CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-252 Original-1

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	May 6, 2010
From	Scott Monroe, MD
Subject	Division Director Summary Review
NDA	NDA 022252
Applicant Name	Bayer HealthCare Pharmaceuticals, Inc
Date of Submission	July 6, 2009
PDUFA Goal Date	May 6, 2010
Proprietary Name	Natazia
Established (USAN) Name	(Estradiol valerate [EV] and estradiol valerate/dienogest [DNG]) tablets
Dosage Forms/Strengths	Oral Tablets: 3 mg EV tablet x 2 days, 2 mg EV/2 mg DNG tablet x 5 days, 2 mg EV/3 mg DNG tablet x 17 days, 1 mg EV tablet x 2 days, placebo tablet x 2 days
Proposed Indication (Primary)	Use by women to prevent pregnancy
Proposed Regimen	One tablet daily x 28 days; See "Dosage Forms/Strengths"
Action	***Approve (see Section 13.1)***

Material Reviewed/Consulted OND Action Package, including:	**Names of Discipline Reviewers**
Medical Officer Review	Gerald Willett MD (primary Clinical Reviewer)
Statistical Review	Xin Fang PhD/Mahboob Sobhan PhD
Pharmacology Toxicology Review	Krishan Raheja DVM PhD/Alexander Jordan PhD
CMC Review	Tarun Mehta PhD/Moo-Jhong Rhee PhD
Microbiology Review	Not required
Clinical Pharmacology Review	Chongwoo Yu PhD/Myong-Jin Kim PharmD
DDMAC	Janice Maniwang PharmD/Carrie Newcomer PharmD
DSI	Roy Blay PhD/Tejashri Purohit-Sheth MD
CDTL Review	Lisa Soule MD (also Clinical Team Leader)
OSE/DMEPA	Jibril Abdus-Samad PharmD/Todd Bridges RPh/Denise Toyer PharmD/Carol Holquist RPh
OSE/DRISK	Robin Duer MBA RN/LaShawn Griffiths MSHS-PH RN/ Mary Willy PhD

ONDE=Office of New Drugs
CMC=Chemistry, Manufacturing and Control
DDMAC=Division of Drug Marketing, Advertising, and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Errors Prevention and Analysis
DSI=Division of Scientific Investigations
DRISK=Division of Risk Management
CDTL=Cross Discipline Team Leader

DIVISION DIRECTOR SUMMARY REVIEW

1. INTRODUCTION

The primary objective of NDA 022252 is to obtain marketing approval for Natazia (estradiol valerate and estradiol valerate/dienogest) tablets for the primary indication of "use by women to prevent pregnancy." (The Applicant also seeks approval for a secondary indication but this Summary Review addresses only issues related to the primary indication). Natazia (hereafter referred to EV/DNG or EV/DNG tablets), if approved, would be the first combination oral contraceptive in the US (1) to contain estradiol valerate (EV) and the progestin dienogest (DNG) and (2) to include 4 different doses of estrogen or estrogen/progestin. Estradiol valerate is currently approved in the US in an injectable formulation. Approved indications for injectable EV include treatment of vasomotor symptoms and treatment of symptoms of vulvar and vaginal atrophy. Dienogest (a 19-nortestosterone derivative) is a new molecular entity (NME) for the US, but has been marketed in Europe since 1995 as a component of a combination oral contraceptive that contains 0.03 mg ethinyl estradiol (EE) and 2 mg DNG. Estradiol valerate (2 mg)/DNG (2 mg) oral tablets also have been marketed in Europe since 2001 for menopausal symptom therapy.

Estradiol valerate/DNG tablets (the product under review in NDA 022252) for prevention of pregnancy was approved in Europe in 2008 and has been marketed since 2009. The Applicant stated that, as of June 2009, EV/DNG tablets are approved for marketing in 27 European Union Member Countries as well as in Australia.

This Application contained the necessary chemistry, manufacturing and control (CMC), preclinical toxicology, and clinical pharmacology information to support approval. The scope of the clinical database also was adequate to support approval of a combination oral contraceptive (COC) containing a NME. No significant preclinical or clinical issues were identified during the review of NDA 022252 for the proposed primary indication of prevention of pregnancy. All review disciplines, including the primary Clinical Reviewer (Dr. Willett) and the Clinical Team Leader (Dr. Soule), have recommended that EV/DNG tablets be approved for use by women for prevention of pregnancy. I concur with their recommendations.

2. BACKGROUND

2.1 Description of the Product

Natazia (EV and EV/DNG) tablets, a combination oral contraceptive that is to be taken over a 28-day cycle, consists of 4 different doses of EV or EV/DNG (referred to as a 4-phasic regimen). The specific dosing regimen is

Cycle Day	Tablet Composition
1-2	3 mg EV
3-7	2 mg EV/2 mg DNG
8-24	2 mg EV/3 mg DNG
25-26	1 mg EV
27-28	Placebo

Estradiol valerate is a prodrug for estradiol as it is rapidly hydrolyzed into 17β-estradiol and valeric acid. Dienogest is a derivative of 19-nortestosterone. Its chemical name is (17α)-17-Hydroxy-3-oxo-19-norpregna-4,9-diene-21-nitrile. According to the Applicant, nonclinical studies in animals and *in vitro* studies have shown that besides progestogenic activities, DNG has antiandrogenic activity and is devoid of estrogenic, androgenic, glucocorticoid, and mineralocorticoid activities.

Division Director's Comments

- *It is not possible, with data provided by the Applicant, to compare in a clinically meaningful manner (e.g., thrombogenic potential) the in vivo activity of EV (1-3 mg per tablet) in EV/DNG tablets to that of ethinyl estradiol (generally 0.02 to 0.035 mg) in currently approved combination oral contraceptives.*
- *The clinical significance of the preclinical finding that DNG has antiandrogenic activity is unknown.*

2.2 Regulatory History

The development program for EV/DNG tablets for prevention of pregnancy was conducted under IND 64,809, which was opened in 2004. The Applicant's clinical development program for the US registration of EV/DNG tablets for the prevention of pregnancy has been conducted in accordance with the recommendations of the Division of Reproductive and Urologic products (DRUP or the Division). Among the guidance provided to the Applicant was the following:

- *"Because dienogest is a new molecular entity (NME), we will require two adequate and well-controlled studies for efficacy and safety."*
- *"We recommend that at least one of your adequate and well-controlled Phase 3 clinical trials include a substantial number of subjects in North America."*

Division Director's Comment

- *The majority of the clinical trial data in support of the safety and efficacy of EV/DNG tablets for the prevention of pregnancy were obtained from non-US populations. The overall clinical trial database for EV/DNG tablets, however, is sizable and consists of more than 30,000 28-day treatment cycles. Of these treatment cycles, almost 6,500 28-day treatment cycles were obtained from Study 304742, which was conducted entirely in the US and Canada.*

2.3 Content of NDA

Overall, the Application contained the necessary chemistry, manufacturing and control (CMC), preclinical toxicology (which focused primarily on DNG), and clinical pharmacology information to support approval.

The primary clinical support for the safety and efficacy of EV/DNG tablets for the prevention of pregnancy is based on two Phase 3 clinical trials (Study 306660 and Study 304742) conducted by the Applicant. A smaller Phase 3 trial (Study 304004) provided comparative efficacy data and additional safety data. These three Phase 3 trials, provided safety and efficacy data from more than 30,000 28-day treatment cycles.

2.4 Recommendations of Primary Clinical Reviewer and Cross-Discipline Team Leader regarding Approvability

The primary Clinical Reviewer, Gerald Willett MD, stated the following in his Clinical Review signed on April 30, 2010:

> *"Approval is recommended for the Applicant's proposed primary indication for EV/DNG, that of "Prevention of pregnancy in women of reproductive age."*
>
> *"The risk benefit assessment is favorable for the primary indication of contraception. There is no evidence in the extensive safety database submitted in this NDA that the use of EV/DNG by women will result in any new safety problem or will result in an increased incidence of any known combined oral contraceptive (COC)-related adverse event compared to similar COCs. The benefit of this product is comparable to other approved COCs.*"

The Cross Discipline Team Leader (CDTL), Lisa Soule MD (who also was the Clinical Team Leader), stated the following in her Review signed May 6, 2010:

> *"I recommend that EV/DNG be approved for the indication of prevention of pregnancy, based on acceptable evidence of efficacy and a favorable risk/benefit profile."*
>
> *"EV/DNG demonstrates an acceptable risk/benefit profile for the contraceptive indication, with a Pearl Index indicating efficacy comparable to other approved oral contraceptives, and no signal of unexpected or higher frequency adverse events in the population of women who enrolled in the contraceptive trials. The bleeding profile is acceptable, although not markedly different from monophasic low dose COC products."*

Division Director's Comment

- *I concur with the recommendations of both Drs. Willett and Soule that EV/DNG tablets should be approved for the indication of "use by women to prevent pregnancy."*

3. CMC

The primary Chemistry Reviewer, Tarun Mehta PhD, made the following statement in the Recommendation and Conclusion on Approvability section of the primary CMC Review signed on March 23, 2010:

> *"This NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product. However, labeling issues are still pending and a site recommendation from the Office of Compliance is overall "Withhold" as of the date of this review. Therefore, from the CMC perspective, this NDA is not recommended for approval until all issues are resolved."*

In an Addendum (signed on May 6, 2010) to his original primary review, Dr. Mehta made the following statements and final recommendation:

> *… the Office of Compliance has issued an overall "Acceptable" recommendation.*
>
> *All the labeling issues are satisfactorily resolved, and the revised PI and labels for carton and blister were submitted.*
>
> *"Therefore, from the CMC perspective, this NDA is now recommended for approval."*

Dr. Mehta found the Applicant's request for a categorical exclusion regarding the potential environmental impact of EV/DNG tablets to be acceptable. Dr. Mehta did not recommend any Phase 4 commitments.

Division Director's Comment

- *I concur with the assessments and final recommendation by Dr. Mehta that from a CMC perspective this NDA can be approved.*

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

No new toxicology studies for EV alone were conducted by the Applicant and were not considered to be necessary by Krishan Raheja DVM/PhD, the primary Nonclinical Pharmacology/Toxicology Reviewer. The reasons for not requiring new toxicology studies for EV included: (1) EV in an injectable formulation is a currently approved drug product in the US; (2) EV is rapidly hydrolyzed into 17β-estradiol and valeric acid; (3) the preclinical toxicology of estradiol has been well studied; and (4) estradiol, either alone or in combination with a progestin, is a component of several currently approved drugs in the US.

The Applicant conducted a complete nonclinical pharmacology/toxicology program for DNG. This program included pharmacology studies, pharmacokinetic and toxicokinetic studies, general toxicology, acute, subchronic and chronic studies, genotoxicity studies, reproductive toxicity studies, and carcinogenicity studies.

Dr. Raheja stated the following in the Summary of Nonclinical Findings section of his primary Review signed on January 27, 2010:

> "*Toxicological findings in the general toxicology studies were generally similar to those reported previously for other approved progestins. No adverse neurological, cardiovascular, pulmonary, renal or gastrointestinal effects were observed in safety pharmacology studies. Dienogest was not mutagenic when tested in Ames assay, chromosomal aberration study using cultured mammalian cells, in mouse lymphoma test, and in in vivo mouse micronucleus assay. Fertility and early development and embryofetal development studies demonstrated no adverse effects on treated females or the fetuses. Carcinogenicity studies conducted in male rats and in male and female mice by oral administration of dienogest for 104 weeks demonstrated findings essentially similar to those with other progestins reviewed and approved previously. These studies were presented to and approved by the Exec-CAC.*"

Dr. Raheja's overall recommendations were:

> **Recommendations on approvability**: Nonclinical data supports approval of NDA 22-252 for Estradiol valerate/Dienogest.
>
> **Recommendations for nonclinical studies**: No additional nonclinical studies are required.
>
> **Recommendations on labeling**: The proposed Prescribing Information is in accordance with the PLR and presented in SPL format and is acceptable.

Division Director's Comment

- *I concur with the conclusions and recommendations of Dr. Raheja.*

5. CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS

According the Clinical Pharmacology Review, the Applicant submitted 32 biopharmaceutical and clinical pharmacology studies including dose linearity, absolute bioavailability (BA), single and multiple-dose pharmacokinetics (PK), metabolism, food effect, and drug-drug interaction (DDI) studies. Out of the 32 submitted studies, Chongwoo Yu PhD (the primary Clinical Pharmacology Reviewer) identified 22 studies that contained information directly pertinent to EV/DNG tablets for the proposed indication of prevention of pregnancy.

According to Dr. Yu's review, significant drug-drug interactions were noted in the clinical pharmacology studies:

- CYP 3A4 Induction: Co-administration of rifampicin (a strong CYP 3A4 inducer) with EV/DNG tablets resulted in:
  - a 52% decrease in the mean Cmax and a 83% decrease in the AUC (0-24 hr) for DNG and
  - a 25% decrease in the mean Cmax and a 44% decrease in AUC (0-24 hr) for estradiol (E2).

  Dr. Yu recommended that to ensure contraceptive reliability strong CYP 3A4 inducers such as rifampicin, phenytoin, St. John's Wort, avasimibe, and carbamazepine should not be co-administered with EV/DNG tablets.
- CYP 3A4 Inhibition: Co-administration of ketoconazole (a strong CYP 3A4 inhibitor) with EV/DNG tablets resulted in:
  - a 94% increase in the mean Cmax and a 186% increase in the AUC (0-24 hr) for DNG and
  - a 65% increase in the mean Cmax and a 57% increase in AUC (0-24 hr) for E2

Dr. Yu's overall recommendation in his review signed on April 2, 2010 was:

> *"The Office of Clinical Pharmacology/Division of Clinical Pharmacology III (OCP/DCP-III) has reviewed NDA 22-252 submitted on July 2, 2009, October 15, 2009, and December 21, 2009. The overall Clinical Pharmacology information submitted to support this NDA is acceptable provided that a satisfactory agreement is reached regarding the labeling language."*

In an Addendum (signed on May 6, 2010) to his April 2, 2010, review, Dr. Yu made the following statement:

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

Dr. Yu did not recommend any Phase 4 commitments.

Division Director's Comments

- *Because of the 52% decrease in the mean Cmax and a 83% decrease in the AUC (0-24 hr) for DNG, labeling will state that women who are taking strong CYP 3A4 inducers should not choose EV/DNG tablets as their method of contraception. This guidance will be included in the Warning and Precautions section of labeling and other sections as appropriate.*
- *I concur with Dr. Yu's overall assessment and his recommendation that the Clinical Pharmacology data are adequate and acceptable to support approval of EV/DNG tablets.*

6. CLINICAL MICROBIOLOGY

A clinical microbiology assessment/consultation was not required for this Application.

7. CLINICAL/STATISTICAL-EFFICACY

7.1 Overview of Phase 3 Clinical Trials

The Applicant conducted three Phase 3 clinical trials to support the efficacy and safety of EV/DNG tablets for the prevention of pregnancy (see Table 1). In study 304742, conducted in the US and Canada, 490 women took at least one dose of study drug and had at least one assessment after the onset of treatment (the population of subjects referred to as the Full Analysis Set [FAS] by the Applicant). Subjects were treated for up to 28 cycles of 28 days each. In study 306660, conducted in Austria, Germany and Spain, 1,377 women (the FAS group) were treated for up to 20 cycles of 28 day each.

Among these 2 studies, the total number of 28-day cycles evaluated for the contraception indication was 29,952 (6,424 cycles in Study 304742 and 23,528 cycles in Study 306660). DRUP, however, currently bases the primary assessment of contraceptive efficacy for new products on the first year of product use (i.e., in this case on the first 13 28-day treatment cycles). Studies 304742 and 306660 provided, in total, 16,151 evaluable 28-day treatment cycles in the first year of use.

Study 304004 provided additional safety data, including comparative data regarding menstrual bleeding patterns, but did not specify contraceptive efficacy as a primary endpoint. This study compared safety and efficacy findings in subjects randomized to EV/DNG tablets to those in subjects randomized to a monophasic oral contraceptive containing 0.020 mg ethinyl estradiol and 0.1 mg levonorgestrel given in a 21/7 day regimen.

Table 1. Overview of Phase 3 Contraceptive Studies

Study	No. and Location of Study Sites	Study Design	Number Subjects (FAS Population) [A]	Duration of Treatment
304742	US: 22 Canada: 9	Multicenter, open-label, uncontrolled one-arm study	490 subjects.	Up to 28 cycles of 28 days each.
306660	Austria: 17 Germany: 28 Spain: 5	Multicenter, open-label, uncontrolled, one-arm study	1377 subjects	20 cycles of 28 days each
304004	Germany: 19 Czech Republic: 5 France: 10	Multicenter, double-blind, double-dummy, active-controlled, randomized study	798 subjects 399 subjects in each of the 2 treatment groups)	7 cycles of 28 days each

A: Subjects who took at least one dose of study drug and had at least one assessment after the onset of treatment
Source: Modified from Table 1 of CDTL Review, signed May 6, 2010.

The following Summary Review primarily focuses on the efficacy and safety findings from Study 304742 and Study 306660 because each of these studies treated subjects for greater than one year. In addition, prevention of pregnancy was not the primary objective of Study 304004.

7.2 Demographics

Demographic and baseline characteristics of the subjects (the FAS group) in Study 306660 and Study 304742 are provided in Table 2. Subjects ranged in age from 18-50 years (Study 306660) and 18-35 years (Study 304742). In Study 306660, 99% of subjects were Caucasian. In Study 304742, the ethnic distribution of subjects more closely approximated that of the US population. The majority of subjects in both studies had previously used oral contraceptives.

Table 2. Demographics and Baseline Characteristics (Studies 306660 and 304742)

Characteristic	Study 306660 N=1,377	Study 304742 N=490
Mean age (years [range])	30.3 [18-50]	25.1 [18-35]
Age group 18-35 years	998 (72.5%)	490 (100%)
Age group > 35 years	379 (27.5%)	0
Ethnic group		
• Caucasian	1,366 (99.2%)	371 (76.0%)
• Black	2 (0.1%)	34 (7.0%)
• Hispanic	3 (0.2%)	64 (13.0%)
• Asian	4 (0.3%)	16 (3.3%)
• Other	2 (0.1%)	5 (1.0%)
Smoker (current)	273 (19.8%)	92 (19.0%)
Mean weight (kg) (SD)	64.2 (9.5)	62.5 (10.2)
Body mass index (kg/m^2) (SD)	22.8 (2.9)	23.3 (3.3)
Prior COC use	1,006 (73.1%)	287 (58.6%)
Naïve COC users	77 (5.6%)	16 (3.3%)

Source: Modified from Table 2 of the CDTL Review signed on May 6, 2010.

Division Director's Comment

- *Women with a BMI of >30kg/m^2 were to be excluded from each of the above Studies. This restriction will be noted in product labeling.*

7.3 Subject Disposition

The disposition of subjects in Study 306660 and Study 304742 is provided in Table 3. A total of 295 subjects (21.4%) in Study 306660 and 235 subjects (48.0%) in Study 304742 discontinued treatment prematurely for the reasons listed in Table 3.

Table 3. Subject Disposition – Full Analysis Set (Studies 306660 and 304742)

Disposition / Reason	Study 306660	Study 304742
Full Analysis Set [A]	**1,377 (100%)**	**490 (100%)**
Completed the study medication	1,074 (78.0%)	243 (49.6%)
Prematurely discontinued from the study	295 (21.4%)	235 (48.0%)
• Adverse event [B]	142 (10.3%)	73 (14.9%)
• Other [C]	71 (5.2%)	40 (8.2%)
• Protocol deviation	26 (1.9%)	6 (1.2%)
• Lost to follow-up	26 (1.9%)	63 (12.9%)
• Withdrawn consent	20 (1.5%)	48 (9.8%)
• Pregnancy	11 (0.8%)	5 (1.0%)
• Death	1 (<0.1%)	0
Study medication status unknown	8 (0.6%)	12 (2.4%)

A: Defined as all randomized subjects who took at least one dose of study drug and had at least one assessment after the onset of treatment; subsequent percents in the Table are based on this denominator.

B: Originally reported as 140 subjects. Two additional subjects were subsequently identified.

C: The "other" category for subjects discontinuing study medication included those who wanted to get pregnant, moved from the area, etc.

Source: Modified from Table 3 of the CDTL Review signed May 6, 2010.

Division Director's Comments

- *The rate of premature discontinuation, as is often observed in contraceptive clinical trials, was higher among US subjects compared to European subjects. US subjects were more likely to discontinue treatment prematurely due to loss to follow-up, withdrawal of consent, and adverse events.*
- *A premature discontinuation rate of 48% (Study 304742) for a 2-year Phase 3 contraceptive clinical trial is not unusually high for a US population. Discontinuation rates of up to 40% have been observed in 1-year trials in the US.*
- *The discontinuation rate of 14.9% in Study 304742 (a 2-year study) due to adverse events is only slightly higher that that observed in other recently reviewed one year Phase 3 contraceptive clinical trials conducted in the US.*

7.4 Efficacy Findings

7.4.1 Primary Assessment of Efficacy (On-Treatment Pregnancies)

The primary efficacy analysis in this and other contraceptive trials is the Pearl Index, which is computed as:

$$\text{Pearl Index} = \frac{\text{(number of "on-treatment" pregnancies) x 13 cycles/year}}{\text{(total number of completed 28-day treatment cycles)*}} \times 100$$

* Only cycles in which no back-up contraceptive methods were used are included

The primary analysis population was the pregnancy intent-to-treat (PITT) population, defined as all subjects who (1) received at least one dose of study drug, (2) were evaluated for pregnancy at least once after beginning study drug, and (3) were between the ages of 18-35 years at entry. All

cycles in which an alternate birth control method (BCM) was used were excluded from the efficacy analyses unless the subject conceived during that cycle. Pregnancies conceived after the onset of treatment with study drug and within 7 days after a subject's last tablet of study drug were defined as "on-treatment pregnancies." Only these pregnancies were included in the calculation of the Pearl Index.

Division Director's Comment

- *The Division's recent thinking on the window in which conceptions are counted as treatment failures is that pregnancies conceived within 7 days after the last pill taken (whether active or placebo pill) are to be counted. This allows for inaccuracy in ultrasound dating of pregnancies, but acknowledges that contraceptive protection is not expected to be maintained beyond the last tablet in a 28-day treatment cycle.*

7.4.2 Primary Efficacy Findings and Analyses

Pearl Index

Although both of the primary Phase 3 clinical trials extended beyond one year of treatment, the primary assessment of efficacy (per DRUP's current practice) was based on the number of on-treatment pregnancies that occurred during the first year of treatment (i.e., first 13 28-day treatment cycles). During this period, a total of 14 pregnancies were noted (9 in 11,274 evaluable cycles in Study 306660 and 5 in 3,969 evaluable cycles in Study 304742). The Pearl Index values (and associated upper bounds of the 95% confidence interval) in Study 306660 and Study 304742 are listed in Table 4.

Table 4. Pearl Index Values for Treatment Failures (Pregnancies) during the First Year of Treatment (Study 306660 and Study 304742)

Study No. (Location)	Number of 28-day cycles	Cycles with back-up contraception	Number of evaluable Cycles [A]	Number of on-treatment pregnancies	Pearl Index	Upper Limit of 95% Confidence Interval
306660 (Europe)	11,576	302	11,274	9	**1.04**	1.97
304742 (US/Canada)	4,575	606	3,969	5	**1.64**	3.82

A: Cycles in which no backup contraception was used.

Source: Table 3.2.1b of the FDA Statistical Review signed on March 31, 2010.

Division Director's Comments

- *The Pearl Index value for each of the 2 studies (1.04 and 1.64) and associated upper limit of the 95% CI (1.97 and 3.82) indicate that EV/DNG tablets are highly effective in preventing pregnancy. These Pearl Index values (1) are consistent with, and in some cases lower than, those for other hormonal contraceptives approved by DRUP and (2) support my recommendation that the efficacy of EV/DNG tablets is acceptable for a hormonal contraceptive product.*
- *As is often seen in data from US and European populations, the Pearl Index value for the US subjects is numerically higher (i.e., the contraceptive product appears to be less effective) than the Pearl Index value for the European subjects.*

- *Women with a body mass index (BMI) of >30 kg/m^2 were excluded from both clinical trials, and this should be reflected in product labeling.*
- *Although not discussed further in this review, it is of note that there were no reported on-treatment pregnancies in the EV/DNG treatment group in Phase 3 Study 304004 in which subjects were treated for up to 7 28-day cycles.*

Life Table Analysis

Life table calculations (Kaplan Meier method) also are commonly used as supportive assessments of contraceptive efficacy. This method provides cumulative rates of treatment failure (i.e., cumulative rates of pregnancy). The FDA statistician provided Kaplan Meier values for method failures for each of the 2 clinical trials. The statistician excluded from the analyses only those treatment cycles in which back-up contraception was used, rather than censoring a subject as soon as she used back-up contraception. The results of these analyses are provided in Table 5. The cumulative failure rates through one year of treatment were 0.0099 and 0.0157 in Study 306660 and Study 304742, respectively.

Table 5. Life Table Estimates (Kaplan Meier Method) for Treatment Failures (Pregnancies) during the First Year of Treatment (Study 306660 and Study 304742)

Study	Relevant exposure (Days)	Probability of no conception	Cumulative failure rate	Lower limit of 95% CI	Upper limit of 95% CI
306660 (Europe)	13	0.9990	0.0010	0.0001	0.0071
	14	0.9980	0.0020	0.0005	0.0081
	69	0.9969	0.0031	0.0010	0.0095
	95	0.9959	0.0041	0.0016	0.0110
	149	0.9947	0.0053	0.0022	0.0126
	201	0.9936	0.0064	0.0029	0.0142
	207	0.9924	0.0076	0.0036	0.0158
	208	0.9913	0.0087	0.0044	0.0174
	280	0.9901	**0.0099**	0.0052	0.0190
304742 (US/ Canada)	75	0.9973	0.0027	0.0004	0.0187
	102	0.9945	0.0055	0.0014	0.0218
	186	0.9878	0.0122	0.0046	0.0323
	203	0.9843	**0.0157**	0.0065	0.0375

Source: Table 3.2.3.3 of the FDA Statistical Review signed on March 31, 2010.

Division Director's Comment

- *Results from the life table analysis are supportive of the estimate of the risk of pregnancy based on the Pearl Index. The Kaplan Meier values also indicate that EV/DNG tablets provide acceptable contraceptive efficacy.*

7.4.3 Statistician's Conclusion regarding the Primary Efficacy Findings

The primary statistical reviewer, Xin Fang PhD, made the following statements in the "Conclusions and Recommendations" section of his statistical review signed on March 31, 2010:

> "*The data supported the efficacy of Estradiol Valerate/Dienogest (EV/DNG) in the prevention of pregnancy as demonstrated by the Pearl Index (PI) of < 2.0 in both the North American and the European studies.*"

"*From a statistical perspective, this application provided adequate data to support the efficacy of the EV/DNG as oral contraceptive.*"

Overall Assessment of Efficacy

The data from the two primary Phase 3 contraceptive efficacy studies conducted by the Applicant have provided robust confirmation of the efficacy of EV/DNG tablets for use by women for the prevention of pregnancy. The Pearl Index values for subjects ≤ 35 years of age at study entry in Study 306660 and Study 304742 (1.04 and 1.64, respectively) and associated upper limits of the 95% confidence intervals (1.97 and 3.82, respectively) are comparable to, and in some cases lower than, those for other combination oral contraceptives approved by DRUP. These findings support my recommendation that the efficacy of EV/DNG tablets is acceptable for a combination oral contraceptive product.

8. SAFETY

The primary Clinical Reviewer (Dr. Willett) has provided a thorough review and discussion of the safety findings for EV/DNG tablets based on the data submitted to NDA 022252. The Clinical Team Leader (Dr. Soule) also thoroughly reviewed the safety data. Neither Medical Officer identified any safety issues that would suggest that the overall safety profile for EV/DNG tablets, when used in accordance with to-be-approved labeling for the indication of prevention of pregnancy, would be less acceptable than that for other currently approved combination oral contraceptives. The following Summary Review of safety is focused mainly on items either of greatest potential concern for a hormonal contraceptive product or of particular interest (e.g., uterine bleeding patterns). The safety reviews by both the primary Clinical Reviewer and the Clinical Team Leader indicate that the overall safety profile of EV/DNG tablets for use by women to prevent pregnancy does not raise any new safety concerns beyond those normally associated with combination oral contraceptives. The following Summary Review focuses primarily on the findings from Study 306660 and Study 304742, the two large Phase 3 studies in which subjects were to be treated for at least one year. Safety findings from 6-month Study 304004, as well as those from other supportive safety studies, have been addressed if pertinent.

8.1 Safety Database and Subject Exposure to Study Drug

The three Phase 3 clinical trials enrolled a total of 2,266 subjects who received at least one dose of EV/DNG tablets and had at least one assessment following treatment onset (see Table 6.) The overall exposure to EV/DNG tablets in these studies was 32,647 28-day treatment cycles.

Table 6. Overview of Exposure to EV/DNG Tables in Phase 3 Contraceptive Studies

Study Number	Duration (number of 28-day cycles)	Number of Subjects (FAS) [A]	Number of completed 28-day cycles	Number of partially completed 28-day cycles	Total women-years of exposure to EV/DNG tablets
306660	20	1,377	23,528	430	1,832.19
304742	28	490	6,424	294	503.07
304004	7	399	2,695	27	208.22
Total		**2,266**	**32,647**	**751**	**2,543.48**

A: "Full Analysis Set" defined as subjects who received at least one dose of EV/DNG and had at least one assessment following treatment onset.
Source: Modified from Table 104 of the primary Clinical Review signed on May 1, 2010.

Division Director's Comments

- *The size of the safety database is acceptable for the proposed product. For a new contraceptive product that contains a NME (i.e., DNG) the Division has generally requested that the safety of the drug product be supported by at least 20,000 28-day treatment cycles.*
- *The safety database, based on number of treatment cycles and clinical findings, is adequate to assess the safety profile of EV/DNG tablets.*

8.2 Deaths and Other Serious Adverse Events

8.2.1 Deaths

Three deaths were reported in the EV/DNG development program (see Table 7). Two of the deaths occurred in Study 306660: one death was related to the Asian tsunami in December 2004 and one death was attributed to a ruptured cerebral aneurysm.

Table 7. Deaths in Clinical Studies Using Either the Final or a Developmental EV/DNG Dosing Regimen

Drug	Study	Subject's Age	Subject No.	Cause of Death
EV/DNG - F	306660	33	3779	Victim of tsunami in Asia
EV/DNG - F	306660	35	4318	Rupture of cerebral aneurysm
EV/DNG - D	301740	30	1357	Murder victim

F: Final dosing regimen of EV/DNG.
D: Developmental dosing regimen of EV/DNG.

Division Director's Comment

- *Neither the primary Clinical Reviewer nor the Clinical Team Leader attributed the death of subject No. 4318 to treatment with EV/DNG. I concur with their assessments.*

8.2.2 Nonfatal Serious Adverse Events

Among the three Phase 3 contraceptive clinical trials, a total of 73 nonfatal serious adverse events (SAEs) were reported among 60 subjects: Study 306660 – 53 SAEs among 45 (3.3%) subjects; Study 304742 – 15 SAEs among 10 (2.0%) subjects; and Study 304004 – 5 SAEs among 5 (1.3%) subjects. Serious adverse assessed by the primary Clinical Reviewer

(Dr. Willett) as possibly or probably related to treatment with EV/DNG tablets in completed Phase 3 clinical trials for contraception or for another indication are listed in Table 8.

Table 8. Serious Adverse Events Assessed by FDA Primary Clinical Reviewer as Possibly or Probably Related to Treatment with EV/DNG Tablets in Completed Phase 3 Clinical Trials

Indication	Study Number	Subject Number	Serious Adverse Event
Contraception	306660	3156	Myocardial infarction
	306660	3617	Rapid growth of uterine leiomyoma
	306660	4147	Deep vein thrombosis
	306660	4082	Focal nodular hyperplasia of liver
	304742	514017	Ovarian cyst rupture
	304004	1127	Ovarian cyst rupture
Other	308960	131003	Myocardial infarction
	308961	852034	Cholecystitis

Source: Modified from Table 107 of the primary Clinical Review signed May 1, 2010.

Division Director's Comments

- *Among adverse events of greatest concern in women using combination oral contraceptives are venous and arterial thrombotic events. Of note, there was only one report of a deep venous thrombosis (DVT) and no reports of pulmonary emboli (PE) in these clinical trials. Considering the size of the safety database, a greater number of reports of DVT and possibly one or more cases of pulmonary emboli might have been expected.*
- *The occurrence of cases of myocardial infarction in hormonal contraceptive trials is uncommon because these trials generally enroll healthy young women. Both women who experienced a myocardial infarction while using EV/DNG, however, had preexisting risk factors:*
  - *Subject No. 3156 (Study 306660) was 46-years old and a smoker with a history of hypertension. The duration of treatment at the time of her myocardial infarction was 228 days. Angiography two days after the onset of her symptoms showed significant stenosis of the right coronary artery.*
  - *Subject No. 131003 (Study 308960) was a 46 year old woman (non-smoker, BMI = 31.4 kg/m^2) who had taken EV/DNG tablets for 194 days. The subject had a positive family history for coronary artery disease.*
- *No cases of stroke were reported in the EV/DNG development program.*
- *Venous and arterial thrombotic events are known risks associated with the use of combination oral contraceptives. The occurrence of one case of DVT and 2 cases of MI (each in a 46 year woman with preexisting risk factors) does not raise any safety concerns beyond those known to be associated with the use of hormonal contraceptive products.*
- *It is not possible from the available safety data for EV/DNG to obtain a precise estimate of both the absolute and relative risk (risk compared to other oral contraceptive products) of venous and arterial thrombosis for users of hormonal contraceptive products pre-approval because of the low prevalence of these events. Such ascertainment requires a large clinical*

trial and longer follow-up than would be feasible pre-approval. The Applicant has committed to conducting such a postmarketing study to assess the thrombotic risk associated with the use of EV/DNG tablets (Section 13.4).

8.3 Discontinuations for Adverse Events

A total of 142 subjects in Study 306660 (10.3%) and 73 subjects in Study 304742 (14.9%) discontinued trial participation prematurely due to adverse events (AEs). Table 9 provides the number (%) of subjects with the most common and most pertinent adverse events leading to early discontinuation in Study 306660 and Study 304742.

Table 9. Number (%) of Subjects with the Most Common and Most Pertinent Adverse Events Leading to Early Discontinuation from Clinical Trial (Study 306660 and Study 304742)

Adverse Event by SOC and PT Classification	Study 306660 N = 1377	Study 304742 N = 490	Total N=1,867
	Number (%) of subjects with event		
Reproductive system and breast disorders			
Breast (breast discomfort, pain, swelling, and tenderness)	6 (0.4)	2 (0.4)	8 (0.4)
Menorrhagia	3 (0.2)	4 (0.8)	7 (0.4)
Menstrual disorder	3 (0.2)	2 (0.4)	5 (0.3)
Metrorrhagia, irregular menstruation	24 (1.7)	12 (2.4)	36 (1.9)
Amenorrhea	2 (0.1)	1 (0.2)	3 (0.2)
Dysfunctional uterine bleeding	--	3 (0.6)	3 (0.2)
Psychiatric disorders			
Depressed mood, depression	10 (0.7)	2 (0.4)	12 (0.6)
Libido decreased, loss of libido	8 (0.6)	1 (0.2)	9 (0.5)
Mood altered, mood swings	2 (0.1)	8 (1.6)	10 (0.5)
Skin and subcutaneous tissue disorders			
Acne	14 (1.0)	9 (1.8)	23 (1.2)
Alopecia	3 (0.2)	--	3 (0.2)
Nervous system disorders			
Headache, migraine	12 (0.9)	7 (1.4)	19 (1.0)
Investigations			
Weight increased	12 (0.9)	2 (0.4)	14 (0.7)
Vascular disorders			
Hypertension	8 (0.6)	--	8 (0.4)
Cardiac disorders			
Myocardial infarction	1 (< 0.1)	--	1 (< 0.1)
Neoplasm (benign, malignant, and unspecified)			
Focal nodular hyperplasia (hepatic)	1 (< 0.1)	--	1 (< 0.1)

SOC = system organ class; PT = preferred term
Source: Table 25 (with slight modification) of the CDTL Review signed May 6, 2010.

Division Director's Comments

- *The types of adverse events associated with premature discontinuation from Study 306660 and Study 304742 and the numbers of subjects reporting them are consistent with those observed in other clinical trials for oral contraceptives.*

- *As would be expected in a clinical trial of a combination oral contraceptive, adverse events related to abnormal uterine bleeding were the most common cause of subject premature discontinuation. Uterine bleeding patterns are described further in Section 8.5.*
- *The types of adverse events leading to premature discontinuations were similar across the 2 trials, with breast, menstrual, and psychiatric disorders, along with acne and headaches, accounting for the majority of discontinuations related to adverse events. These are common causes for premature discontinuation in clinical trials of combination oral contraceptives.*
- *The percentages of subjects who withdrew because of an adverse event (10.3% [Study 306660) and 14.9% [study 304742]) were not excessive for contraceptive clinical trials of 20- and 28-months duration.*

8.4 Common Adverse Events

The most commonly reported adverse events in Study 306660 and Study 304742 are listed in Table 10. Selected individual adverse events, based on preferred terms that refer to closely related disorders (e.g., headache, migraine, and tension headache), have been bundled.

Table 10. Common Adverse Events (>2.0%) in Study 306660 and Study 304742

Preferred Term	Study 306660 N=1,377 n (%)	Study 304742 N=490 n (%)	Total N=1,867 n (%)
Nasopharyngitis + pharyngitis + sinusitis + upper respiratory infection	296 (21.5)	122 (24.9)	418 (22.4)
Vaginal infection + candidiasis + vaginal candidiasis + fungal infection + genital infection fungal + vulvovaginal mycotic infection + vulvovaginitis	207 (15.0)	84 (17.1)	291 (15.6)
Headache + migraine + tension headache	159 (11.5)	87 (17.8)	246 (13.2)
Metrorrhagia + irregular menstruation	85 (6.2)	64 (13.1)	149 (8.0)
Cystitis + urinary tract infection	91 (6.6)	34 (6.9)	125 (6.7)
Breast pain + discomfort + tenderness	89 (6.5)	34 (6.9)	123 (6.6)
Vomiting + nausea	75 (5.4)	46 (9.4)	121 (6.5)
Diarrhea	91 (6.6)	19 (3.9)	110 (5.9)
Abdominal pain + upper + lower	53 (3.8)	40 (8.2)	93 (5.0)
Dysmenorrhea	42 (3.1)	37 (7.6)	79 (4.2)
Acne	44 (3.2)	29 (5.9)	73 (3.9)
Tonsillitis + acute tonsillitis + streptococcal tonsillitis	64 (4.6)	9 (1.8)	73 (3.9)
Gastroenteritis + gastrointestinal infection + viral	49 (3.6)	11 (2.2)	60 (3.2)
Weight increased	37 (2.7)	15 (3.1)	52 (2.8)
Bronchitis + acute bronchitis	36 (2.6)	8 (1.6)	44 (2.4)
Back pain	25 (1.8)	18 (3.7)	43 (2.3)
Influenza	27 (2.0)	13 (2.7)	40 (2.1)
Amenorrhea	2 (0.1)	37 (7.6)	39 (2.1)

Source: Table 27 of the CTDL Review signed May 6, 2010.

Division Director's Comments

- *Because of the granularity of the Applicant's classification of adverse event by preferred terms, selected individual preferred terms that refer to similar or closely related disorders*

(e.g., headache, migraine, and tension headache) were bundled in the above table to provide a better perspective of the occurrence of common adverse events reported in these 2 clinical trials.

- *The commonly reported adverse events and their frequency in these Phase 3 Studies are similar to that reported for other currently approved combination oral contraceptives. These adverse events and their frequency do not raise any safety concerns beyond those generally associated with the use of these products.*

8.5 Uterine Bleeding Patterns

Subjects completed a daily paper diary that recorded the occurrence and intensity of uterine bleeding. Spotting was defined as light bleeding that required no use of sanitary protection aside from panty liners. Spotting/bleeding was characterized as "withdrawal bleeding/spotting" (hereafter called "scheduled bleeding/spotting") if it started on or after Day 21 of the treatment cycle and before starting the next packet of pills (i.e., no later than Day 28). All other bleeding/spotting episodes were considered to be "intracyclic bleeding/spotting" by the Applicant (hereafter referred to as "unscheduled bleeding/spotting"). Unscheduled spotting/bleeding is likely to be more troublesome to subjects because it is unpredictable and more likely to lead to discontinuation of use of an oral contraceptive.

8.5.1 Unscheduled Bleeding/Spotting

Table 11 lists for Cycles 2-13 (1) the percentage of subjects with unscheduled bleeding/spotting and (2) the number of days of unscheduled bleeding/spotting per each 28-day treatment cycle in Study 306660 and Study 304742. The percentages of subjects with unscheduled bleeding/spotting and mean number of days of unscheduled bleeding/spotting per cycle was similar in each of the studies. The percentage of subjects with unscheduled bleeding/spotting tended to be higher during the first several cycles of treatment. After the third treatment cycle, the percentages of subjects with unscheduled bleeding/spotting in any 28-day cycle ranged from 11.2% to 21.6% across the 2 trials.

Table 11. Number of Subjects (%) with Unscheduled Bleeding/Spotting per 28-day Cycle and Mean (SD) Number of Days of Unscheduled Bleeding

Cycle (28-day intervals)	Study 306660		Study 304742	
	N (%) of Subjects	Days of Unscheduled Bleeding	N (%) of Subjects	Days of Unscheduled Bleeding
2	303 of 1263 (24.0%)	1.5 ± 3.7	97 of 337 (28.8%)	1.7 ± 3.5
3	274 of 1238 (22.1%)	1.2 ± 2.9	74 of 317 (23.3%)	1.6 ± 3.7
4	230 of 1198 (19.2%)	1.0 ± 2.8	64 of 296 (21.6%)	1.3 ± 3.2
5	223 of 1180 (18.9%)	1.0 ± 2.7	60 of 280 (21.4%)	0.9 ± 2.4
6	197 of 1162 (17.0%)	0.8 ± 2.4	43 of 269 (16.0%)	0.8 ± 2.6
7	154 of 1133 (13.6%)	0.8 ± 2.6	39 of 250 (15.6%)	0.8 ± 2.4
8	177 of 1123 (15.8%)	0.8 ± 2.3	36 of 243 (14.8%)	0.9 ± 3.0
9	161 of 1114 (14.5%)	0.7 ± 2.4	31 of 241 (12.9%)	0.6 ± 2.2
10	171 of 1103 (15.5%)	0.8 ± 2.5	33 of 234 (14.1%)	0.7 ± 2.1
11	140 of 1080 (13.0%)	0.7 ± 2.4	25 of 224 (11.2%)	0.5 ± 1.9
12	150 of 1072 (14.0%)	0.7 ± 2.4	37 of 220 (16.8%)	0.9 ± 2.6
13	147 of 160 (13.9%)	0.7 ± 2.3	38 of 213 (17.8%)	0.6 ± 1.9

Source: Modified from Tables 27 and 50 of the primary Clinical Review signed May 1, 2010.

Division Director's Comments

- *The percentages of subjects with unscheduled bleeding/spotting and the mean number of days of unscheduled bleeding/spotting appears to be similar to that for other 28-day cyclic combination oral contraceptives.*
- *For those subjects who continued in the clinical trials beyond one year, the overall pattern of unscheduled bleeding/spotting was similar to that shown in Table 11.*

8.5.2 Scheduled Bleeding/Spotting

The majority of subjects experienced scheduled bleeding/spotting at the end of each 28-day treatment cycle. During the first year of treatment, 78.2%-81.6% of subjects (Study 306660) and 64.3%-82.8% of subjects (Study 304742) had scheduled bleeding/spotting at the end of each 28-day treatment cycle. The mean (SD) number of days of schedule bleeding/spotting at the end of any 28-day cycle during the first year of treatment ranged from 3.6 (±1.7) days to 4.7 (±3.7) days.

Division Director's Comment

- *The overall pattern and numbers of days of scheduled and unscheduled bleeding /spotting appears to be comparable to other approved 28-day combination oral contraceptive products. It is unclear if the Applicant's 4-phase dosing regimen offers any clinically meaningful benefit in terms of bleeding/spotting patterns compared to other 28-day cyclic oral contraceptives.*

8.6 Thorough QT Study

The Applicant conducted a thorough QT (TQT) study because DNG is a NME. The primary reviewer, Dr. Joanne Zhang of the Interdisciplinary Review Team for QT Studies, made the following comments in her review signed March 15, 2010:

> "*The effect of [EV/DNG tablets] on QTc prolongation was evaluated in a randomized, double-blind, positive (moxifloxacin 400 mg) and negative (placebo) controlled crossover study in healthy subjects. A total of 53 subjects were administered [EV/DNG tablets] (containing 3 mg dienogest and 2 mg estradiol valerate), dienogest 10 mg, as once daily dose for 4 days. The upper bound of the 90% confidence interval for the largest placebo-adjusted, baseline-corrected QTc based on Fridericia's correction method (QTcF) was below 10 ms, the threshold for regulatory concern*."

8.7 Overall Assessment of Safety

In the Applicant's three Phase 3 clinical trials for the indication of prevention of pregnancy, the safety of EV/DNG tablets was evaluated in more than 2,000 women, representing a total exposure of more than 30,000 28-day treatment cycles. In the Phase 3 trials, there were 2 deaths: one death was related to the Asian tsunami in December 2004 and one death was attributed to a ruptured cerebral aneurysm. Neither was attributed to treatment with EV/DNG tablets by the primary Medical Reviewer or Clinical Team Leader.

Among adverse events of greatest concern in women using combination oral contraceptives are venous and arterial thrombotic events. In the Phase 3 contraceptive clinical trials, there was one report of a DVT and one report of a myocardial infarction. A second case of a myocardial infarction was reported in a Phase 3 trial with EV/DNG tablets for another indication. Both women who experienced a myocardial infarction were 46 years of age and also had other preexisting risk factors. Of note, in the Phase 3 contraceptive trials there were no reports of pulmonary emboli or stroke. In summary, based on the clinical trial data for EV/DNG tablets, there is no reason to believe that women who may use EV/DNG tablets as their method of contraception will be at greater risk for a thrombotic event than women who choose to use another currently approved combination oral contraceptive.

In the two Phase 3 clinical trials in which subjects were treated for up to 20 and 28 months, 10.3% and 14.9% of subjects terminated from the study prematurely because of an adverse event. Changes in menstrual bleeding patterns were the most common reason for premature termination. Other reasons included psychiatric and breast complaints, acne, headaches, and weight gain. The most common adverse events that were likely to be possibly related to the use of EV/DNG tablets were headaches, metrorrhagia and irregular menstruation, breast pain, discomfort or tenderness, nausea and vomiting, acne, and increased weight. The types of adverse events that were most common as well as those leading to premature termination were similar to those generally seen in clinical trials of other combination oral contraceptives. Uterine bleeding

patterns (both scheduled and unscheduled bleeding/spotting) were acceptable and comparable to those associated with the use of other combination oral contraceptives.

In summary, there were no findings from the clinical trials with EV/DNG tablets that raised any new safety concerns beyond those generally associated with the use of combination oral contraceptives.

9. ADVISORY COMMITTEE MEETING

This Application was not presented to an Advisory Committee (AC) because DRUP did not believe that AC guidance was needed to make a regulatory decision concerning the approvability of the Application for prevention of pregnancy. Although DNG is a new molecular entity, the large clinical trial database did not raise any concerns regarding the safety or efficacy of EV/DNG tablets. Both of the primary Phase 3 contraceptive studies were conducted in accordance with well established practices for hormonal contraceptive clinical trials, and both studies provided strong evidence of efficacy. No safety concerns, other than those known to be associated with combination estrogen/progestin oral contraceptives, were identified in the large safety database that included more than 30,000 28-day treatment cycles.

10. PEDIATRICS

The Applicant requested a waiver of pediatric studies. The Pediatric Review Committee (PeRC) granted a partial waiver for pre-menarcheal children because they are not at risk for pregnancy. The remainder of the PREA requirement for pediatric studies has been fulfilled by extrapolation. Clinical experience with a wide variety of oral hormonal contraceptives supports DRUP's expectation that the efficacy and safety of EV/DNG tablets in postmenarcheal adolescents, like that of other previously approved oral contraceptives, will not differ from that in adult women.

The Applicant intends to conduct a large, noninterventional postmarketing study in Europe and the US (see Section 13.4), which has no planned lower age restriction. DRUP has informed the Applicant that (1) this study will be a postmarketing requirement and (2) safety findings from women under the age of 18 will be of particular interest because such women were not studied in the preapproval clinical trials.

11. OTHER RELEVANT REGULATORY ISSUES

Certification of Financial Interests

The Applicant provided financial disclosure information for 3 investigators who had potential conflicts. The primary Clinical Reviewer (Dr. Willett) reviewed the specifics of the financial disclosure information and the contributions of each of the 3 investigators to the overall clinical program. He concluded that because of the limited involvement or limited contribution of each of the 3 investigators to the overall clinical development program for EV/DNG tablets, their potential financial conflicts would have no bearing on the overall assessment of the safety and efficacy of EV/DNG tablets.

Division of Scientific Investigation Inspections

Site inspections by the Division of Scientific Investigation (DSI) were conducted for 3 sites in the contraceptive trials. Sites were selected for inspection on the basis of high enrollment; there were no issues of concern noted that warranted inspection. In addition, inspection of the Applicant's clinical study monitoring and quality control activities was conducted. Although

regulatory violations were noted at 2 of the 3 clinical sites, the final DSI assessment stated that "*the findings are unlikely to impact data integrity…The studies appear to have been conducted adequately, and the data generated by the clinical sites and submitted by the sponsor appear acceptable in support of the respective indication*."

Division Director's Comment

- *The primary Medical Reviewer and Clinical Team Leader concurred with the overall assessment by DSI that the data from the inspected sites and the Applicant's overall monitoring procedures were adequate to support the application.*

12. LABELING

The proprietary name initially proposed by the Applicant, "Qlaira," was found to unacceptable to the Division of Medication Errors Prevention and Analysis (DMEPA). The Applicant subsequently proposed several alternative names. The proprietary name "Natazia" was determined by DMEPA to be acceptable on May 5, 2010.

The package insert for EV/DNG tablets was submitted in the format prescribed by the Physician Labeling Rule (PLR). Combined hormonal oral contraceptives are associated with a number of well-recognized safety concerns. Product labeling for Natazia tablets will be based, for the most part, on class labeling for combination oral contraceptives.

Although the to-be-approved package insert generally follows class labeling for combination oral contraceptives, there were areas of labeling that required special attention or modification as described below:

- In addition to the standard indication for hormonal contraceptives products, which states that the product is "indicated for use by women to prevent pregnancy," the indication section will include the following statement:

  "*The efficacy of Natazia in women with a body mass index (BMI) of > 30 kg/m^2 has not been evaluated."*

- Because of the significant effect of strong inducers of CYP 3A4 on the metabolism of DNG, the Warnings and Precautions section and other sections of labeling will include the following statement:

  "*Women who take medications that are strong CYP3A4 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*."

- Because EV/DNG tablets consists of 4 different dose levels/combinations of EV or EV/DNG (i.e., a 4-phase product), dosing instructions regarding what action a patient is to take if she fails to take one or more tablets have been significantly modified compared to those for a traditional monophasic product.

Final acceptable product labeling (carton and package insert) was received on May 6, 2010.

13. DECISION/ACTION/RISK BENEFIT ASSESSMENT

13.1 Regulatory Action

The Applicant has provided sufficient information for me to conclude that EV/DNG tablets will be a safe and effective combination oral contraceptive when used in accordance with final labeling submitted by the Applicant on May 6, 2010. I therefore recommend that EV/DNG tablets be approved for the indication of "use by women for prevention of pregnancy."

13.2 Risk/Benefit Assessment

The data from the two primary Phase 3 contraceptive efficacy studies conducted by the Applicant have provided strong support for the efficacy of EV/DNG tablets for use by women for the prevention of pregnancy. The Pearl Index values for women ≤ 35 years of age at study entry, based on all on-treatment pregnancies and menstrual cycles during which no back up contraception was used, were 1.04 (Study 306660) and 1.64 (Study 304742). These values indicate that the efficacy of EV/DNG tablets is acceptable for a hormonal contraceptive and comparable to that of other approved combination oral contraceptives.

In the Applicant's three Phase 3 clinical trials for the indication of prevention of pregnancy, the safety of EV/DNG tablets was evaluated in more than 2,000 women, representing a total exposure of more than 30,000 28-day treatment cycles. Among adverse events of greatest concern in women using combination oral contraceptives are venous and arterial thrombotic events. Based on the clinical trial data for EV/DNG tablets, there is no reason to believe that women who may use EV/DNG tablets as their method of contraception will be at greater risk for a thrombotic event than women who choose to use a currently approved combination oral contraceptive. In the two Phase 3 clinical trials in which subjects were treated for up to 20 and 28 months, changes in menstrual bleeding patterns were the most common reason for premature termination. Other reasons included psychiatric and breast complaints, acne, headaches, and weight gain. The types of adverse events that led to premature termination and the percentages of subjects experiencing them in these trials were similar to those generally seen in clinical trials of combination oral contraceptives. Overall uterine bleeding patterns for scheduled and unscheduled bleeding/spotting were acceptable. There were no findings from the clinical trials with EV/DNG tablets that raise any new safety concerns beyond those generally associated with the use of combination oral contraceptives.

In summary, the overall risk/benefit profile for EV/DNG tablets is favorable and acceptable for a combination oral contraceptive.

13.3 Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies (REMS)

No postmarketing risk management activities beyond labeling and the Applicant's standard pharmacovigilance activities are recommended.

13.4 Recommendation for other Postmarketing Requirements and Commitments

It is not feasible to obtain a precise estimate of both the absolute and relative risk (risk compared to other oral contraceptive products) of venous and arterial thrombosis for users of hormonal contraceptive products pre-approval because of the low prevalence of these events. Such ascertainment requires a very large clinical trial and longer follow-up than would be feasible

preapproval. The Applicant has committed to conducting a postmarketing study to assess the thrombotic risk of short and long-term use of EV/DNG tablets. The study will be a prospective, controlled, non-interventional, long-term cohort study that follows a series of cohorts consisting of new users of EV/DNG tablets and new users of oral contraceptives containing other progestins. The study will 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 will enroll a total of at least 50,000 women in the US and Europe combined, who will be followed for at least 3 years. The main clinical outcomes of interest are deep venous thrombosis (DVT), pulmonary embolus (PE), acute myocardial infarction, and cerebrovascular accidents. There should be no age restrictions for entry into the study. The applicant has committed to the following timetable for this postmarketing study:

Final Protocol Submission:	September 1, 2010
Study Completion Date:	September 1, 2015
Final Report Submission:	September 1, 2016

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

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

/s/

SCOTT E MONROE
05/06/2010