Estradiol Valerate and Estradiol Valerate/Dienogest (Natazia) Tablets
The First Four-Phasic Oral Contraceptive
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INTRODUCTION
Oral contraceptives (OCs) have been used worldwide by women for more than 50 years for the purpose of preventing pregnancy. According to the Centers for Disease Control and Prevention (CDC), 10.7 million women in the U.S. used OCs between 2006 and 2008, making these drugs the leading modality for birth control in the U.S. Only 0.3% of women taking OCs, when used as recommended, experienced an unintended pregnancy within the first year of use. These medications have evolved from monophasic to biphasic and triphasic selections, with the goal of imitating pregnancy hormones.

More recently, contraceptives have been a source of controversy because adverse effects appear to be more prevalent. Various combinations and doses have been introduced to reduce adverse effects and to increase the tolerability of OCs. Estradiol valerate is considered to be less potent in terms of inducing he- 
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In May 2010, the FDA approved estradiol valerate and estradiol valerate/dienogest (E2V/DNG, Natazia, Bayer). Natazia contains two female hormones, an estrogen (estradiol valerate) and a progestin (dienogest). “Four- phasic” refers to the progestin and estrogen doses, which vary four times throughout each 28-day treatment cycle.

INDICATIONS AND USAGE
Natazia is indicated for pregnancy prevention.

CLINICAL PHARMACOLOGY
The chemical name of estradiol valerate is Estra-1,3,5(10)-triene-3,17-diol (17β)-17-pentanoate, and its empirical formula is C23H32O3. The empirical formula of dienogest is C20H25NO2.

Mechanism of Action
E2V/DNG prevents pregnancy by suppressing ovulation with its combination of hormones. Changes in the integrity of the endometrium and cervical mucus may occur, resulting in unfavorable conditions for the penetration of sperm and a reduced likelihood of implantation.

Pharmacokinetics
Absorption and distribution: Following oral administration, estradiol valerate is cleaved to 17β-estradiol and valeric acid. Estradiol is bound to albumin (60%) and sex hormone–binding globulin at 40%, whereas dienogest is 90% bound to albumin. Although food increases the peak concentration (Cmax) of estradiol by 23% and decreases the Cmax of dienogest by 28%, the area-under-the-curve (AUC) concentration is unaffected. The apparent volume of distribution was approximately 1.2 L/kg for estradiol and 46 L for dienogest after intravenous (IV) administration.

Metabolism and elimination: The bioavailability of estradiol is 3% following oral administration of estradiol valerate. Estradiol also undergoes a first-pass effect, with 95% of the dose metabolized by the cytochrome P450 (CYP 450) 3A enzyme and entering into systemic circulation. The resulting metabolites of estradiol are estrone and its sulfate and glucuronide conjugates. Dienogest is metabolized via hydroxylation and conjugation.

Estradiol and its metabolites are excreted primarily in the urine, with fecal elimination accounting for about 10% of the total. Dienogest remains essentially in its unchanged form in plasma and is renally excreted in the form of metabolites. The half-lives of estradiol and dienogest are approximately 14 hours and 11 hours, respectively.

CLINICAL TRIALS
Palcios et al.7
An open-label, noncomparative study included 1,377 female subjects between 18 and 50 years of age in 50 centers across Europe. Subjects received E2V/DNG for 20 cycles. The primary efficacy parameter was the number of unintended pregnancies during treatment. The Pearl Index was the primary efficacy endpoint used to evaluate the reliability of the OC in this study. This index is designed to track pregnancies that resulted after the onset of treatment and occurred within seven days after the final tablet was administered.

Thirteen pregnancies were reported during the study. Five pregnancies were reported before treatment was initiated, and 12 pregnancies were reported after treatment was completed. Medication-related adverse drug reactions occurred in 19.8% of the participants.

The most commonly reported AEs included metrorrhagia (1.7%), acne (1.0%), and weight gain (0.9%). Of the women participating in the study, 79.5% reported satisfaction rates that were moderate to very high. At the end of the study, the researchers concluded that this combined OC regimen of E2V/DNG provided effective, reliable contraception.
Ahrendt et al.8

A multicenter, double-blind, double-dummy study, conducted in Germany between 2005 and 2006, was aimed at assessing the safety of E2V/DNG in terms of bleeding patterns and cycle control. A group of 804 healthy women between 18 and 50 years of age were randomly assigned, in a 1:1 ratio, to receive E2V/DNG and placebo or, alternatively, ethinyl estradiol/levonorgestrel (EE/LNG) (e.g., Seasonale, Triphasil) and placebo for 28 days. The primary efficacy endpoints included bleeding patterns and cycle control parameters.

Treatment was initiated on the first day of menses and continued for a period of seven cycles. The women were monitored initially at screening, at the baseline assessment, during treatment, and/or at a final examination or at premature discontinuation. An analysis of bleeding patterns showed significantly fewer bleeding and spotting days in subjects receiving E2V/DNG (17.3 ± 10.4 days; median, 16), compared with those who received EE/LNG (21.5 ± 8.6 days; median, 21) (P < 0.0001).

Another primary outcome measured was cycle control during treatment. Within the E2V/DNG group, 77.7% to 83.2% reported scheduled withdrawal bleeding per cycle, whereas 89.5% to 93.8% in the EE/LNG group reported experiencing withdrawal bleeding (P < 0.0001). More women in the E2V/DNG group experienced an absence of scheduled withdrawal bleeding compared with those in the EE/LNG group. One unintended pregnancy was reported in a woman receiving EE/LNG2. More women in the E2V/DNG group rated the treatment as very satisfactory (39.8%); only 35.3% of women in the EE/LNG group reported high satisfaction rates.

An overall assessment of this study found that OCs containing EE/LNG provided an acceptable bleeding pattern and cycle control profile that was as efficacious as OCs containing EE/LNG.

### ADVERSE DRUG EFFECTS

Nausea, menstrual irregularities, breast tenderness, depression, and decreased sexual desire are common AEs associated with hormonal contraception. Studies of E2V/DNG reported similar AEs in clinical trials.9 In the study by Palacios et al.,9 breast pain (at a rate of 3.6%) was the most commonly reported treatment-related AE.3 Metrorrhagia (1.7%), acne (1%), and weight gain (0.9%) were the most common reasons for study discontinuation. In the study by Endrikat et al., the most common treatment-related AEs were headache (18%), abdominal pain (11.7%), and acne (9.2%).3

There were twice as many discontinuations because of possible treatment-related AEs with higher doses of DNG (i.e., depression, headache, worsening acne, eye irritation, furunculosis, and emotional lability), compared with lower doses.7 Long-term AEs with hormonal contraceptives include cardiovascular diseases such as hypertension, stroke, myocardial infarction (MI), and clotting disorders.9 To date, however, there have not been any long-term studies of E2V/DNG.

### DRUG INTERACTIONS5

The effectiveness of combined OCs may be reduced through CYP 3A4 enzyme induction with the use of drugs and herbal products. Barbiturates, griseofulvin, oxcarbazepine, and topiramate (Topamax, Ortho-McNeil) may decrease the effectiveness of the drug. Women should be counseled to always use a secondary or backup method of contraception when enzyme inducers are used.

Women using carbamazepine (Tegretol, Novartis) phenytoin (Dilantin, Pfizer), rifampicin (Rifampin, Bedford Laboratories), and St. John’s wort should be advised against using Natazia. Serum hormone levels are elevated with the use

### Table 1

<table>
<thead>
<tr>
<th>Study</th>
<th>E2V dose</th>
<th>LNG dose</th>
<th>DNG dose</th>
<th>E2V for</th>
<th>LNG for</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>3 mg</td>
<td>2 mg</td>
<td>DNG for 4 days</td>
<td>2 days</td>
<td>16 days</td>
</tr>
<tr>
<td>2A</td>
<td>3 mg</td>
<td>2 mg</td>
<td>DNG for 5 days</td>
<td>2 days</td>
<td>17 days</td>
</tr>
<tr>
<td>2B</td>
<td>3 mg</td>
<td>2 mg</td>
<td>DNG for 5 days</td>
<td>2 days</td>
<td>17 days</td>
</tr>
<tr>
<td>2C</td>
<td>3 mg</td>
<td>2 mg</td>
<td>DNG for 5 days</td>
<td>2 days</td>
<td>17 days</td>
</tr>
</tbody>
</table>

**Data from Endrikat et al. Contraception 2008;78(3):218–225.3**

**DNG = dienogest; E2V = estradiol valerate.**
of strong CYP 3A4 enzyme inhibitors such as ketoconazole (Nizoral, PriCara). Concomitant administration with ketoconazole has resulted in increases of 186% and 57% in the AUC concentrations of dienogest and estradiol, respectively.

The concomitant administration with HIV protease inhibitors has resulted in either increases or decreases of plasma levels of estradiol and dienogest. Although clinical studies have not proved that antibiotics have consistent effects on serum concentrations of these hormones, pregnancies have been reported. Combined OCs can decrease the plasma concentration of lamotrigine (Lamictal, GlaxoSmithKline) via glucuronidation. As a result, dosage adjustments of lamotrigine may be required.

**CONTRAINDICATIONS**

Natazia is not indicated for patients with a history of thrombotic events. This drug should be discontinued at least four weeks before and two weeks after major surgery to decrease the risk of thrombotic events. Patients with other conditions that increase the risk of thrombotic events (e.g., uncontrolled hypertension and uncontrolled dyslipidemia) should not take Natazia. This medication should be discontinued if jaundice occurs, and it should not be prescribed for women who are taking an inducer such as carbamazepine, phenytoin, rifampicin, or St. John’s wort.

**WARNINGS**

A boxed warning states that Natazia should not be prescribed to women who have a high risk of thrombotic diseases (those who smoke and who are older than 35 years of age). This product has not been studied in women with a body mass index (BMI) greater than 30 kg/m² and is thus not recommended for use in this population.

Women with pulmonary embolism, deep vein thrombosis, cardiovascular or coronary artery disease, uncontrolled hypertension, or diabetes with vascular disease are advised against taking this medication.

**DOSAGE AND ADMINISTRATION**

Tablets should be taken at the same time each day in the order presented in the blister packet. If administration is delayed for over 12 hours, it is considered a missed dose. Table 2 contains instructions for when a dose is missed. A backup (nonhormonal) contraceptive should be used for the first nine days of beginning the blister pack.

Each blister pack contains 28 film-coated tablets in the following order:

- 2 dark yellow tablets containing 3 mg of estradiol valerate
- 5 medium red tablets containing 2 mg of estradiol valerate and 2 mg of dienogest
- 17 light yellow tablets containing 2 mg of estradiol valerate and 3 mg of dienogest
- 2 dark red tablets each containing 1 mg of estradiol valerate
- 2 white inert tablets

**COST**

Table 3 shows a cost comparison of Natazia with other OCs.

**CONCLUSION**

In selecting an OC, one should consider efficacy, safety, compliance and cost. As a novel combination OC, Natazia is efficacious for inhibiting ovulation, but data on its long-term adverse effects are limited. This four-phasic tablet poses some challenges in terms of the dosing schedule and the complexity of dealing with missed doses, which may lead to decreased compliance (see Table 2).
Natazia is also more expensive than other available oral contraceptives (see Table 3). These challenges suggest a remote likelihood of this combination’s becoming the first-line agent for contraception.

**REFERENCES**


![Table 3 Oral Contraceptives, Cost Comparison](Table3.png)