CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021187Orig1s021s022

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	October 4, 2013
From	Lisa M. Soule, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	21-187; SE-8 (Supplement # 021) and PLR conversion (Supplement #022)
Applicant	Organon USA Inc.
Date of Submission	S-021: December 5, 2012 S-022: December 20, 2012
PDUFA Goal Date	S-021: October 5, 2013 S-022: June 20, 2013
Proprietary Name / Established (USAN) names	NuvaRing Etonogestrel (ETO)/ethinyl estradiol (EE) vaginal ring
Dosage forms / Strength	Vaginal ring containing 11.7 mg ETO and 2.7 mg EE, inserted once every 28 days, to be worn continuously for three weeks, followed by a one-week drug-free interval
Proposed Indication(s)	Prevention of pregnancy
Recommended:	***Approval***

1. Introduction

This efficacy supplement seeks to modify labeling language regarding the risk of venous thromboembolic events (VTEs) associated with use of NuvaRing, a combined hormonal contraceptive (CHC), on the basis of two recently completed epidemiologic studies. NuvaRing is a vaginal contraceptive ring that contains ethinyl estradiol (EE) and the progestin etonogestrel (ETO). During the post-launch period, the Division closely monitored reports of thrombotic and thromboembolic events occurring in association with use of CHCs, and in 2007, on the basis of such reports and analyses of these reports by the Division of Pharmacovigilance in the Office of Surveillance and Epidemiology (OSE), the Applicant was asked to conduct a large, multinational, active safety surveillance study that compared the risk of arterial thrombotic and venous thromboembolic events and death for new users of NuvaRing compared to new users of low-dose combined oral contraceptives (COCs). This study, known as the TransAtlantic Active Surveillance on Cardiovascular Safety of NuvaRing (TASC), was completed in 2012.

In addition, a recent FDA-funded study of the VTE risk associated with use of various recently-approved CHC products also included NuvaRing as one of the CHCs evaluated.

The major issues addressed in this review involve the analysis and interpretation of the two epidemiologic studies' results and the appropriateness of the Applicant's proposed labeling. In addition, a labeling supplement providing for conversion of the current label into the format prescribed by the Physician Labeling Rule (PLR), was also submitted, necessitating introduction of several new sections into labeling that had not previously been included in the

nonPLR label. Major changes resulting from the epidemiology data and/or the PLR conversion include:

- Warnings – Thromboembolic Disorders and Other Vascular Problems
- Adverse Reactions – substantially revised to comply with PLR guidance
- Clinical Pharmacology – revised to comply with PLR guidance
- Patient labeling – added text related to VTE risk

2. Background

2.1 DESCRIPTION OF PRODUCT

NuvaRing was approved in October 2001. NuvaRing is inserted vaginally once every 28 days, to be worn continuously for 21 days, then removed at the end of Week 3 to provide a seven-day hormone-free interval. EE is the estrogen used in the vast majority of hormonal contraceptives; ETO is a 19-nortestosterone derivative in the gonane family, and is the main active metabolite of desogestrel, a so-called "third generation" progestin. ETO is also the active ingredient in the progestin-only contraceptive Implanon/Nexplanon.

NuvaRing has an acceptable Pearl Index for the prevention of pregnancy (2.02 in the pivotal US safety and efficacy trial). As for other CHCs, the risk of arterial thrombotic (ATEs) and venous thromboembolic events (VTEs) are among the most significant safety concerns. However, as pregnancy itself is associated with even higher rates of VTEs, the risk-benefit profile of CHCs for prevention of pregnancy is considered favorable.

2.2 REGULATORY HISTORY

CHC labeling has historically included as class labeling a Warning related to the risk of VTEs associated with use of these products. The discussion in non-PLR CHC labels (e.g., the current NuvaRing label) includes the following:

> *An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. Case control studies have found the relative risk of users compared to nonusers to be three for the first episode of superficial venous thrombosis, four to 11 for deep vein thrombosis or pulmonary embolism, and 1.5 to six for women with predisposing conditions for venous thromboembolic disease. Cohort studies have shown the relative risk to be somewhat lower, about three for new cases and about 4.5 for new cases requiring hospitalization. The risk of thromboembolic disease due to oral contraceptives is not related to length of use and disappears after pill use is stopped.*

By the time PLR labeling was implemented, OSE and the Division had reviewed additional literature and determined that there was an effect of duration of use, in that the excess risk of VTE in CHC users compared to non-users appears to be greatest in the first year of use. In PLR CHC labels, the section stated:

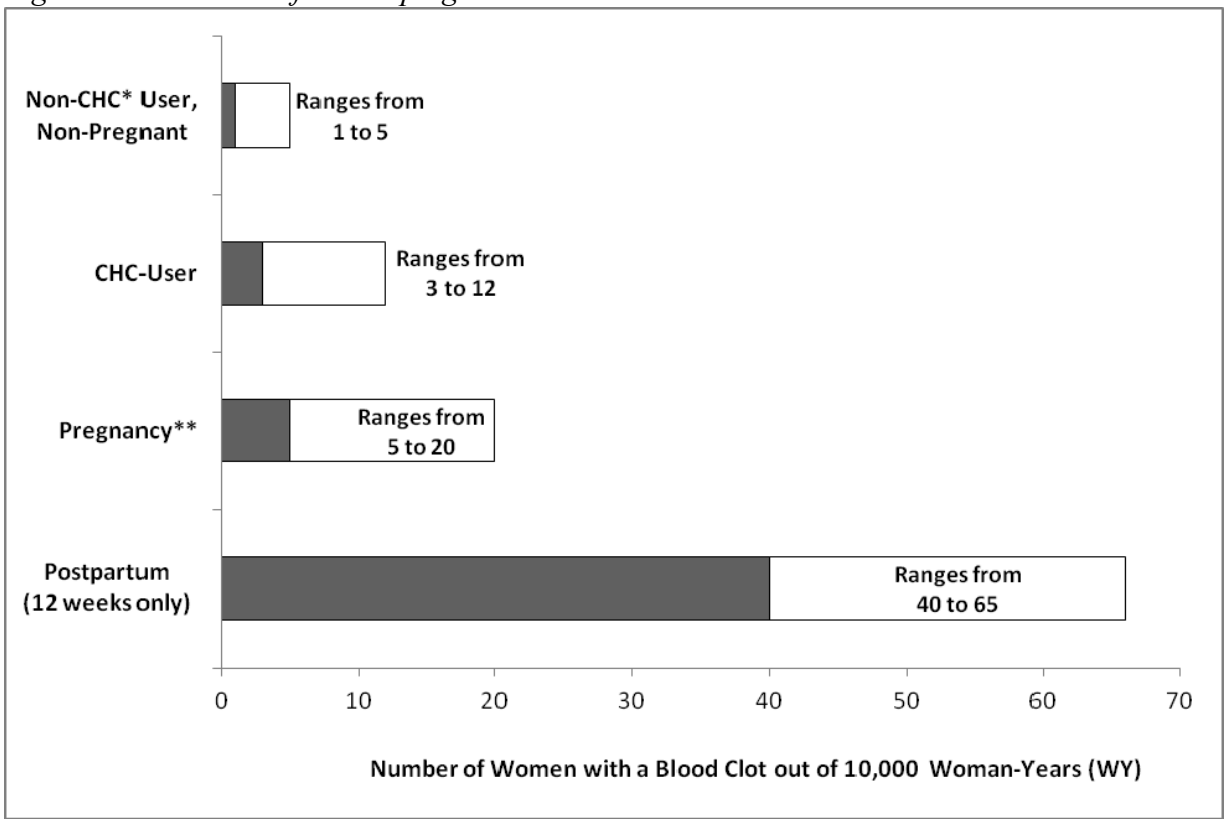
> *Stop [drug] if an arterial or venous thrombotic (VTE) event occurs. Although the use of COCs increases the risk of venous thromboembolism, pregnancy increases the risk of venous thromboembolism as much or more than the use of COCs. The risk of venous thromboembolism in women using COCs is 3 to 9 per 10,000 woman-years.*

> *The risk is highest during the first year of use of a COC. Use of COCs also increases the risk of arterial thromboses such as strokes and myocardial infarctions, especially in women with other risk factors for these events. The risk of thromboembolic disease due to oral contraceptives gradually disappears after COC use is discontinued.*

Subsequent discussion at two Advisory Committee meetings in 2011 focused on the risk/benefit of specific CHCs with respect to potentially increased risk of VTE as demonstrated in epidemiologic studies. These discussions resulted in recommendations that pertinent epidemiologic findings should be clearly conveyed in CHC labeling and that the risk of VTE should be labeled and placed in context by also providing information on the VTE risk in non-CHC users and in women during pregnancy and the postpartum period. Labeling changes were made for drospirenone-containing COCs in April 2012, and for the Ortho Evra transdermal system in August 2012. The new language for Ortho Evra, another non-oral CHC, reads:

> *An increased risk of thromboembolic and thrombotic disease associated with the use of combination hormonal contraceptives (CHCs) is well established. Although the absolute VTE rates are increased for users of CHCs compared to non-users, the rates associated with pregnancy are even greater, especially during the post-partum period (see Figure 6).*
>
> *The frequency of VTE in women using CHCs has been estimated to be 3 to 12 cases per 10,000 woman-years.*
>
> *The risk of VTE is highest during the first year of use of combination hormonal contraception. The risk of thromboembolic disease due to combination hormonal contraceptives gradually disappears after use is discontinued.*
>
> *Figure 6 shows the risk 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 post-partum period.*
>
> *To put the risk of developing a VTE into perspective: If 10,000 women who are not pregnant and do not use CHCs are followed for one year, between 1 and 5 of these women will develop a VTE.*

Figure 6: Likelihood of Developing a VTE



**CHC=combination hormonal contraception **Pregnancy data based on actual duration of pregnancy in the reference studies. Based on a model assumption that pregnancy duration is nine months, the rate is 7 to 27 per 10,000 WY.*

Finally, class labeling for products containing "third generation" progestins has described conflicting epidemiologic findings regarding whether there is an increased risk of VTE associated with these products compared to CHCs that contain "second generation" progestins such as levonorgestrel (LNG). This labeling conveys the information that some studies have found an approximately two-fold increased risk, but that other studies have not found an increase. The Division and OSE responded to a consult from the Office of Regulatory Policy regarding a Citizen Petition that sought to ban "third generation" progestin-containing COCs. Based on an extensive review of the literature provided in these consult responses, earlier this year, FDA denied the Petition and stated that current labeling is adequate and appropriate.

On August 30, 2012, the Applicant submitted the final study report for the TASC study 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 constituted an efficacy supplement that required review of clinical data, and the Division informed the Applicant on October 31, 2012 that the application was considered incomplete because the required user fee for the application had not been received. The user fee for Supplement 021 was paid on December 5, 2012; at this point the 10-month clock for review of an 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 six-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.

2.3 PRIMARY MEDICAL REVIEWER'S RECOMMENDATION FOR APPROVABILITY

The primary reviewer, Dr. Dan Davis, stated in his review, dated September 11, 2013:

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

Dr. Davis' entered an addendum to his review on October 4, 2013, stating:

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

Team Leader Comment:
I concur with Dr. Davis' recommendation for approval of this efficacy supplement and PLR conversion.

3. CMC/Device

No new chemistry, manufacturing and controls data were submitted in these applications (S-021 and 022). The primary Chemistry reviewer, Donna Christner, Ph.D., reviewed the revisions to labeling made in the conversion of the current labeling to PLR format, and noted that the Highlights, Dosage Forms and Strengths, Description and How Supplied/Storage and Handling sections were generally appropriate. Dr. Christner revised the relevant statements about latex to the standard FDA language for products that do not contain latex: "NuvaRing is not made with natural rubber latex." This revision was acceptable to the Applicant.

Dr. Christner made the following recommendations in her review dated September 10, 2013:

This Supplement is recommended for approval from the CMC perspective, with the recommended changes made in the eRoom and captured in the Review Notes.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical data were submitted in efficacy supplement or for the PLR conversion. The primary Toxicology reviewer, Krishan Raheja, D.V.M., Ph.D., reviewed the revisions to labeling made in the conversion of the current labeling to PLR format, and made the following recommendations in his review dated January 22, 2013:

***Regulatory action**: This PLR conversion supplement for NuvaRing is fine from the P/T perspective.*

5. Clinical Pharmacology/Biopharmaceutics

No new clinical pharmacology data were submitted in the efficacy supplement or PLR conversion supplement. The primary Clinical Pharmacology reviewer, Chongwoo Yu, Ph.D.,

reviewed the revisions to labeling made in the conversion of the current labeling to PLR format, and made the following recommendations in his review dated August 30, 2013:

> *The Office of Clinical Pharmacology, Division of Clinical Pharmacology III (OCP/DCP-III) has 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. These supplements are acceptable provided that a satisfactory agreement is reached regarding the labeling language.*

Dr. Yu made several comments on labeling, which were conveyed to the Applicant. He noted that revised labeling submitted by the Applicant was acceptable, and concluded in an addendum dated October 1, 2013:

> *The OCP, DCP3 finds NDA 021187 acceptable from the Clinical Pharmacology perspective.*

No phase 4 commitments or requirements were recommended.

6. Clinical Microbiology

Clinical microbiology consultation was not requested for this application, as no changes were made to the approved formulation of the product.

7. Clinical/Statistical - Efficacy

No clinical efficacy data were submitted in this NDA. The efficacy data reviewed in the original NDA submission were obtained from two one-year open label clinical studies comprising over 23,000 28-day cycles of use in almost 2,400 women. For reasons that are not clear, however, the nonPLR label reports (b) (4)

Based on the original reviews, the Pearl Index was calculated separately for Study 068003 (US and Canada) and for Study 34219 (12 European countries). In the pregnancy intent-to-treat population (PITT; women < 35 at study entry and including only those cycles in which no back-up contraceptive method was used [unless a pregnancy was conceived in such a cycle]), and including those additional pregnancies determined by the FDA reviewers to have occurred on-drug, the US Pearl Index was 2.017 (95% confidence interval [CI] 1.11, 3.37), and the European Pearl Index was 0.648 (95% CI 0.21, 1.53).

Considerations relating to the PLR labeling related to efficacy in the Package Insert (PI), in the Clinical Studies section, are discussed in Section 12.

8. Safety

This review is based on data from TASC and the FDA-funded epidemiology study. The TASC cohort consisted of over 33,000 women in the US and Europe who were "new" users of NuvaRing or a COC beginning in 2007 (Europe) or 2008 (US). These "new" users included first-ever users of a CHC, as well as women who had previously used a different CHC and were switching to the study CHC with no intake break or with a break of less than four weeks (switchers) or after a break of at least four weeks (recurrent users). Women were recruited from routine clinical practice settings and followed for 24 to 48 months, resulting in a total of

about 66,500 women-years (WY) of exposure. US women comprised 52% of the study population; 16,864 women overall used NuvaRing and 16,431 used a COC. A total of 57 confirmed VTEs occurred, 19 in the NuvaRing cohort, while 17 ATEs occurred, 5 in the NuvaRing cohort. Further details of the design and methods are discussed in Dr. Ouellet-Hellstrom's review (see Section 8.1).

The Applicant prespecified two comparator groups of COC users – all study COCs and all study COCs except those that contained the progestins desogestrel or gestodene ("third generation progestins" thought potentially to be associated with a higher risk of VTE). Results pertaining to the risk of VTE are shown in Table 1. The risk of ATE was also not significantly increased for NuvaRing users.

Table 1 VTE Incidence and Hazard Ratios, TASC

Exposure	Adjusted incidence rate per 10,000 WY	HR: vs. All COCs HR (95% CI)	HR: vs. COCs w/o DSG or GSD HR (95% CI)
NuvaRing	8.3 (5.0-12.9)	0.8 (0.5-1.5)	0.8 (0.4-1.7)
COCs w/o DSG or GSD	8.9 (5.5-13.6)	--	Reference
All COCs	9.2 (6.0-13.5)	Reference	--

Source: Tables 3 and 4, review by Rita Ouellet-Hellstrom, Ph.D., dated August 27, 2013

The Applicant also evaluated VTE incidence in women characterized as Starters (first time CHC users), Switchers (women who started a new CHC without a break or after a break of less than four weeks) and Recurrent Users (women who started a new CHC after a break of at least four weeks). Although incidence could not be computed for Starters, as there were no VTEs in this subgroup, the incidence was 5.4 per 10,000 WY for Switchers, and 12.7/10,000 WY for Recurrent Users.

Team Leader Comment:

- **The TASC study was powered to rule out a two-fold increase in VTE risk and a three-fold increase in ATE risk. The results are sufficient to be able to rule out such an increase in risk for each event. While this does not indicate that there is no difference in risk, the point estimates appear similar for NuvaRing users and COC users.**
- **The finding of increased VTE risk in women who resume CHC use after a break of four weeks or longer has been observed in other epidemiologic studies and has been labeled for several CHCs that were evaluated in the EURAS study.**

The FDA-funded study was conducted entirely in the US, in four health plans that included over 835,000 women aged 10 to 55 years who provided almost 900,000 WY of exposure over the period from 2001 through 2007. VTE rates, as well as rates of ATEs, all-cause mortality and cardiovascular mortality, were assessed for users of three recently-approved CHCs compared to four older COC products with similar low EE levels. Risk was calculated for "all users" as well as for "new users," defined as women who did not have prior CHC use of any kind during the study period or in the six-month look-back period. The incidence of confirmed VTEs in the NuvaRing users was 7.75 per 10,000 WY, and compared to users of

Use of NuvaRing was fairly limited in this study population, with 24,445 women contributing just under 24,000 WY of exposure, compared to well over 600,000 WY for the COC comparators. The mean duration of use was also shortest for NuvaRing of all the CHCs evaluated, at 167 days. NuvaRing users had only four ATEs (two among new users) and 25 VTEs (nine among new users), leading to fairly wide confidence intervals around the point estimates. Incidence rates and hazard ratios (HR) for NuvaRing compared to two groups of comparators (all COCs – products that contained 20 or 30 µg EE, and only those with LNG and 30 µg EE) are shown in Table 2. The risks of ATE and mortality were not increased in NuvaRing users.

Table 2 VTE Incidence and Hazard Ratios, FDA-funded Study

Exposure		HR: vs. All COCs	HR: vs. LNG/30 µg EE COCs
	Adjusted incidence rate per 10,000 WY	HR (95% CI)	HR (95% CI)
All Users			
NuvaRing	11.9	1.6 (1.0-2.4)	1.3 (0.8-2.0)
LNG/30 µg EE COCs	6.6	--	Reference
All COCs	6.0	Reference	--
New Users			
NuvaRing	11.4	1.1 (0.6-2.2)	1.0 (0.5-2.0)
LNG/30 µg EE COCs	9.2	--	Reference
All COCs	8.2	Reference	--

Source: Combined hormonal contraceptives (CHCs) and the risk of cardiovascular endpoints. Sidney, S. (primary author) http://www.fda.gov/downloads/Drugs/DrugSafety/UCM277384.pdf, accessed 23-Aug-2013, Tables 10b, 12a and 12b.

Team Leader Comments:

- **The "new user" comparison is felt to be the most appropriate, because continuing users of CHCs are those who have successfully passed through the initial period of highest risk of VTE. "All users" contain a mixed population of new and continuing users, and differential distribution of these cohorts across drugs may skew the comparative VTE risk findings. In particular, when comparing a recently marketed CHC to CHCs that have been marketed for a long time, it is more likely that the users of the newer product are new users and therefore at higher risk, while users of the older products are likely a mix of new and continuing users. For this reason, OSE and the Division agree that labeling should focus on results from the new user cohort.**
- **Given that VTE risk is highest during the early period of use, the relative risk for NuvaRing may be impacted by the shorter duration of use. In the comparator COCs, the mean duration of use averaged about 236 days.**
- **Overall, the 95% CIs around the hazard ratios for NuvaRing contain 1, indicating that there is not a statistically significant increased risk of VTE.**

One other publication has addressed the risk of VTE in users of NuvaRing and other CHCs. A paper by Lidegaard et al[1] described a registry-based cohort study of non-pregnant Danish women without cancer or previous thrombotic disease who were followed from 2001 to 2010. VTE incidence in users of non-oral CHCs compared to non-users of CHCs was the outcome of interest. The author also compared VTE incidence in each of the non-oral products with that in users of LNG-containing COCs. The incidence of confirmed VTE among NuvaRing users was 7.75 per 10,000 WY and, after adjusting for duration of use, the rate ratio compared to LNG-containing COCs was 1.9 (95% CI 1.3, 2.7).

Team Leader Comments:

- **The Lidegaard results are not presented in labeling for several reasons. One is that, for other CHC products that have been evaluated in a number of epidemiologic studies, the decision has been made to focus labeling on studies that have been requested by or conducted by regulatory authorities. This is because these study protocols have had input from FDA (or the European Medicines Agency), and are therefore likely to have been designed in accord with our standards. These studies have also been submitted in full to FDA, allowing for complete review of the data, as opposed to "non-regulatory" studies, which FDA receives only as a journal publication.**
- **In addition, Dr. Ouellet-Hellstrom reviewed the Lidegaard publication (along with an early communication of partial results from TASC) in August 2012, and noted several concerns about the Lidegaard study, including lack of a "new user" design. This is of particular concern given that NuvaRing was not marketed until 2003, while the comparator COCs were marketed (and could have been used) since the 1990's. The known elevated risk among newer users could therefore bias toward a finding of higher risk among NuvaRing users. It is interesting to note that the FDA-funded study also trends toward a higher risk of VTE for NuvaRing users when "all users" are considered, but that this suggestion of increased risk is not observed when the "new user" analysis is selected.**
- **Dr. Ouellet-Hellstrom stated the following conclusions in her 2012 review:**

  In Denmark, use of CHC products differed by age and the distribution differed from that observed in the US. Therefore, when evaluating VTE risk by product type for populations from other countries, caution is needed before extrapolating the risks to a U.S. population.

  The two studies [Lidegaard and an abstract reporting TASC results] … suggest a possible slight increased risk of VTE associated with the vaginal ring when compared to no use or to oral LNG, but not when compared to other COCs [containing different progestins] … based on the preliminary negative results from the TASC study and the incompletely adjusted results from Lidegaard's study, OSE/DEPI does not recommend any labeling changes for the NuvaRing.

8.1 OSE Consultation and Recommendation

Rita Ouellet-Hellstrom, Ph.D., of the Division of Epidemiology II, OSE had previously provided extensive review of the FDA-funded study in preparation of the background briefing document for the 2011 CHC Advisory Committee meetings, and she concurred with the reported incidence rates and hazard ratios. For the current submission, she reviewed the TASC

[1] Lidegaard O et al. Venous thrombosis in users of non-oral hormonal contraception: follow-up study, Denmark 2001-10. BMJ 2012; 344: e2990

results and the biostatistical analysis provided by the Division of Biometrics 7, and made the following conclusions and recommendations in her review dated August 27, 2013:

> *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 recently revised labels.*

Dr. Ouellet-Hellstrom did make two specific recommendations on the VTE labeling:

- That the TASC incidence rates and hazard ratios should be provided only for the pre-specified comparisons for which the study was powered (i.e., NuvaRing compared to all COCs and to all COCs except those containing gestodene or desogestrel, and NOT compared to a *post hoc* comparator of all COCs except those containing gestodene, desogestrel or drospirenone)
- That the FDA-funded study incidence data should be aligned to that presented for TASC (i.e., rather than merely using LNG-containing COCs as the comparator, data should be provided comparing NuvaRing to "other COCs" [containing the progestins norgestimate, norethindrone or LNG] as well

These recommendations were conveyed to and accepted by the Applicant.

8.2 Postmarketing Safety Findings

Dr. Davis has been the primary medical officer reviewing the NuvaRing Periodic Safety Update Reports (PSURs) and Annual Reports since the time of approval. The most recent annual report was submitted December 3, 2012, covering the period October 2011 through September 2012. With the completion of TASC, there are no outstanding postmarketing studies, no new safety signals or trends identified and no outstanding regulatory business.

8.3 Safety Update

No specific safety update was submitted during this review cycle; however, the most recent annual report was reviewed, as discussed in the preceding section.

8.4 Overall Assessment of Safety Findings

This efficacy supplement primarily addresses epidemiologic data regarding the relative risk of VTE associated with use of NuvaRing compared to other CHCs. Data are also provided about the temporal trends in the increased risk of VTE associated with use of CHCs, in particular, the increase in risk associated with recurrent use after a break of four weeks or longer. The TASC data are consistent with the findings of FDA-funded study and results from these studies do not suggest an increased risk of VTE for NuvaRing compared to COCs that contain different progestins.

The fact that CHC users have an increased risk of VTE compared to non-users has been known and described in labeling for years, as has the fact that the increased risk is greatest in the first year of use. Of particular value in the TASC study is the evaluation of VTE risk by exposure status, classifying CHC users as new Starters, Switchers or Recurrent Users (following a break in use of at least four weeks). The finding that VTE risk is elevated in women who resume use following a break of four weeks or greater is important safety information that should be described in labeling.

9. Advisory Committee Meeting

The Division determined that an Advisory Committee was not needed to review this efficacy supplement.

10. Pediatrics

Review by the Pediatric Review Committee (PeRC) was not needed for this efficacy supplement, as no changes in indication, route of administration or population were proposed.

11. Other Relevant Regulatory Issues

No Office of Scientific Investigations inspection was requested for the TASC study; inspections are not typically requested for epidemiologic studies such as this, which was conducted in routine clinical practice settings.

12. Labeling

The NuvaRing label was submitted in PLR format; the currently approved label is not in PLR. The Applicant's conversion to PLR format was modeled substantially on the recently approved PLR label for the Ortho Evra transdermal system, another non-oral CHC. Consultative reviews were provided by the Office of Surveillance and Epidemiology (OSE), the Office of Prescription Drug Promotion (OPDP), the Division of Medical Policy Programs (DMPP) and the Study Endpoints and Label Development (SEALD) team and their comments were incorporated into the label as appropriate. DMPP provided extensive revisions, including development of an Instructions for Use section.

The major issues addressed in labeling negotiations with the Applicant included:

- Description in the Warnings section of the findings regarding temporal trends in VTE risk, and the newly defined increased VTE risk in women who resume COC use following a break; this language has been added to some, but not all, CHCs, based on whether or not epidemiologic studies supporting such a finding included that particular estrogen/progestin combination. Because this increase in VTE risk after a break in use was noted in TASC, it was agreed that this language could be included in the NuvaRing PI.
- Revision of the Adverse Reactions and Pharmacodynamics sections to comply with PLR requirements
- Specification of the Pearl Index, the efficacy measure used for CHCs. Although the nonPLR label provided a general range of pregnancy rates, apparently based on the results of three clinical trials (one US, two non-US), the Division initially requested that the label report only the Pearl Index from the US trial, consistent with general labeling practice for CHCs supported by both US and non-US trials. This distinction is important because the Pearl Index obtained in a non-US (e.g., European) study is generally markedly lower than that observed in US subjects. However, citing a precedent from the recent Ortho Evra PLR conversion, in which a pooled US/non-US study Pearl Index was labeled, the Applicant argued that such a pooled Pearl Index should be accepted for NuvaRing as well. The Division agreed to provide a pooled Pearl Index as long as the Pearl Index from the US study was also described in labeling.

- Revision of the patient labeling in accord with revisions made to the Physician Insert, and to a format consistent with that used for other hormonal contraceptives that have PLR labels

Agreement with the Applicant on labeling was reached on October 4, 2013.

13. Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

I recommend approval of both the efficacy and PLR labeling supplements, because acceptable labeling has been agreed upon with the Applicant.

13.2 Risk Benefit Assessment

The risk/benefit profile for NuvaRing was determined to be acceptable on the basis of the original NDA review, and the epidemiologic data in this supplement do not change that overall assessment. However, I do believe the new information, in particular that relating to the increase in VTE risk noted upon resumption of CHC use following a break of four weeks or longer, is important new information that should be clearly conveyed in labeling.

13.3 Recommendation for Postmarketing Risk Evaluation and Management Strategies

No postmarketing risk management activities beyond labeling are recommended.

13.4 Recommendation for Other Postmarketing Requirements and Commitments

No postmarketing commitments or requirements are recommended.

13.5 Recommended Comments to Applicant

None

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

/s/

LISA M SOULE
10/04/2013

AUDREY L GASSMAN
10/04/2013
I concur with the review and regulatory recommendations in Dr. Soule's review