APPLICATION NUMBER:

021187Orig1s021s022

MEDICAL REVIEW(S)
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
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.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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

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<tr>
<td>Reviewer Name</td>
<td>Daniel Davis, M.D.</td>
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<tr>
<td>Review Completion Date</td>
<td>September 10, 2013</td>
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<tr>
<td>Established Name</td>
<td>(etono)gestrel/ethinyl estradiol vaginal ring)</td>
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<td>Dosing Regimen -</td>
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<td>None</td>
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<td>Women of childbearing age</td>
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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 study1 that evaluated VTE risk and all-cause and cardiovascular mortality for 3 newer combination hormonal contraceptives

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1 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:


**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 based 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)], anxiety, 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...
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:
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 were 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.
TASC evaluated a large number of drug products in the COC drug class (see Table 1 below 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

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<th>Progestins of COCs</th>
<th>US Women</th>
<th>European Women</th>
<th>All Women</th>
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<tr>
<td>DRSP (drospirenone)</td>
<td>25.4</td>
<td>32.9</td>
<td>29.3</td>
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<tr>
<td>NGM (norgestimate)</td>
<td>23.1</td>
<td>1.1</td>
<td>11.7</td>
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<td>NETA (norethindrone)</td>
<td>21.7</td>
<td>N/A</td>
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<tr>
<td>LNG (levonorgestrel)</td>
<td>12.0</td>
<td>15.2</td>
<td>13.7</td>
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<tr>
<td>NET (norethisterone)</td>
<td>8.0</td>
<td>N/A</td>
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<td>DSG (desogestrel)</td>
<td>6.2</td>
<td>14.0</td>
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<tr>
<td>NG (norgestrel)</td>
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<td>Other</td>
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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 DSG/GSD), and 13,811 used COCs containing other progestins (COC op). 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.
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.
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.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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DANIEL DAVIS
09/10/2013

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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.