OFFICE OF CLINICAL PHARMACOLOGY ADDENDUM

NDA: 022252	Submission Dates: 7/2/2009, 10/15/2009, 12/21/2009, 4/27/2010, 5/4/2010, and 5/5/2010
Brand Name	Natazia®
Generic Name	Estradiol Valerate (EV) / Dienogest (DNG)
Reviewer	Chongwoo Yu, Ph.D.
Team Leader	Myong Jin Kim, Pharm.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Reproductive and Urologic Products
Sponsor	Bayer Healthcare Pharmaceuticals
Relevant IND	IND 064809 and (b) (4)
Submission Type	505(b)(1) Original
Formulation, Strength, Regimen	Oral immediate release (IR) film-coated tablets; Once daily 4-phasic (plus placebo phase), 28 day, sequential regimen: Cycle Days 1-2: 3 mg EV Cycle Days 3-7: 2 mg EV/2 mg DNG Cycle Days 8-24: 2 mg EV/3 mg DNG Cycle Days 25-26: 1 mg EV Cycle Days 27-28: placebo
Indication	Prevention of pregnancy

The purpose of this addendum is to address the Clinical Pharmacology related labeling changes that the Sponsor has made according to the Division's recommendations (refer to original Clinical Pharmacology review of NDA 022252, DARRTS, 4/2/2010). Important changes include:

- **Highlights**: Insertion of "Women taking strong CYP 3A4 inducers (for example, carbamazepine, phenytoin, rifampicin, and St. John's wort) should not choose Natazia as their oral contraceptive due to the possibility of decreased contraceptive efficacy" under the WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS sections.
- **Full Prescribing Information**:
    - Insertion of "Women who take medications that are strong CYP 3A4 inducers (for example, carbamazepine, phenytoin, rifampicin, and St. John's wort) should not choose Natazia as their oral contraceptive while using these inducers and for at least 28 days after discontinuation of these

inducers due to the possibility of decreased contraceptive efficacy" in Sections 5.13, 7.1, 12.3, and 17.1.
    - Drug Interaction study results are added in Sections 7.1 and 12.3
    - Several places in Section 12 (CLINICAL PHARMACOLOGY) including the *Pharmacokinetics* subsection were revised accordingly to reflect the study findings.
- **FDA-Approved Patient Labeling**:
    - Insertion of "You should not choose Natazia as your birth control pill if you take carbemazepine, phenytoin, rifampicin or St. John's wort, because these medicines may make Natazia ineffective. Some other medicines and herbal products may make birth control pills less effective, including: Barbiturates, Bosentan, Felbamate, Griseofulvin, Oxcarbazepine, and Topiramate. Consider using another birth control method when you take medicines that may make birth control pills less effective" in the Section of *What Else Should I Know about Taking Natazia?*

The final agreed upon label between the Sponsor and the Division was submitted by the Sponsor on 5/5/2010 (Supporting document number: 33). There are no outstanding Clinical Pharmacology issues.

1.1 Recommendation

The Division of Clinical Pharmacology 3, Office of Clinical Pharmacology finds NDA 022252 acceptable from a Clinical Pharmacology perspective.

1.2 Phase IV Commitments

None

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22252	ORIG-1	BAYER HEALTHCARE PHARMACEUTICALS INC	Natazia

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/s/

CHONGWOO YU
05/06/2010

MYONG JIN KIM
05/06/2010