

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**021187Orig1s021s022**

**MEDICAL REVIEW(S)**

## CLINICAL REVIEW ADDENDUM

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NDA: 021187/S-021 and S-022	Submission Dates: 8/30/2012 (S-021; SDN 791), 12/20/2012 (S-022; SDN 815), 3/12/2013 (S-021; SDN 845), 9/4/2013 (S-021; SDN 877), and 9/19/2013 (S-021; SDN 878)
Brand Name:	NuvaRing®
Generic Name:	Etonogestrel / ethinyl estradiol (EE)
Clinical Primary Reviewer:	Daniel Davis, MD, MPH
Clinical Secondary Reviewer:	Lisa Soule, MD
OND Division:	Division of Bone, Reproductive, and Urologic Products (DBRUP)
Sponsor:	Organon USA Inc.
Submission Type:	Efficacy Supplement (S-021) and prior approval labeling supplement (S-022)
Formulation, Strengths, and Dosing Regimen:	Vaginal ring; etonogestrel 11.7 mg + EE 2.7 mg; one ring should be inserted in the vagina and remain in place continuously for 3 weeks followed by a 1 week ring-free interval
Indication	Prevention Of pregnancy

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The purpose of this addendum is to address the original clinical review and recommendation on Supplements 021 and 022 to NDA 021187.

In the original clinical review of these supplements to NDA 021187 dated September 10, 2013 in DARRTS, the clinical reviewer reviewed the efficacy (S-021) and labeling (S-022) supplements submitted to NDA 021187 on August 30, 2012, December 20, 2012, and March 12, 2013. Approval of NuvaRing (NDA 21187) Supplements S-021 and S-022 was recommended pending acceptable labeling.

This reviewer finds the Sponsor's most recent proposed product labeling language to be acceptable from the clinical perspective. The final agreed upon product label between the Sponsor and the DBRUP will be attached to the Approval Letters. There are no outstanding clinical labeling issues.

## **1. Recommendation**

The clinical (medical officer) reviewer finds the NDA 021187 revised PI and PPI label acceptable from the clinical perspective.

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/s/  
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DANIEL DAVIS

10/04/2013

Memo to the label changes S-021 and S-022.

LISA M SOULE

10/04/2013

I concur with Dr. Davis' recommendation for approval.

Clinical Review  
Daniel Davis, M.D.  
NDA 021187 (Nuvaring) Supplements S-021 and S-022

## CLINICAL REVIEW

Application Type	NDA (Supplement)
Application No.	021187
Supplement No.	SE-8 (Supplement S-021) and PLR conversion (Supplement S-022)
Priority or Standard	Standard
Submit Date	S-021: December 5, 2012 S-022: December 20, 2012
PDUFA Goal Date	S-021: October 5, 2013 S-022: June 20, 2013
Division / Office	Division of Bone, Reproductive and Urologic Products (DBRUP) / Office of Drug Evaluation III (ODE III)
Reviewer Name	Daniel Davis, M.D.
Review Completion Date	September 10, 2013
Established Name	(etonogestrel/ethinyl estradiol vaginal ring)
Trade Name	NuvaRing
Therapeutic Class	Hormonal contraceptive
Applicant	Organon USA Inc.
Formulation	Vaginal ring
Dosing Regimen -	One ring inserted for Days 1-21; no ring Days 22-28
Primary Indication	Contraception
Secondary Indications	None
Intended Population	Women of childbearing age

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## List of Abbreviations

AE	Adverse event
AMI	Acute myocardial infarction
BMI	Body mass index
CI	Confidence interval
CMC	Chemistry, Manufacturing and Controls
COC	Combination oral contraceptive
CHF	Congestive heart failure
CT	Computed tomography
CVA	Cerebrovascular accident
DRUP	Division of Reproductive and Urologic Products
DRSP	Drospirenone
DVT	Deep venous thrombosis
ECG	Electrocardiogram
EE	Ethinyl estradiol
EURAS	European Active Surveillance
FDA	Food and Drug Administration
INAS	International Active Surveillance
IND	Investigational New Drug (application)
IRB	Institutional review board
LASS	Long-Term Active Surveillance Study
MedDRA	Medical Dictionary for Drug Regulatory Activities
MI	Myocardial infarction
MRI	Magnetic resonance imaging
NDA	New Drug Application
OB	Office of Biostatistics
OC	Oral contraceptive
ODE III	Office of Drug Evaluation III
OSE	Office of Surveillance and Epidemiology
PADER	Periodic adverse drug experience report
PE	Pulmonary embolism
PMDD	Premenstrual dysphoric disorder
PSUR	Periodic safety update report
SAE	Serious adverse event
SD	Standard deviation
VTE	Venous thromboembolism
WY	Women-years



## **1 Recommendations/Risk Benefit Assessment**

### **1.1 Recommendation on Regulatory Action**

Approval of NuvaRing (NDA 21187) Supplements S-021 and S-022 is recommended pending acceptable labeling.

### **1.2 Risk Benefit Assessment**

In the efficacy supplement S-021, the Applicant is seeking to add new information to the labeling for NuvaRing based on the findings of two epidemiologic studies that evaluated the risk of venous thromboembolic events (VTEs) compared to other combination hormonal contraceptives.

Since the original approval in October 2001, there have been reports of thromboembolic events associated with the use of NuvaRing. Based on a series of reviews by the then-Division of Drug Risk Evaluation (DDRE) in the Office of Surveillance and Epidemiology (OSE) between 2004 and 2007, the Agency requested on September 7, 2007 that the Sponsor conduct an epidemiological study (with US data) to evaluate the risk of serious thrombotic and thromboembolic events and deaths for NuvaRing users compared to users of low dose combination oral contraceptive (COC) products. The study was entitled, "Transatlantic Active Surveillance on Cardiovascular Safety of NuvaRing (TASC)." It was a large, multinational, controlled, prospective, active surveillance study that followed two cohorts: new users (starters and switchers) of NuvaRing and marketed COCs. Each cohort consisted of 15,000 participants; 50% recruited from US sites, 50% from European sites.

OSE reviewed the TASC protocol and provide comments to the Sponsor. In addition, there have been regular (approximately every 6 months) interim reports of data from the TASC study and these have been reviewed by OSE and the Division of Bone, Reproductive and Urologic Products (DBRUP). Jurgen Dinger, MD, PhD of the Berlin Center for Epidemiology and Health Research is the primary author for the reports. The final study report was submitted to the Division on August 30, 2012 as document SD-791.

There has been additional data on the VTE risk associated with NuvaRing from a large FDA-funded epidemiology study<sup>1</sup> that evaluated VTE risk and all-cause and cardiovascular mortality for 3 newer combination hormonal contraceptives

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<sup>1</sup> Sidney S, Cheetham TC, Connell FA, Ouellet-Hellstrom R, Graham DJ, Davis D, Sorel M, Quesenberry Jr. CP, Cooper WO. *Recent combined hormonal contraceptives (CHCs) and the risk of thromboembolism and other cardiovascular events in new users.* Contraception. 2013; 87:93-100.

(CHCs) compared to 4 older CHCs with similar low estrogen levels. This study was performed because the FDA believed that there was not sufficient epidemiological data for 3 “more recently approved” hormonal contraceptives (NuvaRing is one) compared to much older oral hormonal contraceptives for VTE and arterial thrombotic events (ATE) risk plus all-cause and cardiovascular mortality.

Review of this supplemental information for the NuvaRing label was performed not only by DBRUP, but also by OSE and the Office of Biostatistics (OB).

The following documents were reviewed in detail by OSE:

1. *Transatlantic Active Surveillance on Cardiovascular Safety of NuvaRing (TASC). Final Study Report.* Jürgen Dinger, August 9, 2012.
2. Dinger J and Pineda A. *Risk of Venous Thromboembolism in Users of an Etonogestrel/Ethinyl estradiol Containing Vaginal Ring. Final Results from the TASC Study.* Slides 2012.
3. Proposed PLR label (01-proposed-wrm-uspi-mk8342amg-plr-tasc.pdf ); EDR Link:  
<http://darrrts.fda.gov:9602/darrrts/viewEDR.do?suppDocId=8262273>
4. Jessica Kim: Division of Biometrics VII, OB. July 26, 2013 Comments on the *Transatlantic Active Surveillance on Cardiovascular Safety of NuvaRing (TASC), Final Study Report.* By Jürgen Dinger, August 9, 2012.

**Reviewer’s comment:**

In the TASC study, the incidence rate for VTE events per 10,000 woman-years (WY) for NuvaRing, other COCs and COCs without desogestrel or gestodene is 8.3, 9.2, and 8.9 respectively, all with overlapping confidence intervals. This does not suggest that the risk of VTE is higher for NuvaRing compared to certain other CHCs.

In the FDA-funded retrospective cohort study, the VTE incidence for new users of NuvaRing was 11.4 events per 10,000 WY and for new users of a levonorgestrel (LNG)-containing COCs was 9.2 events per 10,000 WY, and 8.2 for the other COCs (this did not include any gestodene and desogestrel products).

The overall conclusion – the VTE incidence for NuvaRing users in both studies does not appear to be statistically significantly increased compared to other COCs. This reviewer concurs with OSE and OB’s assessment and recommendations for labeling revisions. See Sections 4.6 Office of Surveillance and Epidemiology, 7.3.2, and 9.1 Labeling Recommendations for further details.

### **1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies**

There are no recommendations for postmarketing risk evaluation or mitigation strategies based on this submission.

## **1.4 Recommendations for Postmarket Requirements and Commitments**

There are no additional recommendations for postmarketing requirements or commitments base on this submission.

## **2 Introduction and Regulatory Background**

### **2.1 Product Information**

NuvaRing is a CHC that contains ethinyl estradiol and etonogestrel released over a 21-day period as the active contraceptive hormones. Ethinyl estradiol is the estrogen found in nearly all COCs. The progestin etonogestrel is found in NuvaRing and the subdermal implants Implanon and Nexplanon.

### **2.2 Currently Available Treatments for Proposed Indication**

Contraceptive methods for females include:

- Barrier methods (condom, diaphragm, cervical cap)
- COCs
- Progestin-only oral contraceptives
- Intrauterine devices (levonorgestrel-containing and copper-containing)
- Injectable contraceptives
- Contraceptive implants
- Contraceptive vaginal rings
- Surgical sterilization (tubal ligation, intratubal obstructive devices)

### **2.3 Availability of Proposed Active Ingredients in the United States**

Ethinyl estradiol is used in nearly all combination oral contraceptives in the US. One exception is the recently approved Natazia product that incorporates estradiol valerate as the estrogenic component. Etonogestrel is found in 3 hormonal contraceptives.

### **2.4 Important Safety Issues with Consideration to Related Drugs**

For the purposes of this efficacy supplement, the primary focus is on the following:

- Vascular events, which may rarely be fatal, including:
  - Deep venous thrombosis, pulmonary embolism, other venous thromboses
  - Myocardial infarction (especially in women >35 years who smoke)
  - Stroke (both ischemic and hemorrhagic types reported)

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

In the submission dated August 30, 2012, the Sponsor submitted the final report of the epidemiological study entitled, "Transatlantic Active Surveillance on Cardiovascular Safety of NuvaRing (TASC)" along with a Prior Approval labeling Supplement that sought to update labeling with the results of TASC and the FDA-funded study. Following discussions with the FDA User Fees group, it was determined that the submission properly constituted an efficacy supplement that required review of clinical data. The Division (DBRUP) informed the Applicant on October 31, 2012 that the application was considered incomplete because the required user fee had not been received. The user fee for Supplement 021 was paid on December 5, 2012; at this point the 10-month review of the efficacy supplement was started.

The Division also informed the Applicant on September 26, 2012 that conversion of the existing labeling into PLR format was overdue and requested the Applicant to submit a PLR conversion as a Prior Approval labeling supplement. The PLR conversion (S-022) was received on December 20, 2012 and had a 6-month review clock. However, because of the ongoing review of S-021, it was decided that it would be most efficient to take a single action on both supplements.

Later, the Sponsor submitted a revision on March 12, 2013, with one proposed labeling update for NuvaRing based on the TASC study. The Sponsor proposed to change the VTE incidence from 8.9 to 8.5 for women using COCs, excluding desogestrel, gestodene, and drospirenone.

The second requested revision needed is located in the Serious Adverse Reactions section under Clinical Trials Experience of the proposed USPI. The Sponsor noted that the event listed as "Transient Ischemic Attack" submitted to the Agency on December 20, 2012 should have been listed as anxiety attack as stated in the clinical trial report of 068003 submitted to FDA on December 28, 1999 as part of the original NDA submission. Therefore, the Sponsor has also requested the following correction to the proposed USPI:

**Serious Adverse Reactions:** deep vein thrombosis [see Warnings and Precautions (5.1)], (b) (4) anxiety (b) (4) (b) (4) cholelithiasis, and vomiting.

### Reviewer's comment:

The original COC-associated VTE incidence of 8.9 per 10,000 WY was based on evaluation of COCs that do not contain the progestins desogestrel or gestodene. The VTE incidence is lower (the Applicant's proposed (b) (4)) if drospirenone-containing COCs were also excluded from the analysis. However, OSE determined that the analysis excluding drospirenone was not the pre-specified

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analysis, and recommended retaining the data based upon the COC comparator excluding only COCs that contain desogestrel or gestodene (i.e., the incidence rate of 8.9). I recommend that the 8.9 VTE incidence be used in the label.

The requested change in Section 6.1, Serious Adverse Reactions is acceptable as the Applicant offers a clear explanation.

## **2.6 Other Relevant Background Information**

All of the relevant background information was conveyed in the preceding sections.

## **3 Ethics**

In the TASC study, the protocol was submitted to the relevant Ethics Committees and Institutional Review Boards for approval. Adverse events were monitored per protocol.

Financial disclosure information is not required for these postmarketing safety studies that form the basis for labeling changes sought in this supplement.

## **4 Significant Efficacy/Safety Issues Related to Other Review Disciplines**

### **4.1 Chemistry Manufacturing and Controls**

The submitted data do not require CMC review.

### **4.2 Clinical Microbiology**

Microbiology was not required for this application.

### **4.3 Preclinical Pharmacology/Toxicology**

The submitted data do not require a Pharmacology/Toxicology review.

### **4.4 Clinical Pharmacology**

The submitted data do not require a Clinical Pharmacology review.

### **4.5 Biostatistics**

See Section 4.6 for biostatistics review relating to the labeling changes for NuvaRing based on the final TASC data.

#### **4.6 Office of Surveillance and Epidemiology (OSE)**

OSE was consulted regarding the Applicant's submission of the VTE-related labeling for NuvaRing on July 5, 2013. OSE was asked to review 1) the final TASC study report submitted to the Agency on August 30, 2012, 2) the Applicant's proposed labeling relating to the risk of VTE associated with use of NuvaRing, and 3) to indicate if OSE/DEPI concurs with the proposed language in the revised label. They reviewed the submission and pertinent medical literature. They also utilized the Office of Biostatistics (OB) for confirmation and reanalysis of the TASC data.

**OSE/DEPI has two recommendations specific to the NuvaRing label information based on results of the TASC study and the recent FDA-funded epidemiological study. Here are their comments:**

First, the TASC study was powered to assess no less than a twofold risk of VTE for NuvaRing when compared to all other oral contraceptives (COCs) and to COCs that do not contain the progestins desogestrel (DSG) and gestodene (GSD). Although VTE risks for NuvaRing were compared to COCs that excluded DSG, GSD and drospirenone (DRSP), the latter [excluding DRSP] was an ad hoc comparison for which this study lacked power to do. OSE/DEPI recommends including the incidence rates and hazard ratio risk estimates for the comparison initially proposed and powered for the study.

The second recommendation is to align the VTE incidence rate (IR) information for the FDA funded study to those presented for the TASC study (for NuvaRing, other COCs) rather than limiting incidence rates to NuvaRing and to levonorgestrel-containing COCs as calculated in the FDA study. The IR for other COCs is available for this study as well. Although the differences are minor, the text in the label that presents incidence information should compare the incidence rates of comparable groups for the two studies since the information is available.

The epidemiologic information proposed for the revised NuvaRing PLR label is generally acceptable and follows the format of the information included in the label of other contraceptive products with labels revised recently.

**Reviewer's comment:**

**I concur with the above two recommendations from OSE/DEPI and these changes are reflected in Section 5.1 of the final label.**

## **5 Sources of Clinical Data**

### **5.1 Summary**

See Sections 5.2 and 5.3 that follow.

### **5.2 Review Strategy**

The clinical review strategy was to review the following:

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- TASC final study report
- FDA-funded study results
- Periodic adverse drug experience reports (PADERs) for NuvaRing

### **5.3 Discussion of TASC Study**

The Transatlantic Active Surveillance on Cardiovascular Safety of NuvaRing (TASC) study was a large, four-year multinational, prospective, observational active surveillance study of new hormonal contraceptive NuvaRing users compared to users of other marketed combined oral contraceptives (COCs). The study recruited 33,295 women on these treatments in routine clinical practice settings between September 2007 and September 2009. Women were followed for 24 to 48 months depending on when they were recruited. The study was started in Europe (Austria) in September 2007. The first US women were enrolled in late February 2008. Women from Austria, France, Germany, Italy, Russia and the United States participated in the study.

The main clinical outcomes of interest were VTEs and ATEs and the risks of short- and long-term use of NuvaRing compared to users of certain COCs. Reported serious adverse events were validated by contacting the diagnosing and treating physicians and by reviewing relevant source documents.

#### **Reviewer's comment:**

**For a very detailed review of the TASC Study Report and analysis of the data and findings, see the review by Rita Ouellet-Hellstrom, PhD, Division of Epidemiology II in OSE.**

## **6 Review of Efficacy**

The data in this supplement relate only to safety. The clinical data being reviewed to support revision of labeling language for NuvaRing is reviewed in Section 7.

## **7 Review of Safety**

### **7.1 Components Used to Evaluate Safety and Labeling Changes**

The key components to NDA 21187 regarding safety findings impacting labeling are found in the Final TASC Study Report, the Sponsor's PADERs, and labeling submissions. Selected data from the FDA-funded study of VTE, ATE, and mortality risks was also used.

### **7.2 Adequacy of Safety Assessments**

### **7.2.1 Overall Exposure**

For the TASC study, there over 15,000 NuvaRing users and over 15,000 COC users; 50% were European women and 50% were US women. Exposure was defined as first use of a CHC, either the NuvaRing or a COC. The study recruited women who were starters, switchers, or recurrent users of CHCs. Starters were first-ever users of hormonal contraceptives. Switchers were users who switched from one CHC to another CHC - e.g., from a COC to NuvaRing or from a norgestimate-containing COC to a levonorgestrel-containing COC - without an intake break or with an intake break of less than 4 weeks. Recurrent users were women who restarted contraceptive use with NuvaRing or a COC after an intake break of at least 4 weeks.

Two additional exposure cohorts were developed during the long follow-up of this study as some women changed their contraceptive method to other hormonal contraceptives (OHC) or completely stopped using hormonal contraception during the follow up period ('no-use' cohorts).

Study subjects who discontinued the study medication continued to be followed over the course of the study provided that they did not withdraw consent. Reason(s) for treatment discontinuation was obtained during follow-up.

For the FDA-funded study, there was over 23,900 person-years of exposure to etonogestrel (NuvaRing) and over 617,000 person-years of exposure to the comparator CHCs. Although this is not a huge exposure to NuvaRing, some conclusions relative to NuvaRing risk were made.

#### **Reviewer's comment:**

**This is adequate exposure for drawing conclusions about VTE and safety risks associated with use of NuvaRing compared to other hormonal contraceptive products.**

### **7.2.2 Explorations for Dose Response**

Not applicable for this submission.

### **7.2.3 Special Animal and/or In Vitro Testing**

Not applicable for this submission.

### **7.2.4 Routine Clinical Lab Testing**

Not applicable for this submission.

### **7.2.5 Metabolic, Clearance, and Interaction Workup**

Not applicable for this submission.



## 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

TASC evaluated a large number of drug products in the COC drug class (see Table 1 below **Error! Reference source not found.** for a list of progestin components evaluated). In the FDA-funded study, only 7 products were evaluated based on the study's objectives and the 4 healthcare systems databases that were used. Because the overall databases were so large, assessment of adverse events, common and rare, for similar drugs (hormonal contraceptives) is possible.

**Table 1: Progestins Used by Type and Region**

	US Women	European Women	All Women
<b>Progestins of COCs</b>			
DRSP (drospirenone)	25.4	32.9	29.3
NGM (norgestimate)	23.1	1.1	11.7
NETA (norethindrone)	21.7	N/A	10.5
LNG (levonorgestrel)	12.0	15.2	13.7
NET (norethisterone)	8.0	N/A	3.9
DSG (desogestrel)	6.2	14.0	10.3
NG (norgestrel)	2.8	NA	1.4
Other	0.8	0.3	0.4
GSD (gestodene)	NA	12.4	6.4
DNG (dinogest)	NA	11.6	6.1
CMA (chlomadinacetate)	NA	6.9	3.6
CPA (cyproteracetate)	NA	5.6	2.9
N/A – not approved in the region			

Source: Modified Table 2 from page 11, review by Rita Ouellet-Hellstrom, PhD.

## 7.3 Safety Results from TASC Pertaining to this Supplement

### 7.3.1 Enrollment Data

For the TACS study, a total of 33,295 women with complete analyzable baseline records were enrolled: 16,864 women used NuvaRing, 16,431 used COCs. Among the COC users, 2,620 used COCs containing desogestrel (DSG) or gestodene (GSD) (COC<sub>DSG/GSD</sub>), and 13,811 used COCs containing other progestins (COC<sub>op</sub>). Of the 33,295 women, 17,381 (52.2%) were from the US and 15,914 (47.8%) were European, mostly from Germany and Russia (78% of Europeans). In general, US women were heavier (BMI ~ 26-27) than European women (BMI ~22-23) and more European women smoked (30%) than US women (15%), but within each region there was no difference by treatment.

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For the FDA-funded study, the final cohort included 189,211 person-years of exposure to drospirenone, 67,867 person-years of exposure to norelgestromin, 23,912 person-years of exposure to etonogestrel, and 617,291 person-years of exposure to the comparator CHC's.

**Reviewer's comment:**

By design, the TASC study had approximately 50% NuvaRing users in both the US and non-US cohorts. The FDA study was different by design and the percentage of NuvaRing users reflected the use in the 4 databases that were analyzed.

### **7.3.2 Incidence and Incidence Rate Ratios for VTEs**

**Reviewer's comment:**

In the TASC study, the incidence rate for VTE events per 10,000 woman-years (WY) for NuvaRing, other COCs and COCs without desogestrel or gestodene is 8.3, 9.2, and 8.9 respectively, all with overlapping confidence intervals. This does not suggest that the risk of VTE is higher for NuvaRing compared to certain other CHCs.

In the FDA-funded retrospective cohort study, the VTE incidence for new users of NuvaRing was 11.4 events per 10,000 WY and for new users of a levonorgestrel (LNG)-containing COCs was 9.2 events per 10,000 WY, and 8.2 for the other COCs (this did not include any gestodene and desogestrel products).

The overall conclusion – the VTE incidence for NuvaRing users in both studies does not appear to be statistically significantly increased compared to other COCs.

## **7.4 Supportive Safety Results**

### **7.4.1 Common Adverse Events**

Not applicable for this application

### **7.4.2 Laboratory Findings**

Not applicable for this application

### **7.4.3 Vital Signs / Body Weight**

Not applicable for this application

### **7.4.4 Electrocardiograms (ECGs)**

Not applicable for this application

#### **7.4.5 Special Safety Studies/Clinical Trials**

TASC, which is the subject of this review, could be described as a special post-approval safety study because of its focus on thromboembolic and cardiovascular safety evaluation. The Division requested the Sponsor in September 2007 to begin a US epidemiological study to evaluate the risk of serious thrombotic and thromboembolic events for NuvaRing users as compared to users of low dose COCs. The final study report was submitted (SD-791) on August 30, 2012.

#### **7.4.6 Immunogenicity**

Not applicable for this application.

#### **7.5 Other Safety Explorations**

Not applicable for this application.

##### **7.5.2 Time Dependency for Adverse Events**

Not applicable for this application

##### **7.5.3 Drug-Demographic Interactions**

Not applicable for this application.

##### **7.5.4 Drug-Disease Interactions**

Not applicable for this application.

##### **7.5.5 Drug-Drug Interactions**

Not applicable.

#### **7.6 Additional Safety Evaluations**

##### **7.6.1 Human Carcinogenicity**

Not applicable for this application.

##### **7.6.2 Human Reproduction and Pregnancy Data**

Not applicable for this application.

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### **7.6.3 Pediatrics and Assessment of Effects on Growth**

Not applicable for this application.

### **7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound**

Not applicable for this application.

## **7.7 4-Month Safety Update**

A separate 4-month safety report was not required because the Division had adequate up-to-date safety reporting (PADERS) and regular annual reports.

## **8 Postmarketing Experience**

### **8.1 Periodic Adverse Drug Experience Reports (PADERS)**

The Sponsor has submitted annual safety reports on a regular basis for 12 years. The latest report was Safety Report 26, submission SD-813 with a Stamp Date of 12-03-12. It has been increasingly difficult to interpret the reports of SAEs because of enhanced reporting rates due to attorney submissions, duplicate reports, and lack of sufficient medical information in many of the reports.

#### **Reviewer's comment:**

**These recent postmarketing safety reports do not appear to represent any significant change in the safety profile and do not impact the labeling changes related to TASC data in this submission.**

## **9 Appendices**

### **9.1 Labeling Recommendations**

The following consults were requested by DBRUP:

- OSE-DEPI II on July 5, 2013
- OPDP (DDMAC)- Carrie Newcomer- on August 26,2013
- DMPP- Patient Labeling Team- on August 26,2013

Labeling discussions are ongoing at the time of this review. Several areas will be updated because of the PRL conversion:

- new Highlights section
- harmonizing Sections 5, 7 and 12 with current class labeling
  - adding a Table with the hazard ratios estimates of VTE risk based on the data from the epidemiological studies

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- adding a Figure for the likelihood of developing a VTE for women who are not pregnant and do not use CHCs, for women who use CHCs, for pregnant women, and for women in the postpartum period
- developing an appropriate Section 6.2 to reflect the content and format for PLR labels
- minor changes in Section 7 Drug Interactions
- deleting the Trussell Table from Section 14 Clinical Studies

Section 5.1 Thromboembolic Disorders and Other Vascular Problems of the label will be revised based on the data from TASC, the FDA-funded study, and the safety reports for NuvaRing. Class labeling for CHCs will be included as appropriate. The recommendations from the OSE review noted in Section 4.6 of this clinical review will be incorporated into Section 5.1 of the final NuvaRing label.

### **9.2 Advisory Committee Meeting**

An advisory committee meeting was not required for this supplement.

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/s/  
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DANIEL DAVIS

09/10/2013

LISA M SOULE

09/11/2013

I concur with Dr. Davis' recommendation of approval for the efficacy supplement to NDA 21-187 as well as the PLR conversion.