

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**22-252, Original 1**

**OFFICE DIRECTOR MEMO**



## FDA CENTER FOR DRUG EVALUATION AND RESEARCH

---

### MEMORANDUM

---

DATE: May 6, 2010

TO: NDA 022252/Original 1 and NDA 022252/Original 2  
Natazia (estradiol valerate and dienogest) Tablets  
Bayer HealthCare Pharmaceuticals Inc.

FROM: Julie Beitz, M.D.  
Director, Office of Drug Evaluation III

RE: Approval Action for NDA 022252/Original 1  
Clock Extension for NDA 022252/Original 2

---

Natazia (estradiol valerate and dienogest) Tablets are combined oral contraceptives (COCs) containing estradiol valerate, a synthetic prodrug of 17 $\beta$ -estradiol, and the progestin dienogest. Dienogest is a new molecular entity that displays properties of 19-nortestosterone derivatives as well as properties associated with progesterone derivatives. Nonclinical studies in animals and *in vitro* have shown that dienogest is devoid of estrogenic, androgenic, glucocorticoid and mineralocorticoid activities. Natazia Tablets are administered in a regimen consisting of 26 active tablets (2 tablets each containing 3 mg estradiol valerate, 5 tablets each containing 2 mg estradiol valerate and 2 mg dienogest, 17 tablets each containing 2 mg estradiol valerate and 3 mg dienogest, and 2 tablets each containing 1 mg estradiol valerate), followed by two inactive tablets.

**Pregnancy Prevention.** This memorandum documents my concurrence with the Division of Reproductive and Urologic Product's (DRUP's) approval recommendation for Natazia (estradiol valerate and dienogest) Tablets for use by women to prevent pregnancy (NDA 022252/Original 1). Discussions regarding product labeling and postmarketing study requirements have been satisfactorily concluded and there are no inspectional issues that would preclude product approval.

(b) (4)



## Regulatory History

NDA 022252, submitted on July 2, 2009 and received on July 6, 2009, was granted a standard review. (b) (4)

On April 16, 2010, DRUP sent the applicant a draft marked-up label that included information relevant only to the pregnancy prevention indication. On April 22, 2010, the applicant informed DRUP that it would accept DRUP's proposed revisions to the indication statement in the product label, allowing DRUP to move forward with approval of the pregnancy prevention indication by the May 6, 2010 goal date.

(b) (4)

NDA 022252/Original 1, pertaining to the pregnancy prevention indication, will be approved. (b) (4)

The progestin component of Natazia Tablets, dienogest, is a new molecular entity. This application was not referred to the Reproductive Health Drugs Advisory Committee for a discussion of pregnancy prevention because the clinical study design was acceptable, the application did not raise significant safety or efficacy issues, the application did not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment or prevention of a disease, and outside expertise was not necessary.

## Efficacy

**Pregnancy Prevention.** The efficacy of Natazia Tablets was demonstrated in two multicenter, open-label, single-arm trials. One trial, conducted in the US and Canada, enrolled 490 healthy subjects aged 18-35 years (mean 25 years) who were treated for up to 28 cycles of 28 days each. The body mass index or BMI of enrolled subjects ranged from 14 to 30 kg/m<sup>2</sup> (mean of 23 kg/m<sup>2</sup>). The primary efficacy endpoint, the Pearl Index or PI, was calculated using the number of pregnancies occurring within the first 13 cycles or within 7 days of the last pill taken, and assumed that all subjects were at risk of pregnancy in all cycles unless backup contraception was documented. The estimated PI in this trial was 1.64 (with the upper bound of the 95% CI = 3.82). The second trial, conducted in Europe, enrolled 1,377 healthy subjects aged 18-50 (mean age 30 years) who were treated for 20 cycles of 28 days each. The BMI of enrolled subjects ranged from 15 to 32 kg/m<sup>2</sup> (mean of 23 kg/m<sup>2</sup>). The estimated PI in this trial for women aged 18-35 years was 1.04 (the upper bound of the 95% CI = 1.97).

The indication statement will specify that the efficacy of Natazia Tablets in women with a BMI of  $\geq 30 \text{ kg/m}^2$  has not been evaluated.

### **Safety**

Combined oral contraceptives are associated with a number of well-recognized safety concerns. Product labeling for Natazia Tablets will carry identical warnings as other COCs including: a boxed Warning for the risk of cigarette smoking and cardiovascular events, and warnings regarding the risks of 1) thrombotic and other vascular events, 2) carcinoma of the breast and reproductive organs, 3) liver disease, including hepatic adenomas, hepatic nodular hyperplasia and cholestasis, 4) hypertension, 5) gall bladder disease, 6) glucose intolerance and adverse lipid changes, 7) headaches, 8) bleeding irregularities, 9) emotional disorders, and 10) interference with certain laboratory tests.

Labeling for Natazia Tablets will also carry a Warning regarding concomitant use with strong CYP 3A4 inducers, such as carbamazepine, phenytoin, rifampicin, and St. John's wort. Dienogest is a substrate of CYP3A4. The effect of rifampicin was evaluated in an open label study of 16 healthy postmenopausal women who received 2 mg estradiol valerate and 3 mg dienogest combination tablets, dosed once daily over 17 days, and rifampicin 600 mg, which was administered once daily on days 12 to 16. The pharmacokinetics of estradiol and dienogest on days 11 and 17 were compared. Co-administration of rifampicin with estradiol valerate/dienogest tablets led to a 52% and 83% decrease in the mean  $C_{\text{max}}$  and AUC (0-24hr), respectively, for dienogest, and a 25% and 44% decrease in  $C_{\text{max}}$  and AUC (0-24hr), respectively, for estradiol at steady state.

Labeling will recommend that women should not choose Natazia Tablets as their oral contraceptive while using strong CYP 3A4 inducers and for at least 28 days after discontinuing these inducers due to the possibility of decreased contraceptive efficacy. Additionally, women who take medications that are moderate or weak CYP 3A4 inducers should consider using an alternative method of contraception or a back-up method, and to continue back-up contraception for 28 days after discontinuing the enzyme inducer to ensure contraceptive reliability.

Adverse reactions commonly reported in clinical trials by users of Natazia Tablets include headache (including tension headaches and migraines) (13.2%), metrorrhagia and irregular menstruation (8.0%), breast pain, discomfort or tenderness (6.6%), nausea or vomiting (6.5%), acne (3.9%) and increased weight (2.8%).

### **Pediatric Considerations**

**Pediatric Use.** The safety and efficacy of Natazia Tablets have been established in women of reproductive age, and are expected to be the same for postpubertal adolescents under the age of 18 as for users 18 years and older.

**Required Pediatric Studies.** Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for pre-menarcheal patients because they are not at risk of becoming pregnant, and use of this product before menarche is not indicated. The applicant has fulfilled the pediatric study requirement for post-menarcheal pediatric patients by extrapolation of adult data.

### **Postmarketing Requirements under 505(o)**

Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)).

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the known serious risks of venous and arterial thromboembolic events associated with the use of Natazia Tablets and other combined hormonal oral contraceptives.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that the applicant is required to conduct a prospective, controlled, non-interventional, long-term cohort study that follows a series of cohorts consisting of new users of Natazia Tablets and new users of oral contraceptives containing other progestins. This study should be conducted by expanding the ongoing European postmarketing comparative safety surveillance study entitled *International Active Surveillance Study of Women Taking EV/DNG (INAS-EV)* to include US women. The expanded study should enroll a total of at least 50,000 women in the US and Europe who will be followed for at least three years. The main clinical outcomes of interest are deep vein thrombosis, pulmonary embolus, acute myocardial infarction, and cerebrovascular accidents.

### **Tradename Review**

The Division of Medication Error Prevention and Analysis (DMEPA), in consultation with the Division of Drug Marketing, Advertising, and Communications (DDMAC), have concluded that the tradename “Natazia” is acceptable. The product has been marketed in Europe under the tradename “Qlaira” since May 2009.

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

-----  
NDA-22252

-----  
ORIG-1

-----  
BAYER  
HEALTHCARE  
PHARMACEUTICA  
LS INC

-----  
Natazia

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

JULIE G BEITZ  
05/06/2010