Call your health care provider.
- Use backup contraception (such as condoms and spermicides) anytime you have sex and keep taking 1 pill each day.

women with BMI > 30 and smokers over age 30.³⁰ While the safety of the drug was judged based on the experience of all the study participants, the contraceptive efficacy was based on the pregnancies in women ≤ 35 years. A total of 13 pregnancies occurred, 12 in the target younger population; five pregnancies were classified as method failure. The Pearl Index for the total study was 1.04. The adjusted Pearl Index

was 0.40 for women 18–35 years. E₂V/DNG was found to be as effective in women age 25 as age 35.⁵¹ The Kaplan–Meier estimate of contraceptive failure at the end of 1 year was 0.010 and the cumulative failure rate for the full 20 cycles was 0.0142 (95% CI: 0.0080–0.251) for women 18–35 years. Overall, 79.5% of subjects were satisfied or very satisfied with their therapy.³⁰

The second trial conducted in North America was another multicenter, open-label, single-arm study of 490 healthy women aged 18–35 years treated for up to 28 cycles.⁵² The weight range for these women ranged from 40–100 kg, but the maximum BMI was again 30 kg/m². Pregnancies were counted if they occurred in women within 7 days following their last day of pill use. Cycles in which pregnancy did not take place but a second contraceptive method was used were deleted from the calculations. The Pearl Index for this trial was 1.64 pregnancies per 100 women-years. The contraceptive failure rate at the end of the first 12 months was 0.016.

Efficacy data also derived from a comparative trial of E₂V/DNG versus 30 mcg EE/LNG, in which 399 women age 18–50 received seven-cycles of E₂V/DNG. No pregnancies occurred during this trial.⁵³

A pooled analysis of these three trials as well as one previously unpublished study reported that for the total 2266 women who received E₂V/DNG, the adjusted first-year Pearl Index was 0.72. The unadjusted PI was 1.27.⁵²

Bleeding profiles

The bleeding pattern with E₂V/DNG pills was rated by the majority of subjects to be satisfactory or very satisfactory, but the bleeding patterns with this formulation may be different from what women expect with combination pills. Counseling patients about those expected patterns in advance may reduce calls from patients and potential dissatisfaction.

Information about the bleeding profile with the E₂V/DNG formulation derives from bleeding diaries maintained by subjects in the three efficacy trials described above. The primary outcomes for bleeding patterns in these studies included the number of bleeding or spotting days and the number and length of bleeding or spotting episodes. Because of the differences in pill dosing regimens, it is important to study the definitions that were used in these trials. Bleeding was defined as blood loss that was heavy enough to require the use of more than one sanitary protection product a day. All other bleeding was defined as spotting. A bleeding episode included all days of spotting or bleeding with ≤2 days of no bleeding or spotting before or after the episode. Scheduled bleeding was defined as an episode of bleeding or spotting that began not more than 4 days before the progestin withdrawal (pill day 20 for E₂V/DNG and pill day 17 for EE/LNG). Absence of scheduled bleeding was the lack of bleeding until that day in the next cycle. All other bleeding was classified as unscheduled (intracyclic) bleeding.⁹

Mean duration of bleeding was 4.0–4.6 days. The median was 4.0 days. The maximum intensity of bleeding

was predominantly spotting or light bleeding.⁵² Amenorrhea occurred in 19.0%–24.0% of cycles. Unscheduled spotting and bleeding generally decreased over time, but in every cycle, 10%–23% of women experienced intracyclic bleeding.⁵² In this formulation, there are only two placebo pills (pills 27 and 28), but pills 25 and 26 contain no progestin. As a result, the median day that the scheduled progestin-withdrawal bleeding started was cycle day 26. However, some women did not start their bleeding until they started their next pack of pills. Women need to be counseled to initiate the next pack of pills on time and not to wait for the onset of bleeding. They also need to understand that delayed scheduled bleeding is not “breakthrough bleeding,” and, therefore, should not raise any concerns about decreased efficacy.

In the multicenter, double-blind, double-dummy controlled, randomized study directly comparing E₂V/DNG to the 20 mcg EE/LNG 100 mcg formulation, 798 women aged 18–50 were randomized and followed for seven cycles of pill use. The duration of scheduled bleeding episodes with E₂V/DNG was 4.5 days; with the EE/LNG pills, the duration was 5.1 days ($P < 0.05$).^{51,53} Significantly more women rated their scheduled bleeding as “spotting” or “light” with the E₂V/DNG formulation ($P < 0.0001$) (see Figure 2). Amenorrhea rates were also significantly higher (19.4% vs 7.7%) among E₂V/DNG users ($P < 0.0001$).⁵³ The majority of E₂V/DNG users (56.9%) experienced at least one cycle without any bleeding, but 74% of the women who had amenorrhea on E₂V/DNG pills missed only one or two bleeding episodes. Intracyclic bleeding was not statistically different overall in any cycle between the two formulations. Combining all the days of the bleeding (scheduled and unscheduled) during the first 90-day reference period, the E₂V/DNG users experienced 17.3 days of bleeding compared to 21.5 days for EE/LNG users ($P < 0.0001$). The number of days of bleeding decreased in both groups during the second 90-day reference period, but the E₂V/DNG group still experienced significantly fewer days of any bleeding or spotting (13.4 vs 15.9 days) ($P < 0.0001$). The proportion of women who rated themselves as somewhat satisfied or very satisfied with treatment was identical in the two arms (79.4% E₂V/DNG and 79.9% EE/LNG). Only 0.3% discontinued pill use due to adverse events. Interestingly, no subject in the E₂V/DNG arm discontinued pill use for reasons related to bleeding complaints.⁵³

Clinical application: treatment of HMB

The light bleeding and the high rates of amenorrhea that subjects experienced in the pivotal contraceptive trials

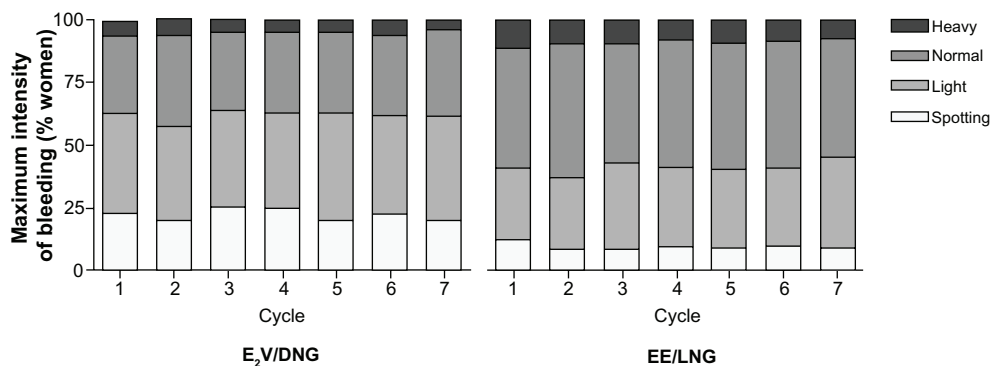


Figure 2 Maximal intensity of scheduled withdrawal bleeding in women treated with E₂V/DNG and EE/LNG in cycles 1–7.

Note: Copyright © 2012, Elsevier. Reproduced with permission from Ahrendt HJ, Makalová D, Parke S, Mellinger U, Mansour D. Bleeding pattern and cycle control with an estradiol-based oral contraceptive: a seven-cycle, randomized comparative trial of estradiol valerate/dienogest and ethinyl estradiol/levonorgestrel. *Contraception*. 2009;80(5):436–444.

suggested that E₂V/DNG might have potential as a treatment for excessive menstrual blood loss.

Heavy menstrual bleeding is reported to affect 10%–30% of all reproductive-age women and 22% of women over age 35.^{54–56} Heavy menstrual bleeding can have significant adverse impacts on a woman's health, including anemia, fatigue, and even death. A woman's quality of life is clearly diminished by these adverse health impacts, but HMB also diminishes her quality of life in many other dimensions, including the social embarrassment of accidental spills, pain, and the restriction on her activities on heavy flow days. The impact of heavy bleeding has on decreasing a woman's annual salary was estimated by Côté in the late 1990s to average more than \$1600.⁵⁷ The out-of-pocket costs for sanitary protection in women with heavy bleeding requiring 48 tampons/month has been estimated to total \$300 annually.⁵⁸

More recently, an analysis of health care resource use by women with newly diagnosed idiopathic HMB found that women with such HMB had significantly higher all-cause resource use than did controls. Relative risks for hospitalization (2.7), ER visits (1.35), and outpatient visits (1.29) were all statistically significantly greater in women with HMB than in control women. Average annualized all-cause costs were \$2607 higher, with \$1313 of that cost being directly related to HMB.⁵⁹

To evaluate the efficacy of E₂V/DNG for the treatment of heavy and/or prolonged menstrual bleeding without organic pathology, two double-blind, randomized, placebo-controlled studies were conducted on nonanemic women over 18 years of age.⁶⁰ The pooled results of those two trials are presented here. To identify women with idiopathic bleeding problems, preadmission tests included endometrial biopsy, pelvic ultrasound, and serum tests for thyroid dysfunction and bleeding disorders. Prior to randomization, women had to demonstrate in a 90-day run in evaluation that their bleeding

was excessive (at least two episodes with blood loss \geq 80 mL based on standardized modified alkaline hematin method), prolonged (at least 2 episodes lasting \geq 8 days), and/or frequent (\geq 5 episodes with \geq 20 days of bleeding). Only women with documented idiopathic excessive bleeding were randomized. In a 2:1 allocation, 269 women received E₂V/DNG and 152 received placebo. Barrier methods were used by all women in the trial.

All 421 women who received at least one dose of study medicine were included in the intent-to-treat (ITT) study population, upon which the results listed below were derived.⁶⁰ Heavy bleeding was the most common problem studied; 85% of the E₂V/DNG group and 89% of the placebo group had that problem. In the ITT group, reduction of menstrual blood loss was rapid and sustained over the seven-cycles of treatment. Median blood loss for all women with any bleeding disorder was reduced in the last cycle by 88% in the E₂V/DNG group and by 24% in the placebo group (see Figure 3). The mean total reduction in 90-day menstrual blood loss from baseline to the last 90-day reference period for this group was 414 \pm 373 mL for the E₂V/DNG arm and 109 \pm 300 mL for the placebo group ($P < 0.0001$). Women in the study for heavy blood loss experienced an even greater reduction in blood loss of 454 \pm 375 mL with E₂V/DNG and 118 \pm 302 mL with placebo. Overall, a 20%, 50%, and 80% reduction in blood loss was achieved by 92%, 80%, and 40% of E₂V/DNG users, respectively. The median number of standardized sanitary protection products per cycle was reduced by 52% from 79 to 38 products, but the range included one woman who used 215 fewer products. Mean ferritin levels increased by 42.4% in the E₂V/DNG group, rising from 17.9 to 25.5 ng/mL, whereas the placebo group experienced a 14% increase rising from 17.2 to 18.7 ng/mL. As the authors point out, this 88% reduction in blood loss is significantly more impressive than the 40.4% reduction associated with oral tranexamic

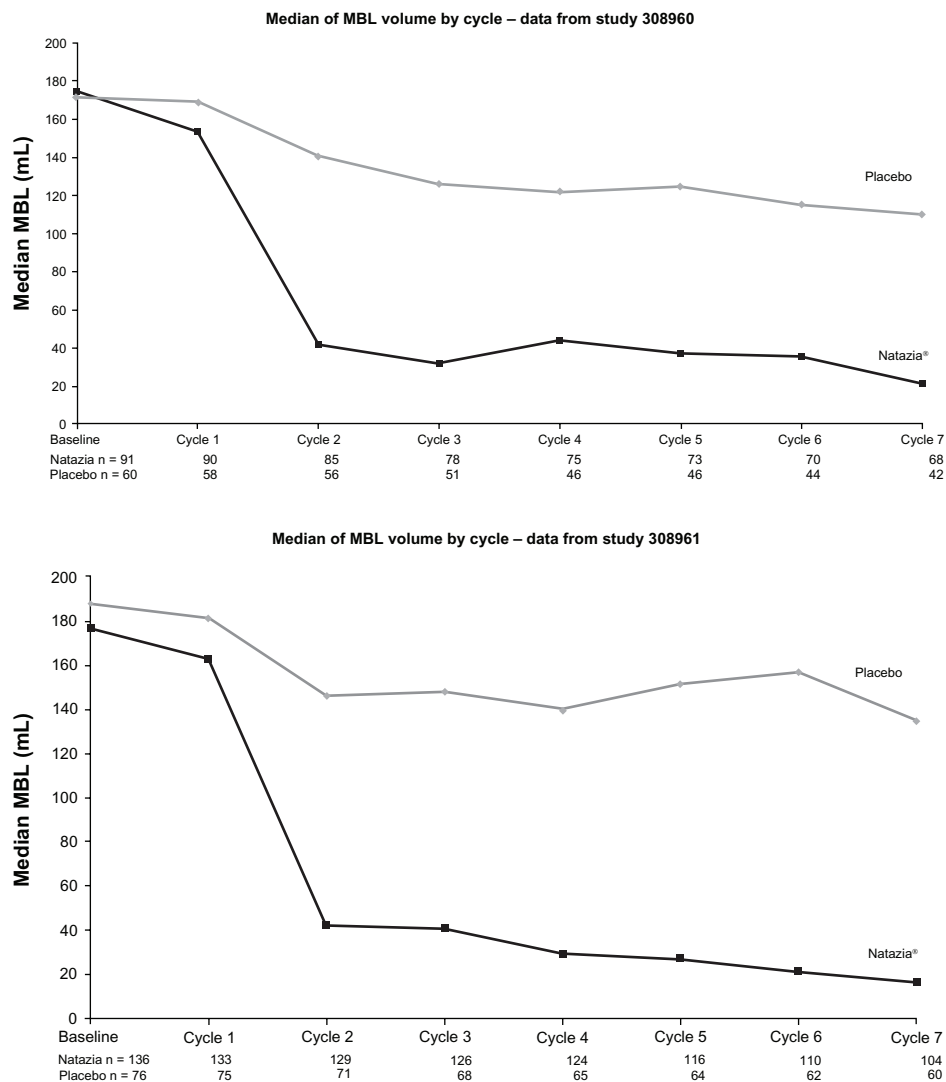


Figure 3 Median menstrual blood loss volume by cycle in women who entered the studies with symptoms specific to heavy menstrual bleeding.⁴⁶

acid, the only other oral product that is FDA-approved for treatment of HMB.⁶¹ There are no head-to-head comparative trials between E₂V/DNG and any other oral contraceptive for the treatment of HMB. However, in a study comparing the LNG IUS to a 21/7 regimen with 20 mcg EE/1 mg NETA, blood loss reduction for the pill measured by PBAC scores was 68% at 12 months.⁶² In a second trial comparing the LNG IUS to use of a 30 mg EE/150 mcg LNG pill, in which blood loss was quantified using the alkaline hematin method, the mean reduction in MBL at 12 months with that pill was 35%.⁶³

Clinical applications: other

Given that the hormone-free interval has been previously identified as being associated in pills with the 21/7 regimens, with increased prevalence of unpleasant symptoms, such as pain and need for medication, it was thought that

the shortened hormone-free interval and the shorter, lighter scheduled bleeding episodes associated with E₂V/DNG might be associated with less physical discomfort than seen with the use of other popular pill formulations.

In two different multicenter, international clinical trials, the frequency and intensity with which the most common menstrual problems (pelvic pain and headaches) occurred with E₂V/DNG pills were compared in one study with the frequency and intensity of those problems with use of Ortho Tri-Cyclen® Lo® (Janssen Pharmaceuticals, Titusville NJ) and in another study with use of Microgynon (Bayer Healthcare, Berlin, Germany) (20 mcg EE/100 mcg LNG). In a six-cycle study with Ortho-Tri-Cyclen Lo, 400 symptomatic women had their baseline hormone-withdrawal symptoms compared with symptoms during cycle days 22–28 of cycle 6. Both pills rapidly and profoundly reduced the pain scores for headache

and pelvic pain in both individual scores and in combined scores, but the impact of E₂V/DNG was statistically superior for the combined scores ($P < 0.05$) (ClinicalTrials.gov identifier NCT 00754065). The same results were seen in the second trial that compared E₂V/DNG and EE/LNG pills; both pills significantly and promptly reduced those pain scores for headache and pelvic pain, but E₂V/DNG reduced scores much more significantly ($P < 0.0001$). Positive outcomes were also seen with E₂V/DNG in rescue medication use and clinical global assessments made by the blinded investigators. (ClinicalTrials.gov identifier NCT 00778609).

Building on that same logic, a double blind, double-dummy, multicenter, randomized, controlled, parallel group study was conducted to assess the safety and efficacy of E₂V/DNG compared to a 20 EE/100 mcg LNG pill in the treatment of primary dysmenorrhea in the CALM study. This study compared VAS scores during a run-in baseline two-cycle period to similar scores during the two cycles of pill use. Both agents significantly reduced pain scores, but in this case, there was no statistically significant difference in their efficacy in pain reduction (ClinicalTrials.gov identifier NCT 00909857).

Another study reported that pretreatment with E₂V/DNG prior to office operative hysteroscopy shorted procedure time and made the procedure easier for the surgeon and less painful for the patient compared to no treatment.⁶⁴

Safety and tolerability Hemostatic and metabolic effects

Historically, studies have shown that estradiol has less impact on hepatic protein synthesis than EE.^{10–12,62} The hemostatic effects of E₂V/DNG were compared to those of a 30 mcg EE 150 mcg LNG pill in a randomized, open-label crossover 3-cycle study that measured the impacts of selected different hemostatic parameters.⁶⁶ It was found that prothrombin fragments 1 + 2 and D-dimer levels were relatively unchanged but the authors concluded that the intraindividual absolute changes in prothrombin 1+2 and D-dimer from baseline to cycle three were less pronounced with estradiol valerate/DNG than with ethinyl estradiol/levonorgestrel. In a randomized open-label, single-center seven-cycle study of E₂V/DNG and a triphasic LNG pill with 30 mg EE. mean prothrombin fragment 1 + 2 and D-dimer levels were relatively unchanged with E₂V (−0.6% and −2.1%), but increased in the EE/LNG group (117.3% and 62.9%).⁶⁴ In a third open-label crossover study, women were randomized to E₂V/DNG or monophasic 30 mcg EE/LNG pills. Women used one study pill for 3 months, had

a 2-month wash out, and then used the other study pill. The intraindividual absolute change in prothrombin fragment 1 + 2 for E₂V/DNG vs EE/LNG was 0.00 nmol/L vs 0.03 nmol/L. For D-dimers, those changes were 38.9 vs 157.9 ($P = 0.01$).⁶⁸ Caution should be exercised when interpreting the results of these studies because these factors have not been shown to predict thrombosis risk.⁶⁹ Changes seen in vasoactive marker with E₂V/DNG use suggests a possible estrogenic vasorelaxant effect, but the clinical relevance of those changes has not been identified.⁷⁰

The impacts of E₂V/DNG pills on lipids were also studied extensively. In a randomized, open-label 7-cycle study, that pill was compared to a triphasic LNG pill. HDL cholesterol increased with E₂V/DNG by 7.9% and decreased by 2.3% with EE/LNG ($P = 0.055$). Mean LDL-C decreased by 6.5% with E₂V/DNG and by 3.0% with EE/LNG ($P = 0.458$). Other metabolic impacts, such as changes in SHBG, CBG and carbohydrate metabolism, were generally less pronounced with E₂V/DNG than with EE/LNG pills.⁶⁷ In contrast to EE containing formulations, prolactin levels tended to rise more over time with E₂V formulations.⁷¹

The endometrial safety of E₂V/DNG was established by endometrial biopsies done in a subset of women during the efficacy trial. Histology was compared at baseline (283 women) and between days 12–19 of cycle 20 (218 women). The second biopsy found no endometrial disease; 80.9% of women had atrophic, inactive or secretory endometrial findings.⁷²

Adverse event reporting

Pooling the data from the four pivotal trials involving 2131 women 18–54 years of age (1867 studied for up to 28 cycles and 264 studied for up to seven cycles), it was found that 11.4% of women discontinued due to adverse reactions.⁵² The most common complaints leading to discontinuation were menstrual disorders (2.4%), mood changes (1.2%), acne (1.1%), headaches (1.1%), and increased weight (0.7%). The common adverse events reported by more than 2% of women during their use of E₂V/DNG pills are shown in Table 2. In the comparative trial, more women in the E₂V/DNG arm complained of breast pain than those in the EE/LNG arm.⁷³ Serious adverse events included two cases of myocardial infarction (one in a 47-year-old smoker), two cases of ruptured ovarian cysts, deep vein thrombosis in a woman with a sprained ankle 9 days after cessation of E₂V/DNG, and focal nodular hyperplasia of the liver, uterine leiomyoma, acute cholecystitis, and chronic acalculous cholecystitis.

Table 2 Adverse events reported by $\geq 2\%$ of women in pivotal trials⁵²

Adverse event	Percent of women reporting (%)
Headache	12.7
Breast pain, tenderness	7.0
Menstrual disorders	6.9
Nausea or vomiting	6.0
Acne	3.9
Mood changes	3.0
Increased weight	2.9

Complaints of decreased libido or other sexual dysfunction issues were very infrequently mentioned by subjects using E₂V/DNG. However, there was concern that the relatively low androgenicity of the formulation might adversely affect sexual desire and other sexual parameters that in the past have been attributed to “androgen sensitivity.”⁷⁵ To test the impacts of E₂V/DNG on female sexual function, that pill was directly compared in a prospective clinical trial (Clinical Trials.gov identifier NCT 00764881) to a pill that is frequently prescribed to women who complain of low desire when using birth control pills, Microgynon. Women who had been diagnosed with oral contraception (OC)-associated female sexual dysfunction were enrolled in the 6-month comparative trial. The primary outcome was the change from baseline to cycle 6 in the nonweighted sum of Female Sexual Function Index sexual desire and sexual arousal component scores. Secondary efficacy variables encompassed most of the other tools available to gauge female sexual function (see Table 3). The most interesting finding was that both formulations raised female sexual dysfunction scores for combined desire and arousal scores to the point that the women no longer could be considered symptomatic. There were no differences in the impacts of the two different pills. All the mean changes from baseline for all the Female Sexual Functions Index

Table 3 Secondary end points of sexual function studied in HARMONY trials

Absolute values and change from baseline to cycle 2, cycle 4, and cycle 6 in each of the following:

- Female Sexual Function Index (FSFI) (component scores desire, arousal, lubrication, orgasm, satisfaction, pain, and total score)
- Female Sexual Distress Scale – Revised (FSDS-R) questionnaire results
- Quality of Life, Enjoyment and Satisfaction Questionnaire (Q-LES-Q) short version results
- Psychosocial General Wellbeing Index (PGWBI) questionnaire results
- Clinical Global Impression (CGI) assessment
- Vaginal pH measurements
- Atrophy Symptom Questionnaire (ASQ)
- Vaginal Health Assessment (VHA)

domains and the Psychological General Well-being Index showed improvements. There were some slight differences in the degree of improvement seen in anxiety where E₂V/DNG did better and in depressed mood where EE/LNG did better. The authors of the current study also concluded that, on oral contraceptives, female sexual function is complex and not related to androgenicity of the formulation the woman uses. The results of this study are consistent with findings of other investigators⁷⁶ who have determined that there is no relationship in reproductive-age women between sexual desire and serum testosterone levels.

Quality of life issues

Any contraceptive that significantly reduces the risk that a sexually active woman will become pregnant provides her enormous health benefits and contributes both to her quality of life and to her socioeconomic well-being. When that method also reduces discomfort associated with bleeding, these benefits are enhanced.⁷⁷ E₂V/DNG showed reduction in bleeding episodes, duration, and volume. For women with HMB, the use of E₂V/DNG provides additional benefits.

A post hoc analysis of the impact of E₂V/DNG on quality of life and daily function was performed based on the 7-month North American trial of heavy and prolonged menstrual bleeding.⁷⁴ The mean baseline work productivity impairment score was 4.1 on a 10-point Likert scale in the US and 4.0 in Canada. Those treated with E₂V/DNG had greater improvement in impairment scores and greater reduction in scores from baseline than the placebo users. (46.2%–47.3% vs 13.1%–16.1%). Average daily living impairment scores were 5.1 (US) and 4.6 (Canada); their reduction with E₂V/DNG was greater than with placebo (53.0%–56.0%) vs (24.8%–28.0%). In one clinical trial, more than 86% of women rated their physical and emotional well-being on E₂V/DNG as the same, better, or much better when compared to their pretreatment scores.³⁰

One recent study, which concluded that use of E₂V/DNG improved sexual quality of life, with enjoyment and desire improvements, noted as well a decrease in dyspareunia. Interestingly, investigators found that intracyclic peaking of desire, arousal, orgasm, enjoyment and sexual activity shifted from cycle day 14 in early months of the trial to cycle day 7 with longer use of the pill.⁷⁸

Candidates who may be particularly appropriate for E₂V/DNG use

Having evaluated the unique compounds of this new formulation (a weaker and shorter acting estrogen; a potent

progesterin with profound endometrial suppression), which, together with the unique dosing regimen, results in fewer, shorter, and lighter scheduled bleeding episodes, less discomfort from headaches and pelvic pain during those episodes and with no detectable adverse impact on sexual arousal or desire, it follows that many different women might want to use this formulation. The most obvious choice would be a woman with HMB who wants to use birth control pills as her method of contraception. Along these same lines, women who have significant pain with menses but still desire to have scheduled bleeding would benefit from this choice. Beyond that, women who prefer to use contraceptives that use less synthetic hormones might prefer to use a product with an estrogen that circulates as estradiol and all its natural metabolites. These women would be the reproductive-age counterparts of postmenopausal women who prefer “natural” estradiol to the more traditional conjugated estrogen products. Some experts have suggested that one group of women to consider as candidates for this pill would be the perimenopausal women.

Counseling messages that may improve contraceptive success with E₂V/DNG

There are several features about this new product that might raise questions or be helpful to address proactively with potential users.

- The pill packet itself is brighter with an array of different colored pills. Some have suggested that all the different colored pills may increase the risk of pill-taking errors.⁷⁹
 - Let women know that this formulation has been tailor-made to provide consistent estrogen levels throughout the month and to reduce unscheduled bleeding.
- The initial pill is to be started on the first day of bleeding. There is no flexibility in using Quick Start/Same Day Start protocols with this pill.⁸⁰
- The first two pills do not offer any substantial pregnancy protection; backup methods must be used for 9 days following pill initiation.
- Bleeding will typically be significantly different with this pill than women usually experience with other pills, but all of these changes are healthy, not at all harmful.
 - Bleeding will be lighter and shorter in duration.
 - Expect that occasionally there may be no bleeding between pill packs.
 - Pregnancy testing is needed only for symptomatic women and for those who miss two consecutive bleeds.
- Scheduled bleeding may start before all the pills in one packet are done (before the placebo pills) or it may not start until the woman has taken one or more pills from the next pack. This does not mean that the pill is not working.
- The missed-pill instructions in the prescribing information and in the patient counseling sections are far more complicated than with other formulations. There are applications that women can download to help them remember to take Natazia on a daily basis (QlairApp) and will also provide instructions on what to do if a pill is missed. The problem is that some of these recommendations are not feasible in certain settings. This is particularly true in situations in which the instructions direct the woman to throw away her current pill pack and start a new pack early. For them, suggest that they take two tablets the day they notice their problem, then continue to take one tablet a day and use backup for 9 days. When they arrive at pill 25, they should start a new pack using pill number 3. If they need EC, LNG-EC can be used on the first day, followed by once-a-day pill taking until pill 25 is reached, as noted above. Bleeding patterns may be disrupted by this approach, but pregnancy protection should be maintained.
- Women who report decreased libido with pill use or voice concerns about the possibility of decreased libido with pill use might appreciate this formulation.
- Even though a more natural and potentially safer estrogen is being used in this formulation, it is not possible to say that this pill will be any safer than existing EE-containing pills. To estimate the risk for the rare serious adverse events, an extensive multicenter study in many countries is monitoring outcomes of over 100,000 women using a variety of modern pills under the direction of the FDA. Those results will be available after 2014.

Conclusion

This new formulation with E₂V/DNG in a unique dosing pattern provides stable but lower estrogen levels, good ovulation suppression with less pronounced inhibition of gonadotropins, good endometrial control and fewer metabolic changes, especially in hepatic protein synthesis. For the patient, these features translate into good contraceptive efficacy, shortened and lighter bleeding episodes, high satisfaction ratings, fewer problems with bleeding-associated headaches and pelvic pain, and no adverse OC-

related sexual dysfunction. Women with HMB will enjoy significant reduction in their blood loss and improvement in both iron levels and hemoglobin. The importance of the reduced metabolic impacts observed in clinical trials of E₂V/DNG formulations is being investigated in an ongoing, large-scale postmarketing prospective, international, controlled, noninterventional, cohort active surveillance study called INAS-SCORE (International Active Surveillance Study-Safety of Contraception: Role of Estrogen), which is comparing arterial and venous thromboembolism of Natazia®/Qlaira® to other oral contraceptives in real-world use.

Disclosure

The author serves on the advisory board for Bayer and has received honoraria for serving on their speaker's bureau. The author's clinic receives research grants for contraceptive studies.

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