CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 21187/S021

Trade Name: NuvaRing®

Generic Name: etonogestrel/ethinyl estradiol vaginal ring

Sponsor: Organon USA Inc.

Approval Date: 10/04/2013

Indication: NuvaRing is an estrogen/progestin combination hormonal contraceptive (CHC) indicated for use by women to prevent pregnancy.

CENTER FOR DRUG EVALUATION AND RESEARCH

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APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21187/S-021

SUPPLEMENT APPROVAL

Organon USA Inc.
Attention: Ripal Shah, PharmD
Associate Director, Worldwide Regulatory Affairs
2015 Galloping Hill Road, MS-3175
Kenilworth, NJ 07033

Dear Dr. Shah:

Please refer to your Supplemental New Drug Application (sNDA) dated August 30, 2012, and received December 5, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for NuvaRing (etonogestrel/ethinyl estradiol vaginal ring).

We acknowledge receipt of your amendments dated December 20, 2012, January 9, March 12, September 4 and 19, and October 1 2, and 4, 2013.

This "Prior Approval" supplemental new drug application provides for revisions to the labeling based on the results of two epidemiologic studies that evaluated the risk of venous thromboembolic events (VTEs) associated with use of NuvaRing compared to the risk associated with use of other combination hormonal contraceptives (CHCs).

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the

patient package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of

promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Charlene Williamson, Regulatory Project Manager, at (301) 796-1025.

Sincerely,

{See appended electronic signature page}

Audrey Gassman, M.D.
Deputy Director
Division of Bone, Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

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

/s/

AUDREY L GASSMAN
10/04/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use NuvaRing safely and effectively. See full prescribing information for NuvaRing.

NuvaRing® (etonogestrel/ethinyl estradiol vaginal ring)
Initial U.S. Approval: 2001

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS
See full prescribing information for complete boxed warning.

- **Women over 35 years old who smoke should not use NuvaRing. (4)**
- **Cigarette smoking increases the risk of serious cardiovascular events from combination hormonal contraceptive (CHC) use. (4)**

----------RECENT MAJOR CHANGES----------
Warnings and Precautions (5.1) 10/2013

----------INDICATIONS AND USAGE----------
NuvaRing is an estrogen/progestin combination hormonal contraceptive (CHC) indicated for use by women to prevent pregnancy. (1)

----------DOSAGE AND ADMINISTRATION----------
One NuvaRing is inserted in the vagina. The ring must remain in place continuously for three weeks, followed by a one-week ring-free interval. (2)

----------DOSAGE FORMS AND STRENGTHS----------
NuvaRing is a polymeric vaginal ring containing 11.7 mg etonogestrel and 2.7 mg ethinyl estradiol, which releases on average 0.12 mg/day of etonogestrel and 0.015 mg/day of ethinyl estradiol. (3)

----------CONTRAINDICATIONS----------
- A high risk of arterial or venous thrombotic diseases (4)
- Breast cancer or other estrogen- or progestin-sensitive cancer (4)
- Liver tumors or liver disease (4)
- Undiagnosed abnormal uterine bleeding (4)
- Pregnancy (4)
- Hypersensitivity to any of the components of NuvaRing (4)

----------WARNINGS AND PRECAUTIONS----------
- Vascular risks: Stop NuvaRing use if a thrombotic event occurs. Stop NuvaRing use at least 4 weeks before and through 2 weeks after major surgery. Start no earlier than 4 weeks after delivery, in women who are not breastfeeding. (5.1)
- Toxic Shock Syndrome (TSS): If patient exhibits signs or symptoms of TSS, consider the possibility of this diagnosis and initiate appropriate medical evaluation and treatment. (5.2)
- Liver disease: Discontinue NuvaRing use if jaundice develops.(5.3)
- High blood pressure: If used in women with well-controlled hypertension, monitor blood pressure and stop NuvaRing use if blood pressure rises significantly. (5.4)
- Carbohydrate and lipid metabolic effects: Monitor prediabetic and diabetic women. Consider an alternate contraceptive method for women with uncontrolled dyslipidemia. (5.7)
- Headache: Evaluate significant change in headaches and discontinue NuvaRing use if indicated. (5.8)
- Uterine bleeding: Evaluate irregular bleeding or amenorrhea. (5.9)

---------- ADVERSE REACTIONS ----------
The most common adverse reactions (≥2%) in clinical trials were: vaginitis, headache (including migraine), mood changes (e.g., depression, mood swings, mood altered, depressed mood, affect lability), device-related events (e.g., expulsion/discomfort/foreign body sensation), nausea/vomiting, vaginal discharge, increased weight, vaginal discomfort, breast pain/discomfort/tenderness, dysmenorrhea, abdominal pain, acne, and decreased libido. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Merck, Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
Drugs or herbal products that induce certain enzymes, such as CYP3A4, may decrease the effectiveness of CHCs or increase breakthrough bleeding. Counsel patients to use a back-up or alternative method of contraception when enzyme inducers are used with CHCs. (7)

---------- USE IN SPECIFIC POPULATIONS ----------
- Nursing mothers: Not recommended; can decrease milk production. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

Cigarette smoking increases the risk of serious cardiovascular events from combination hormonal contraceptive (CHC) use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, CHCs, including NuvaRing, should not be used by women who are over 35 years of age and smoke. *[See Contraindications (4).]*

1 INDICATIONS AND USAGE

FOR VAGINAL USE ONLY

NuvaRing® is indicated for use by females of reproductive age to prevent pregnancy.

2 DOSAGE AND ADMINISTRATION

2.1 How to Use NuvaRing

To achieve maximum contraceptive effectiveness, NuvaRing must be used as directed *[see Dosing and Administration (2.2)]*. One NuvaRing is inserted in the vagina. **The ring is to remain in place continuously for three weeks.** It is removed for a one-week break, during which a withdrawal bleed usually occurs. A new ring is inserted one week after the last ring was removed.

The user can choose the insertion position that is most comfortable to her, for example, standing with one leg up, squatting, or lying down. The ring is to be compressed and inserted into the vagina. The exact position of NuvaRing inside the vagina is not critical for its function. The vaginal ring must be inserted on the appropriate day and left in place for three consecutive weeks. This means that the ring should be removed three weeks later on the same day of the week as it was inserted and at about the same time.

NuvaRing can be removed by hooking the index finger under the forward rim or by grasping the rim between the index and middle finger and pulling it out. The used ring should be placed in the sachet (foil pouch) and discarded in a waste receptacle out of the reach of children and pets (do not flush in toilet).

After a one-week break, during which a withdrawal bleed usually occurs, a new ring is inserted on the same day of the week as it was inserted in the previous cycle. The withdrawal bleed usually starts on Day 2-3 after removal of the ring and may not have finished before the next ring is inserted. In order to maintain contraceptive effectiveness, the new ring must be inserted exactly one week after the previous one was removed even if menstrual bleeding has not finished.

2.2 How to Start Using NuvaRing

IMPORTANT: Consider the possibility of ovulation and conception prior to the first use of NuvaRing.

No Hormonal Contraceptive Use in the Preceding Cycle:

The woman should insert NuvaRing on the first day of her menstrual bleeding. NuvaRing may also be started on Days 2-5 of the woman's cycle, but in this case a barrier method, such as male condoms with spermicide, should be used for the first seven days of NuvaRing use in the first cycle.

Changing From a CHC:

The woman may switch from her previous CHC on any day, but at the latest on the day following the usual hormone-free interval, if she has been using her hormonal method consistently and correctly, or if it is reasonably certain that she is not pregnant.

Changing From a Progestin-Only Method (progestin-only pill [POP], Implant, or Injection or a Progestin-Releasing Intrauterine System [IUS]):

The woman may switch from the POP on any day; instruct her to start using NuvaRing on the day after she took her last POP. She should switch from an implant or the IUS on the day of its removal, and from an injectable on the day when the next injection would be due. In all of these cases, the woman should use an additional barrier method such as a male condom with spermicide, for the first seven days.

Use after Abortion or Miscarriage

The woman may start using NuvaRing within the first five days following a complete first trimester abortion or miscarriage, and she does not need to use an additional method of contraception. If use of NuvaRing is not started within five days following a first trimester abortion or miscarriage, the woman should follow the instructions for "No Hormonal Contraceptive Use in the Preceding Cycle." In the meantime, she should be advised to use a non-hormonal contraceptive method.

Start NuvaRing no earlier than four weeks after a second trimester abortion or miscarriage, due to the increased risk of thromboembolism. *[See Contraindications (4), and Warnings and Precautions (5.1).]*

Following Childbirth

The use of NuvaRing may be initiated no sooner than four weeks postpartum in women who elect not to breastfeed, due to the increased risk of thromboembolism in the postpartum period. *[See Contraindications (4), and Warnings and Precautions (5.1).]*

Advise women who are breastfeeding not to use NuvaRing but to use other forms of contraception until the child is weaned.

If a woman begins using NuvaRing postpartum, instruct her to use an additional method of contraception, such as male condoms with spermicide, for the first seven days. If she has not yet had a period, consider the possibility of ovulation and conception occurring prior to initiation of NuvaRing.

2.3 Deviations from the Recommended Regimen

To prevent loss of contraceptive efficacy, advise women not to deviate from the recommended regimen. NuvaRing should be left in the vagina for a continuous period of three weeks.

Inadvertent Removal or Expulsion

NuvaRing can be accidentally expelled, for example, while removing a tampon, during intercourse, or with straining during a bowel movement. NuvaRing should be left in the vagina for a continuous period of three weeks. If the ring is accidentally expelled and is left outside of the vagina for **less than three hours**, contraceptive efficacy is not reduced. NuvaRing can be rinsed with cool to lukewarm (not hot) water and **reinserted as soon as possible,** but at the latest within three hours. If NuvaRing is lost, a new vaginal ring should be inserted and the regimen should be continued without alteration.

If NuvaRing is out of the vagina for more than three continuous hours:

During Weeks 1 and 2: Contraceptive efficacy may be reduced. The woman should reinsert the ring as soon as she remembers. A barrier method such as condoms with spermicides must be used until the ring has been used continuously for seven days.

During Week 3: The woman should discard that ring. One of the following two options should be chosen:

1. Insert a new ring immediately. Inserting a new ring will start the next three-week use period. The woman may not experience a withdrawal bleed from her previous cycle. However, breakthrough spotting or bleeding may occur.

2. Insert a new ring no later than seven days from the time the previous ring was removed or expelled, during which time she may have a withdrawal bleed. This option should only be chosen if the ring was used continuously for at least seven days prior to inadvertent removal/expulsion.

In either case, a barrier method such as condoms with spermicides must be used until the new ring has been used continuously for seven days.

Prolonged Ring-Free Interval

If the ring-free interval has been extended beyond one week, consider the possibility of pregnancy, and an additional method of contraception, such as male condoms with spermicide, **MUST** be used until NuvaRing has been used **continuously for seven days.**

Prolonged Use of NuvaRing

If NuvaRing has been left in place for up to one extra week (i.e., up to four weeks total), the woman will remain protected. NuvaRing should be removed and the woman should insert a new ring after a one-week ring-free interval.

If NuvaRing has been left in place for longer than four weeks, instruct the woman to remove the ring, and rule out pregnancy. If pregnancy is ruled out, NuvaRing may be restarted, and an additional method of contraception, such as male condoms with spermicide, **MUST** be used until a new NuvaRing has been used **continuously for seven days.**

Ring Breakage

There have been reported cases of NuvaRing disconnecting at the weld joint. This is not expected to affect the contraceptive effectiveness of NuvaRing. In the event of a disconnected ring, vaginal discomfort or expulsion (slipping out) is more likely to occur. If a woman discovers that her NuvaRing has disconnected, she should discard the ring and replace it with a new ring.

2.4 In the Event of a Missed Menstrual Period

1. If the woman has not adhered to the prescribed regimen (NuvaRing has been out of the vagina for more than three hours or the preceding ring-free interval was extended beyond one week), consider the possibility of pregnancy at the time of the first missed period and discontinue NuvaRing use if pregnancy is confirmed.

2. If the woman has adhered to the prescribed regimen and misses two consecutive periods, rule out pregnancy.

3. If the woman has retained one NuvaRing for longer than four weeks, rule out pregnancy.

2.5 Use with Other Vaginal Products

NuvaRing may interfere with the correct placement and position of a diaphragm. A diaphragm is therefore not recommended as a back-up method with NuvaRing use.

Pharmacokinetic data show that the use of tampons has no effect on the systemic absorption of the hormones released by NuvaRing.

3 DOSAGE FORMS AND STRENGTHS

NuvaRing (etonogestrel/ethinyl estradiol vaginal ring) is a non-biodegradable, flexible, transparent, colorless to almost colorless, combination contraceptive vaginal ring, with an outer diameter of 54 mm and a cross-sectional diameter of 4 mm. It is made of ethylene vinylacetate copolymers and magnesium stearate, and contains 11.7 mg etonogestrel and 2.7 mg ethinyl estradiol. When placed in the vagina, each ring releases on average 0.120 mg/day of etonogestrel and 0.015 mg/day of ethinyl estradiol over a three-week period of use. NuvaRing is not made with natural rubber latex.

4 CONTRAINDICATIONS

Do not prescribe NuvaRing to women who are known to have the following:

- A high risk of arterial or venous thrombotic diseases. Examples include women who are known to:
  - Smoke, if over age 35 *[see Boxed Warning and Warnings and Precautions (5.1)]*
  - Have deep vein thrombosis or pulmonary embolism, now or in the past *[see Warnings and Precautions (5.1)]*
  - Have cerebrovascular disease *[see Warnings and Precautions (5.1)]*
  - Have coronary artery disease *[see Warnings and Precautions (5.1)]*
  - Have thrombogenic valvular or thrombogenic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease, or atrial fibrillation) *[see Warnings and Precautions (5.1)]*
  - Have inherited or acquired hypercoagulopathies *[see Warnings and Precautions (5.1)]*
  - Have uncontrolled hypertension *[see Warnings and Precautions (5.4)]*
  - Have diabetes mellitus with vascular disease *[see Warnings and Precautions (5.7)]*
  - Have headaches with focal neurological symptoms or migraine headaches with aura *[see Warnings and Precautions (5.8)]*
    - Women over age 35 with any migraine headaches *[see Warnings and Precautions (5.8)]*
- Liver tumors, benign or malignant or liver disease *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.7)]*
- Undiagnosed abnormal uterine bleeding *[see Warnings and Precautions (5.9)]*
- Pregnancy, because there is no reason to use CHCs during pregnancy *[see Warnings and Precautions (5.8) and Use in Specific Populations (8.1)]*
- Breast cancer or other estrogen- or progestin-sensitive cancer, now or in the past *[see Warnings and Precautions (5.13)]*
- Hypersensitivity to any of the components of NuvaRing *[see Adverse Reactions (6)]*

5 WARNINGS AND PRECAUTIONS

5.1 Thromboembolic Disorders and Other Vascular Problems

Stop NuvaRing use if an arterial thrombotic or venous thromboembolic event (VTE) occurs. Stop NuvaRing use if there is unexplained loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions. Evaluate for retinal vein thrombosis immediately. *[See Adverse Reactions (6).]*

If feasible, stop NuvaRing at least four weeks before and through two weeks after major surgery or other surgeries known to have an elevated risk of thromboembolism, and during and following prolonged immobilization.

Start NuvaRing no earlier than 4 weeks after delivery, in women who are not breastfeeding. The risk of postpartum thromboembolism decreases after the third postpartum week, whereas the risk of ovulation increases after the third postpartum week.

The use of CHCs increases the risk of VTE. Known risk factors for VTE include smoking, obesity, and family history of VTE, in addition to other factors that contraindicate use of CHCs *[see Contraindications (4)].*

Two epidemiologic studies[1, 2, 3] that assessed the risk of VTE associated with the use of NuvaRing are described below.

In these studies, which were required or sponsored by regulatory agencies, NuvaRing users had a risk of VTE similar to COC users (see Table 1 for adjusted hazard ratios). A large prospective, observational study, the Transatlantic Active Surveillance on Cardiovascular Safety of NuvaRing (TASC), investigated the risk of VTE for new users, and women who were switching to or restarting NuvaRing or COCs in a population that is representative of routine clinical users. The women were followed for 24 to 48 months. The results showed a similar risk of VTE among NuvaRing users (VTE incidence 8.3 per 10,000 WY) and women using COCs (VTE incidence 9.2 per 10,000 WY). For women using COCs that did not contain the progestins desogestrel (DSG) or gestodene (GSD), VTE incidence was 8.9 per 10,000 WY.

A retrospective cohort study using data from 4 health plans in the US (FDA-funded Study in Kaiser Permanente and Medicaid databases) showed the VTE incidence for new users of NuvaRing to be 11.4 events per 10,000 WY, for new users of a levonorgestrel (LNG)-containing COC 9.2 events per 10,000 WY, and for users of other COCs available during the course of the study[*] 8.2 events per 10,000 WY.

[*] Includes low-dose COCs containing the following progestins: norgestimate, norethindrone, or levonorgestrel.

Table 1: Estimates (Hazard Ratios) of Venous Thromboembolism Risk in Users of NuvaRing Compared to Users of Combined Oral Contraceptives (COCs)

Epidemiologic Study (Author, Year of Publication) Population Studied	Comparator Product(s)	Hazard Ratios (HR) (95% CI)
TASC (Dinger, 2012) Initiators, including new users, switchers and restarters	All COCs available during the course of the study *	HR[†]: 0.8 (0.5-1.5)
	COCs available excluding DSG- or GSD -containing OCs	HR[†]: 0.8 (0.4-1.7)
FDA-funded Study in Kaiser Permanente and Medicaid databases (Sidney, 2011) First use of a combined hormonal contraceptive (CHC) during the study period	COCs available during the course of the study[‡]	HR[§]: 1.1 (0.6-2.2)
	LNG/0.03 mg ethinyl estradiol	HR[§]: 1.0 (0.5-2.0)

* Includes low-dose COCs containing the following progestins: chlormadinone acetate, cyproterone acetate, desogestrel, dienogest, drospirenone, ethynodiol diacetate, gestodene, levonorgestrel, norethindrone, norgestimate, or norgestrel

[†] Adjusted for age, BMI, duration of use, VTE history

[‡] Includes low-dose COCs containing the following progestins: norgestimate, norethindrone, or levonorgestrel

[§] Adjusted for age, site, year of entry into study

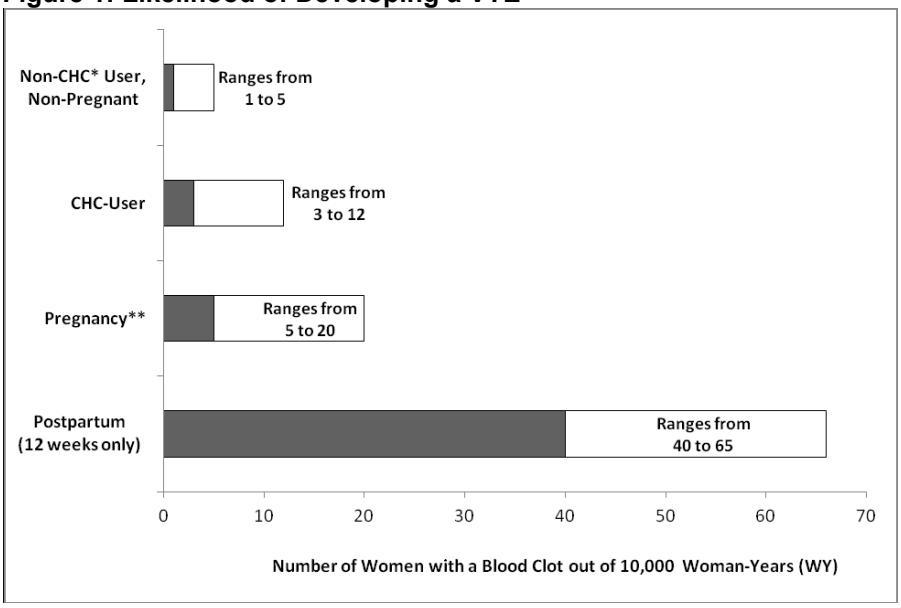
An increased risk of thromboembolic and thrombotic disease associated with the use of CHCs is well-established. Although the absolute VTE rates are increased for users of CHCs compared to non-users, the rates associated with pregnancy are even greater, especially during the post-partum period (see Figure 1).

The frequency of VTE in women using CHCs has been estimated to be 3 to 12 cases per 10,000 women-years.

The risk of VTE is highest during the first year of CHC use and after restarting a CHC following a break of at least four weeks. The risk of VTE due to CHCs gradually disappears after use is discontinued.

Figure 1 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 postpartum 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 1: Likelihood of Developing a VTE



*CHC=combina ion 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.

Several epidemiology studies indicate that third generation oral contraceptives, including those containing desogestrel (etonogestrel, the progestin in NuvaRing, is the biologically active metabolite of desogestrel), may be associated with a higher risk of VTE than oral contraceptives containing other progestins. Some of these studies indicate an approximate two-fold increased risk. However, data from other studies have not shown this two-fold increase in risk.

Use of CHCs also increases the risk of arterial thromboses such as strokes and myocardial infarctions, especially in women with other risk factors for these events. CHCs have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes). In general, the risk is greatest among older (>35 years of age), hypertensive women who also smoke.

Use NuvaRing with caution in women with cardiovascular disease risk factors.

5.2 Toxic Shock Syndrome (TSS)

Cases of TSS have been reported by NuvaRing users. TSS has been associated with tampons and certain barrier contraceptives, and, in some cases the NuvaRing users were also using tampons. A causal relationship between the use of NuvaRing and TSS has not been established. If a patient exhibits signs or symptoms of TSS, consider the possibility of this diagnosis and initiate appropriate medical evaluation and treatment.

5.3 Liver Disease

Impaired Liver Function

Do not use NuvaRing in women with liver disease such as acute viral hepatitis or severe (decompensated) cirrhosis of the liver *[see Contraindications (4)]*. Acute or chronic disturbances of liver function may necessitate the discontinuation of CHC use until markers of liver function return to normal and CHC causation has been excluded *[see Use in Specific Populations (8.7)]*. Discontinue NuvaRing use if jaundice develops.

Liver Tumors

NuvaRing is contraindicated in women with benign and malignant liver tumors *[see Contraindications (4)].* Hepatic adenomas are associated with CHC use. An estimate of the attributable risk is 3.3 cases per 100,000 CHC users. Rupture of hepatic adenomas may cause death through intra-abdominal hemorrhage.

Studies have shown an increased risk of developing hepatocellular carcinoma in long term (>8 years) CHC users. However, the attributable risk of liver cancers in CHC users is less than one case per million users.

5.4 High Blood Pressure

NuvaRing is contraindicated in women with uncontrolled hypertension or hypertension with vascular disease *[see Contraindications (4)].* For women with well-controlled hypertension, monitor blood pressure and stop NuvaRing use if blood pressure rises significantly.

An increase in blood pressure has been reported in women using CHCs and this increase is more likely in older women and with extended duration of use. The incidence of hypertension increases with increasing concentrations of progestin.

5.5 Vaginal Use

NuvaRing may not be suitable for women with conditions that make the vagina more susceptible to vaginal irritation or ulceration. Vaginal/cervical erosion or ulceration in women using NuvaRing has been reported. In some cases, the ring adhered to vaginal tissue, necessitating removal by a healthcare provider.

Some women are aware of the ring on occasion during the 21 days of use or during intercourse, and sexual partners may feel NuvaRing in the vagina.

5.6 Gallbladder Disease

Studies suggest a small increased relative risk of developing gallbladder disease among CHC users. Use of CHCs may also worsen existing gallbladder disease.

A past history of CHC-related cholestasis predicts an increased risk with subsequent CHC use. Women with a history of pregnancy-related cholestasis may be at an increased risk for CHC-related cholestasis.

5.7 Carbohydrate and Lipid Metabolic Effects

Carefully monitor prediabetic and diabetic women who are using NuvaRing. CHCs may decrease glucose tolerance.

Consider alternative contraception for women with uncontrolled dyslipidemia. Some women will have adverse lipid changes while on CHCs.

Women with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis when using CHCs.

5.8 Headache

If a woman using NuvaRing develops new headaches that are recurrent, persistent, or severe, evaluate the cause and discontinue NuvaRing if indicated.

Consider discontinuation of NuvaRing in the case of an increased frequency or severity of migraine during CHC use (which may be prodromal of a cerebrovascular event) *[see Contraindications (4)]*.

5.9 Bleeding Irregularities and Amenorrhea

Unscheduled Bleeding and Spotting

Unscheduled bleeding (breakthrough or intracyclic) bleeding and spotting sometimes occur in women using CHCs, especially during the first three months of use. If bleeding persists or occurs after previously regular cycles, check for causes such as pregnancy or malignancy. If pathology and pregnancy are excluded, bleeding irregularities may resolve over time or with a change to a different CHC.

Bleeding patterns were evaluated in three large clinical studies. In the North American study (US and Canada, N=1,177), the percentages of subjects with breakthrough bleeding/spotting ranged from 7.2% to 11.7% during cycles 1-13. In the two non-US studies, the percentages of subjects with breakthrough bleeding/spotting ranged from 2.6% to 6.4% (Europe, N=1,145) and from 2.0% to 8.7% (Europe, Brazil, Chile, N=512).

Amenorrhea and Oligomenorrhea

If scheduled (withdrawal) bleeding does not occur, consider the possibility of pregnancy. If the patient has not adhered to the prescribed dosing schedule, consider the possibility of pregnancy at the time of the first missed period and take appropriate diagnostic measures.

Occasional missed periods may occur with the appropriate use of NuvaRing. In the clinical studies, the percent of women who did not have withdrawal bleeding in a given cycle ranged from 0.3% to 3.8%.

If the patient has adhered to the prescribed regimen and misses two consecutive periods, rule out pregnancy.

Some women may experience amenorrhea or oligomenorrhea after discontinuing CHC use, especially when such a condition was pre-existent.

5.10 Inadvertent Urinary Bladder Insertion

There have been reports of inadvertent insertions of NuvaRing into the urinary bladder, which required cystoscopic removal. Assess for ring insertion into the urinary bladder in NuvaRing users who present with persistent urinary symptoms and are unable to locate the ring.

5.11 CHC Use Before or During Early Pregnancy

Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. Studies also do not suggest a teratogenic effect, particularly in so far as cardiac anomalies and limb reduction defects are concerned, when taken inadvertently during early pregnancy. Discontinue NuvaRing if pregnancy is confirmed.

5.12 Depression

Carefully observe women with a history of depression and discontinue NuvaRing use if depression recurs to a serious degree.

5.13 Carcinoma of the Breasts and Cervix

NuvaRing is contraindicated in women who currently have or have had breast cancer because breast cancer is a hormonally-sensitive tumor *[see Contraindications (4)]*.

There is substantial evidence that CHCs do not increase the incidence of breast cancer. Although some past studies have suggested that CHCs might increase the incidence of breast cancer, more recent studies have not confirmed such findings.

Some studies suggest that CHCs are associated with an increase in the risk of cervical cancer or intraepithelial neoplasia. However, there is controversy about the extent to which these findings may be due to differences in sexual behavior and other factors.

5.14 Effect on Binding Globulins

The estrogen component of CHCs may raise the serum concentrations of thyroxine-binding globulin, sex hormone-binding globulin, and cortisol-binding globulin. The dose of replacement thyroid hormones or cortisol therapy may need to be increased.

5.15 Monitoring

A woman who is using NuvaRing should have a yearly visit with her healthcare provider for a blood pressure check and for other indicated healthcare.

5.16 Hereditary Angioedema

In women with hereditary angioedema, exogenous estrogens may induce or exacerbate symptoms of angioedema.

5.17 Chloasma

Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation while using NuvaRing.

6 ADVERSE REACTIONS

The following serious adverse reactions with the use of CHCs are discussed elsewhere in the labeling.

- Serious cardiovascular events and stroke *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Vascular events *[see Warnings and Precautions (5.1)]*
- Liver disease *[see Warnings and Precautions (*5.3*)]*

Adverse reactions commonly reported by CHC users are:

- Irregular uterine bleeding
- Nausea
- Breast tenderness
- Headache

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Trials with a duration of 6 to 13 28-day cycles provided safety data. In total, 2,501 women, aged 18 to 41 contributed 24,520 cycles of exposure.

Common Adverse Reactions (≥ 2%): vaginitis (13.8%), headache (including migraine) (11.2%), mood changes (e.g., depression, mood swings, mood altered, depressed mood, affect lability) (6.4%), device-related events (e.g., expulsion/discomfort/foreign body sensation) (6.3%), nausea/vomiting (5.9%), vaginal discharge (5.7%), increased weight (4.9%), vaginal discomfort (4.0%), breast pain/discomfort/tenderness (3.8%), dysmenorrhea (3.5%), abdominal pain (3.2%), acne (2.4%), and decreased libido (2.0%).

Adverse Reactions (≥ 1%) Leading to Study Discontinuation: 13.0% of the women discontinued from the clinical trials due to an adverse reaction; the most common adverse reactions leading to discontinuation were device-related events (2.7%), mood changes (1.7%), headache (including migraine) (1.5%) and vaginal symptoms (1.2%).

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

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of NuvaRing. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune system disorders: hypersensitivity

Nervous system disorders: stroke/cerebrovascular accident

Vascular disorders: arterial events (including arterial thromboembolism and myocardial infarction), aggravation of varicose veins

Skin and subcutaneous tissue disorders: urticaria, chloasma

Reproductive system and breast disorders: penile disorders, including local reactions on penis (in male partners of women using NuvaRing)

7 DRUG INTERACTIONS

Consult the labeling of all concurrently-used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.

7.1 Effects of Other Drugs on CHCs

Substances decreasing the plasma concentrations of CHCs and potentially diminishing the effectiveness of CHCs

Drugs or herbal products that induce certain enzymes, including cytochrome P450 3A4 (CYP3A4), may decrease the plasma concentrations of CHCs and potentially diminish the effectiveness of CHCs or increase breakthrough bleeding. Some drugs or herbal products that may decrease the effectiveness of hormonal contraceptives include: phenytoin, barbiturates, carbamazepine, bosentan, felbamate, griseofulvin, oxcarbazepine, rifampicin, topiramate, rifabutin, rufinamide, aprepitant, and products containing St. John's wort. Interactions between CHCs and other drugs may lead to breakthrough bleeding and/or contraceptive failure. Counsel women to use an alternative method of contraception or a back-up method when enzyme inducers are used with NuvaRing, and to continue back-up contraception for 28 days after discontinuing the enzyme inducer to ensure contraceptive reliability.

The serum concentrations of etonogestrel and ethinyl estradiol were not affected by concomitant administration of oral amoxicillin or doxycycline in standard dosages during 10 days of antibiotic treatment. The effects of other antibiotics on etonogestrel or ethinyl estradiol concentrations have not been evaluated.

Substances increasing the plasma concentrations of CHCs

Co-administration of atorvastatin and certain CHCs containing ethinyl estradiol increase AUC values for ethinyl estradiol by approximately 20-25%. Ascorbic acid and acetaminophen may increase plasma ethinyl estradiol concentrations, possibly by inhibition of conjugation. CYP3A4 inhibitors such as itraconazole, voriconazole, fluconazole, grapefruit juice, or ketoconazole may increase plasma hormone concentrations. Co-administration of vaginal miconazole nitrate and NuvaRing increases the serum concentrations of etonogestrel and ethinyl estradiol by up to 40% *[see Clinical Pharmacology (12.3)]*.

Human immunodeficiency virus (HIV)/ Hepatitis C Virus (HCV) protease inhibitors and non-nucleoside reverse transcriptase inhibitors:

Significant changes in the plasma concentrations of the estrogen and /or progestin have been noted in some cases of co-administration with HIV protease inhibitors (decrease [e.g., nelfinavir, ritonavir,

darunavir/ritonavir, (fos)amprenavir/ritonavir, lopinavir/ritonavir, and tipranavir/ritonavir] or increase [e.g., indinavir and atazanavir/ritonavir]) /HCV protease inhibitors (decrease [e.g., boceprevir and telaprevir]) or with non-nucleoside reverse transcriptase inhibitors (decrease [e.g., nevirapine] or increase [e.g., etravirine]).

7.2 Effects of CHCs on Other Drugs

CHCs containing ethinyl estradiol may inhibit the metabolism of other compounds (e.g., cyclosporine, prednisolone, theophylline, tizanidine, and voriconazole) and increase their plasma concentrations. CHCs have been shown to decrease plasma concentrations of acetaminophen, clofibric acid, morphine, salicylic acid and temazepam. A significant decrease in the plasma concentrations of lamotrigine has been shown, likely due to induction of lamotrigine glucuronidation. This may reduce seizure control, therefore, dosage adjustments of lamotrigine may be necessary.

Women on thyroid hormone replacement therapy may need increased doses of thyroid hormone because serum concentrations of thyroid-binding globulin increase with use of CHCs.

7.3 Interference with Laboratory Tests

The use of contraceptive steroids may influence the results of certain laboratory tests, such as coagulation factors, lipids, glucose tolerance, and binding proteins.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

There is little or no increased risk of birth defects in women who inadvertently use CHCs during early pregnancy. Epidemiologic studies and meta-analyses have not found an increased risk of genital or non-genital birth defects (including cardiac anomalies and limb-reduction defects) following exposure to low dose CHCs prior to conception or during early pregnancy.

The administration of CHCs to induce withdrawal bleeding should not be used as a test for pregnancy. CHCs should not be used during pregnancy to treat threatened or habitual abortion.

8.3 Nursing Mothers

The effects of NuvaRing in nursing mothers have not been evaluated and are unknown. When possible, advise the nursing mother to use other forms of contraception until she has completely weaned her child. CHCs can reduce milk production in breastfeeding mothers. This is less likely to occur once breastfeeding is well-established; however, it can occur at any time in some women. Small amounts of contraceptive steroids and/or metabolites are present in breast milk.

8.4 Pediatric Use

Safety and efficacy of NuvaRing have been established in women of reproductive age. Efficacy is expected to be the same for postpubertal adolescents under the age of 18 and for users 18 years and older. Use of this product before menarche is not indicated.

8.5 Geriatric Use

NuvaRing has not been studied in postmenopausal women and is not indicated in this population.

8.6 Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of NuvaRing has not been studied. Steroid hormones may be poorly metabolized in patients with impaired liver function. Acute or chronic disturbances of liver function may necessitate the discontinuation of CHC use until markers of liver function return to normal. *[See Contraindications (4) and Warnings and Precautions (5.3).]*

8.7 Renal Impairment

The effect of renal impairment on the pharmacokinetics of NuvaRing has not been studied.

10 OVERDOSAGE

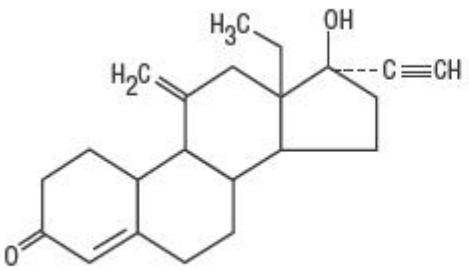
There have been no reports of serious ill effects from overdose of CHCs. Overdosage may cause withdrawal bleeding in females and nausea. If the ring breaks, it does not release a higher dose of hormones. In case of suspected overdose, all NuvaRing rings should be removed and symptomatic treatment given.

11 DESCRIPTION

NuvaRing (etonogestrel/ethinyl estradiol vaginal ring) is a non-biodegradable, flexible, transparent, colorless to almost colorless, combination contraceptive vaginal ring containing two active components, a progestin, etonogestrel (13-ethyl-17-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one) and an estrogen, ethinyl estradiol (19-nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol). When placed in the vagina, each ring releases on average 0.120 mg/day of etonogestrel and 0.015 mg/day of ethinyl estradiol over a three-week period of use. NuvaRing is made of ethylene vinylacetate copolymers (28% and 9% vinylacetate) and magnesium stearate and contains 11.7 mg etonogestrel and 2.7 mg ethinyl estradiol. NuvaRing is not made with natural rubber latex. NuvaRing has an outer diameter of 54 mm and a cross-sectional diameter of 4 mm. The molecular weights for etonogestrel and ethinyl estradiol are 324.46 and 296.40, respectively.

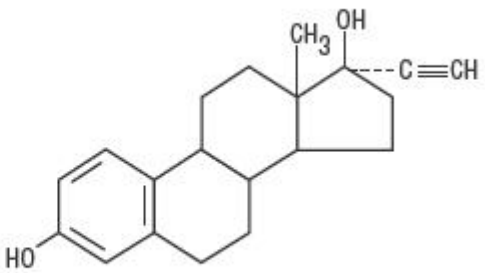
The structural formulas are as follows:

ETONOGESTREL



$C_{22}H_{28}O_2$

ETHINYL ESTRADIOL



$C_{20}H_{24}O_2$

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Combination hormonal contraceptives act by suppression of gonadotropins. Although the primary effect of this action is inhibition of ovulation, other alterations include changes in the cervical mucus (which increase the difficulty of sperm entry into the uterus) and the endometrium (which reduce the likelihood of implantation).

12.3 Pharmacokinetics

Absorption

Etonogestrel: Etonogestrel released by NuvaRing is rapidly absorbed. The bioavailability of etonogestrel after vaginal administration is approximately 100%. The serum etonogestrel and ethinyl estradiol concentrations observed during three weeks of NuvaRing use are summarized in Table 2.

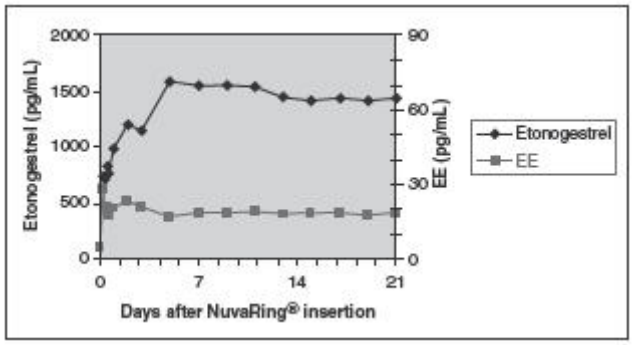
Ethinyl estradiol: Ethinyl estradiol released by NuvaRing is rapidly absorbed. The bioavailability of ethinyl estradiol after vaginal administration is approximately 56%, which is comparable to that with oral administration of ethinyl estradiol. The serum ethinyl estradiol concentrations observed during three weeks of NuvaRing use are summarized in Table 2.

Table 2: Mean (SD) Serum Etonogestrel and Ethinyl Estradiol Concentrations (n=16)

	1 week	2 weeks	3 weeks
etonogestrel (pg/mL)	1578 (408)	1476 (362)	1374 (328)
ethinyl estradiol (pg/mL)	19.1 (4.5)	18.3 (4.3)	17.6 (4.3)

The pharmacokinetic profile of etonogestrel and ethinyl estradiol during use of NuvaRing is shown in Figure 2.

Figure 2: Mean Serum Concentration-Time Profile of Etonogestrel and Ethinyl Estradiol during Three Weeks of NuvaRing Use



The pharmacokinetic parameters of etonogestrel and ethinyl estradiol were determined during one cycle of NuvaRing use in 16 healthy female subjects and are summarized in Table 3.

Table 3: Mean (SD) Pharmacokinetic Parameters of NuvaRing (n=16)

Hormone	C_{max} pg/mL	T_{max} hr	$t_{1/2}$	CL L/hr
etonogestrel	1716 (445)	200.3 (69.6)	29.3 (6.1)	3.4 (0.8)
ethinyl estradiol	34.7 (17.5)	59.3 (67.5)	44.7 (28.8)	34.8 (11.6)

C_{max}- maximum serum drug concentration
T_{max}- time at which maximum serum drug concentration occurs
$t_{1/2}$ - elimination half-life, calculated by $0.693/K_{elim}$
CL - apparent clearance

Prolonged use of NuvaRing: The mean serum etonogestrel concentration at the end of the fourth week of continuous use of NuvaRing was 1272 ± 311 pg/mL compared to a mean concentration range of 1578 ± 408 to 1374 ± 328 pg/mL at the end of weeks one to three. The mean serum ethinyl estradiol concentration at the end of the fourth week of continuous use of NuvaRing was 16.8 ± 4.6 pg/mL compared to a mean concentration range of 19.1 ± 4.5 to 17.6 ± 4.3 pg/mL at the end of weeks one to three.

Distribution

Etonogestrel: Etonogestrel is approximately 32% bound to sex hormone-binding globulin (SHBG) and approximately 66% bound to albumin in blood.

Ethinyl estradiol: Ethinyl estradiol is highly but not specifically bound to serum albumin (98.5%) and induces an increase in the serum concentrations of SHBG.

Metabolism

In vitro data shows that both etonogestrel and ethinyl estradiol are metabolized in liver microsomes by the cytochrome P450 3A4 isoenzyme. Ethinyl estradiol is primarily metabolized by aromatic hydroxylation, but a wide variety of hydroxylated and methylated metabolites are formed. These are present as free metabolites and as sulfate and glucuronide conjugates. The hydroxylated ethinyl estradiol metabolites have weak estrogenic activity. The biological activity of etonogestrel metabolites is unknown.

Excretion

Etonogestrel and ethinyl estradiol are primarily eliminated in urine, bile and feces.

Drug Interactions

[See also Drug Interactions (7).]

The drug interactions of NuvaRing were evaluated in several studies.

A single-dose vaginal administration of an oil-based 1200-mg miconazole nitrate capsule increased the serum concentrations of etonogestrel and ethinyl estradiol by approximately 17% and 16%, respectively. Following multiple doses of 200 mg miconazole nitrate by vaginal suppository or vaginal cream, the mean serum concentrations of etonogestrel and ethinyl estradiol increased by up to 40%.

A single-dose vaginal administration of 100-mg water-based nonoxynol-9 spermicide gel did not affect the serum concentrations of etonogestrel or ethinyl estradiol.

The serum concentrations of etonogestrel and ethinyl estradiol were not affected by concomitant administration of oral amoxicillin or doxycycline in standard dosages during 10 days of antibiotic treatment.

Tampon Use

The use of tampons had no effect on serum concentrations of etonogestrel and ethinyl estradiol during use of NuvaRing *[see Dosage and Administration (2.5)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 24-month carcinogenicity study in rats with subdermal implants releasing 10 and 20 mcg etonogestrel per day, (approximately 0.3 and 0.6 times the systemic steady-state exposure of women using NuvaRing), no drug-related carcinogenic potential was observed. Etonogestrel was not genotoxic in the in vitro Ames/Salmonella reverse mutation assay, the chromosomal aberration assay in Chinese hamster ovary cells or in the in vivo mouse micronucleus test. Fertility returned in rats after withdrawal from treatment.

14 CLINICAL STUDIES

In three large one-year clinical trials enrolling 2,834 women aged 18-40 years, in North America, Europe, Brazil, and Chile, the racial distribution was 93% Caucasian, 5.0% Black, 0.8% Asian, and 1.2% Other. Women with BMI ≥ 30 kg/m^2 were excluded from these studies.

Based on pooled data from the three trials, 2,356 women aged < 35 years completed 23,515 evaluable cycles of NuvaRing use (cycles in which no back-up contraception was used). The pooled pregnancy rate (Pearl Index) was 1.28 (95% CI [0.8, 1.9]) per 100 women-years of NuvaRing use. In the US study, the Pearl Index was 2.02 (95% CI [1.1, 3.4]) per 100 women-years of NuvaRing use.

15 REFERENCES

1. Dinger, J et. al., Cardiovascular risk associated with the use of an etonogestrel-containing vaginal ring. Obstetrics & Gynecology 2013; 122(4): 800-808.
2. Sidney, S. et. al., Recent combined hormonal contraceptives (CHCs) and the risk of thromboembolism and other cardiovascular events in new users. Contraception 2013; 87: 93–100.
3. 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.

16 HOW SUPPLIED/STORAGE AND HANDLING

Each NuvaRing (etonogestrel/ethinyl estradiol vaginal ring) is individually packaged in a reclosable aluminum laminate sachet consisting of three layers, from outside to inside: polyester, aluminum foil, and low-density polyethylene. The ring should be replaced in this reclosable sachet after use and discarded in a waste receptacle out of the reach of children and pets. It should not be flushed down the toilet.

Box of 3 sachets NDC 0052-0273-03

16.1 Storage

Prior to dispensing to the user, store refrigerated 2-8°C (36-46°F). After dispensing to the user, NuvaRing can be stored for up to 4 months at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Avoid storing NuvaRing in direct sunlight or at temperatures above 30°C (86°F).

For the Dispenser: When NuvaRing is dispensed to the user, place an expiration date on the label. The date should not exceed either 4 months from the date of dispensing or the expiration date, whichever comes first.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information and Instructions for Use).

Counsel patients regarding the following:

- Cigarette smoking increases the risk of serious cardiovascular events from use of NuvaRing, and women who are over 35 years old and smoke should not use NuvaRing.

- The increased risk of VTE compared to non-users of CHCs is greatest after initially starting a CHC or restarting (following a 4-week or greater CHC-free interval) the same or a different CHC.
- NuvaRing does not protect against HIV infection (AIDS) and other sexually transmitted infections.
- The Warnings and Precautions associated with NuvaRing.
- NuvaRing is not to be used during pregnancy. If pregnancy is planned or occurs during treatment with NuvaRing, instruct the patient to discontinue NuvaRing use.
- The proper usage of NuvaRing and what to do if she does not comply with the labeled timing of insertion and removal.
- The need to use a barrier method of contraception when the ring is out for more than three continuous hours until NuvaRing has been used continuously for at least seven days.
- The proper disposal of a used NuvaRing.
- Use a back-up or alternative method of contraception when enzyme inducers are used with NuvaRing.
- CHCs may reduce breast milk production. This is less likely to occur if breastfeeding is well established.
- Women who start NuvaRing postpartum and have not yet had a normal period should use an additional non-hormonal method of contraception for the first seven days.
- Amenorrhea may occur. Rule out pregnancy in the event of amenorrhea if NuvaRing has been out of the vagina for more than three consecutive hours, if the ring-free interval was extended beyond one week, if the woman has missed a period for two or more consecutive cycles, and if the ring has been retained for longer than four weeks.

Manufactured for: Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

Manufactured by: N.V. Organon, Oss, The Netherlands, a subsidiary of
Merck & Co., Inc., Whitehouse Station, NJ 08889, USA

U.S. Patent Nos.: 5,989,581.

Revised: 10/2013

uspi-mk8342a-rng-1310r04

Patient Information

NuvaRing® (NEW-vah-ring)
(etonogestrel/ethinyl estradiol vaginal ring)

What is the most important information I should know about NuvaRing?

Do not use NuvaRing if you smoke cigarettes and are over 35 years old. Smoking increases your risk of serious cardiovascular side effects (heart and blood vessel problems) from combination hormonal contraceptives (CHCs), including death from heart attack, blood clots or stroke. This risk increases with age and the number of cigarettes you smoke.

Hormonal birth control methods help to lower the chances of becoming pregnant. They do not protect against HIV infection (AIDS) and other sexually transmitted infections.

What is NuvaRing?

NuvaRing (NEW-vah-ring) is a flexible birth control vaginal ring used to prevent pregnancy.

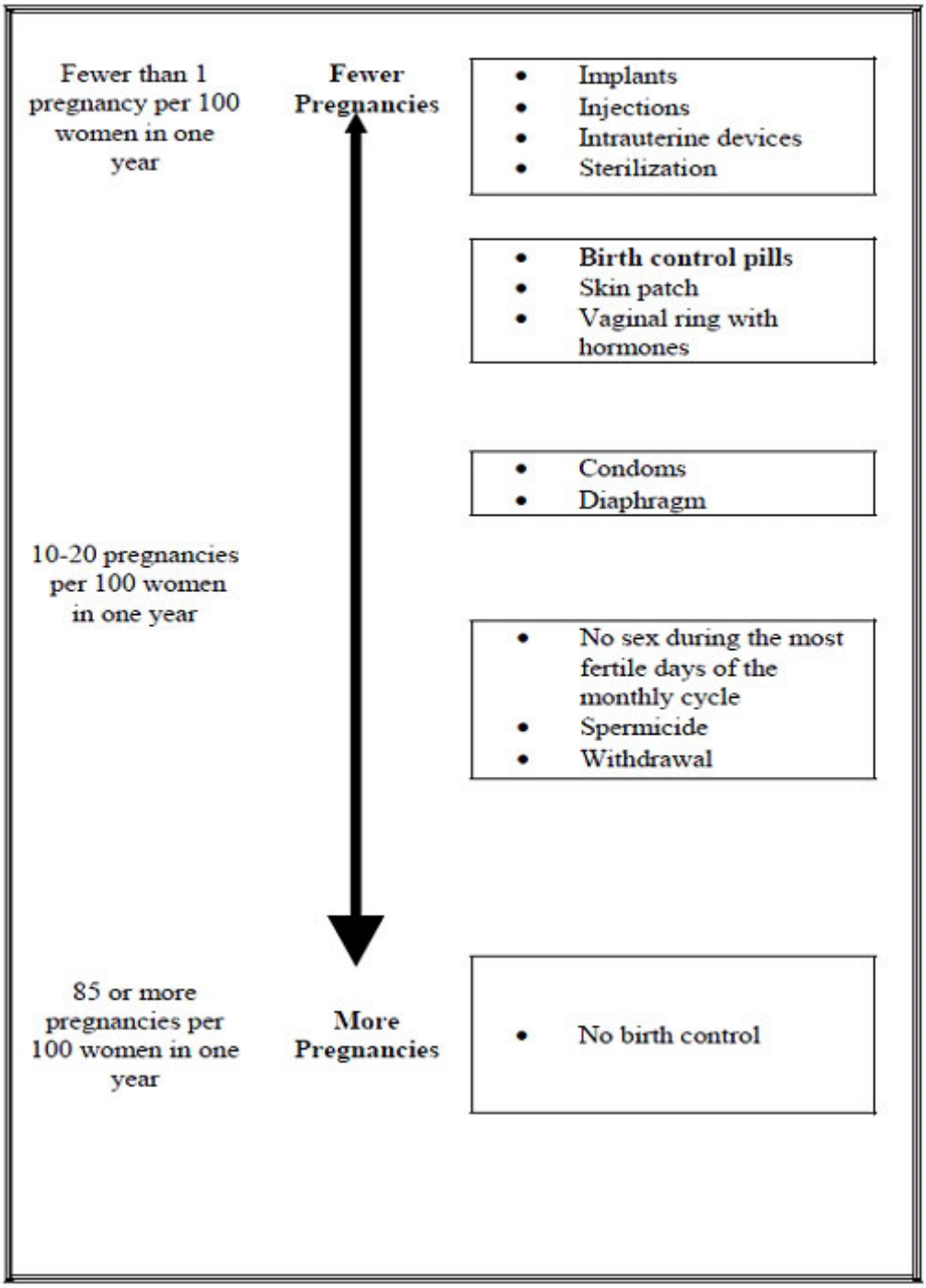
NuvaRing contains a combination of a progestin and estrogen, 2 kinds of female hormones. Birth control methods that contain both an estrogen and a progestin are called combination hormonal contraceptives (CHCs).

How well does NuvaRing work?

Your chance of getting pregnant depends on how well you follow the directions for using NuvaRing. The better you follow the directions, the less chance you have of getting pregnant.

Based on the results of a US clinical study, approximately 1 to 3 women out of 100 women may get pregnant during the first year they use NuvaRing.

The following chart shows the chance of getting pregnant for women who use different methods of birth control. Each box on the chart contains a list of birth control methods that are similar in effectiveness. The most effective methods are at the top of the chart. The box on the bottom of the chart shows the chance of getting pregnant for women who do not use birth control and are trying to get pregnant.



Who should not use NuvaRing?

Do not use NuvaRing if you:

- smoke and are over 35 years old
- have or have had blood clots in your arms, legs, eyes or lungs
- have an inherited problem with your blood that makes it clot more than

normal

- have had a stroke
- have had a heart attack
- have certain heart valve problems or heart rhythm problems that can cause blood clots to form in the heart
- have high blood pressure that medicine can't control
- have diabetes with kidney, eye, nerve, or blood vessel damage
- have certain kinds of severe migraine headaches with aura, numbness, weakness, or changes in vision, or have any migraine headaches if you are over age 35
- have liver disease, including liver tumors
- have unexplained vaginal bleeding
- are pregnant or think you may be pregnant. NuvaRing is not for pregnant women.
- have or have had breast cancer or any cancer that is sensitive to female hormones
- are allergic to etonogestrel, ethinyl estradiol or any of the ingredients in NuvaRing. See the list of ingredients in NuvaRing at the end of this leaflet.

Hormonal birth control methods may not be a good choice for you if you have ever had jaundice (yellowing of the skin or eyes) caused by pregnancy or related to previous use of hormonal birth control.

Tell your healthcare provider if you have ever had any of the conditions listed above. Your healthcare provider can suggest another method of birth control.

What should I tell my healthcare provider before using NuvaRing?

Before you use NuvaRing tell your healthcare provider if you:

- have any medical conditions
- smoke
- are pregnant or think you are pregnant
- recently had a baby
- recently had a miscarriage or abortion
- have a family history of breast cancer
- have or have had breast nodules, fibrocystic disease, an abnormal breast x-ray, or abnormal mammogram
- use tampons and have a history of toxic shock syndrome
- have been diagnosed with depression
- have had liver problems including jaundice during pregnancy

- have or have had elevated cholesterol or triglycerides
- have or have had gallbladder, liver, heart, or kidney disease
- have diabetes
- have a history of jaundice (yellowing of the skin or eyes) caused by pregnancy (also called cholestasis of pregnancy)
- have a history of scanty or irregular menstrual periods
- have any condition that makes the vagina become irritated easily
- have or have had high blood pressure
- have or have had migraines or other headaches or seizures
- are scheduled for surgery. NuvaRing may increase your risk of blood clots after surgery. You should stop using NuvaRing at least 4 weeks before you have surgery and not restart it until at least 2 weeks after your surgery.
- are scheduled for any laboratory tests. Certain blood tests may be affected by hormonal birth control methods.
- are breastfeeding or plan to breastfeed. Hormonal birth control methods that contain estrogen, like NuvaRing, may decrease the amount of milk you make. A small amount of hormones from NuvaRing may pass into your breast milk. Consider another non-hormonal method of birth control until you are ready to stop breastfeeding.

Tell your healthcare provider about all medicines and herbal products you take, including prescription and over-the-counter medicines, vitamins and herbal supplements.

Some medicines and herbal products may make hormonal birth control less effective, including, but not limited to:

- certain anti-seizure medicines (such as barbiturates, carbamazepine, felbamate, oxcarbazepine, phenytoin, rufinamide, topiramate)
- medicine to treat fungal infections (griseofulvin)
- certain combinations of HIV medicines, (such as nelfinavir, ritonavir darunavir/ritonavir, (fos)amprenavir/ritonavir, lopinavir/ritonavir, and tipranavir/ritonaivr)
- certain hepatitis C (HCV) medicines (such as boceprevir, telaprevir)
- non-nucleoside reverse transcriptase inhibitors (such as nevirapine)
- medicine to treat tuberculosis (such as rifampicin and rifabutin)
- medicine to treat high blood pressure in the vessels of the lung (bosentan)
- medicine to treat chemotherapy-induced nausea and vomiting (aprepitant)
- St John’s wort

Use an additional birth control method (such as a male condom with spermicide) when you take medicines that may make NuvaRing less effective. Continue back-up birth control for 28 days after stopping the medicine to help prevent you from becoming pregnant.

Some medicines and grapefruit juice may increase the level of ethinyl estradiol in your blood if used together, including:

- the pain reliever acetaminophen
- ascorbic acid (vitamin C)
- medicines that affect how your liver breaks down other medicines (such as itraconazole, ketoconazole, voriconazole, and fluconazole)
- certain HIV medicines (atazanavir/ritonavir, indinavir)
- non-nucleoside reverse transcriptase inhibitors (such as etravirine)
- medicines to lower cholesterol such as atorvastatin and rosuvastatin

Hormonal birth control methods may interact with lamotrigine, a medicine used for seizures. This may increase the risk of seizures, so your healthcare provider may need to adjust your dose of lamotrigine.

Women on thyroid replacement therapy may need increased doses of thyroid hormone.

Ask your healthcare provider if you are not sure if you take any of the medicines listed above. Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

- **How should I use NuvaRing?**

- Read the **Instructions for Use** at the end of this Patient Information that comes with your NuvaRing for information about the right way to use NuvaRing.
- Use NuvaRing exactly as your healthcare provider tells you to use it.
- NuvaRing is used in a 4 week cycle.
  - Insert 1 NuvaRing in the vagina and keep it in place for 3 weeks (21 days).
  - Remove the NuvaRing for a 1 week break (7 days). During the 1-week break (7 days), you will usually have your menstrual period.

    Note: Insert and remove NuvaRing on the same day of the week and at the same time:
    - For example, if you insert your NuvaRing on a Monday at 8:00 am, you should remove it on the Monday 3 weeks later at 8:00 am.
    - After your 1 week (7 days) break, you should insert a new NuvaRing on the next Monday at 8:00 am.

- While using NuvaRing, you should not use a vaginal diaphragm as your back-up method of birth control because NuvaRing may interfere with the correct placement and position of a diaphragm.
- Use of spermicides or vaginal yeast products will not make NuvaRing less effective at preventing pregnancy.
- Use of tampons will not make NuvaRing less effective or stop NuvaRing from working.
- If NuvaRing has been left inside your vagina for more than 4 weeks (28 days), you may not be protected from pregnancy and you should see your healthcare provider to be sure you are not pregnant. Until you know the results of your pregnancy test, you should use an extra method of birth control, such as male condoms with spermicide, until the new NuvaRing has been in place for 7 days in a row.
- Do not use more than 1 NuvaRing at a time. Too much hormonal birth control medicine in your body may cause nausea, vomiting, or vaginal bleeding.

Your healthcare provider should examine you at least 1 time a year to see if you have any signs of side effects from using NuvaRing.

What are the possible side effects of using NuvaRing?

See "What is the most important information I should know about NuvaRing?"

NuvaRing may cause serious side effects, including:

blood clots. Like pregnancy, combination hormonal birth control methods increase the risk of serious blood clots (see following graph), especially in women who have other risk factors, such as smoking, obesity, or age greater than 35. This increased risk is highest when you first start using a combination hormonal birth control method or when you restart the same or different combination hormonal birth control method after not using it for a month or more. Talk with your healthcare provider about your risk of getting a blood clot before using NuvaRing or before deciding which type of birth control is right for you.

In some studies of women who used NuvaRing, the risk of getting a blood clot was similar to the risk in women who used combination birth control pills.

Other studies have reported that the risk of blood clots was higher for women who use combination birth control pills containing desogestrel (a progestin similar to the progestin in NuvaRing) than for women who use combination birth control pills that do not contain desogestrel.

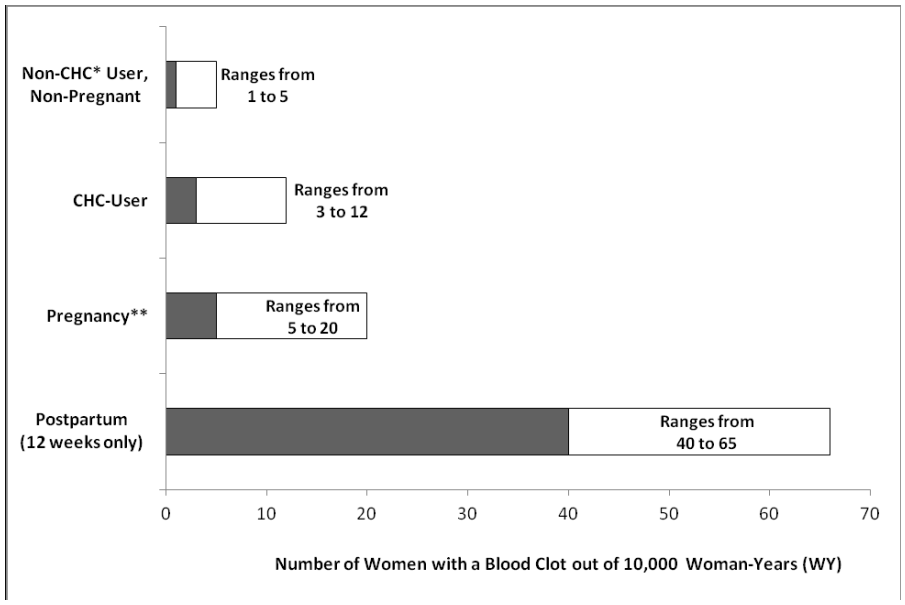
It is possible to die or be permanently disabled from a problem caused by a blood clot, such as heart attack or stroke. Some examples of serious blood clots are blood clots in the:

- legs (deep vein thrombosis)
- lungs (pulmonary embolus)

- eyes (loss of eyesight)
- heart (heart attack)
- brain (stroke)

To put the risk of developing a blood clot into perspective: If 10,000 women who are not pregnant and do not use hormonal birth control are followed for one year, between 1 and 5 of these women will develop a blood clot. The figure below shows the likelihood of developing a serious blood clot for women who are not pregnant and do not use hormonal birth control, for women who use hormonal birth control, for pregnant women, and for women in the first 12 weeks after delivering a baby.

Likelihood of Developing a Serious Blood Clot (Venous Thromboembolism [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.

Call your healthcare provider right away if you have:

- leg pain that does not go away
- sudden shortness of breath
- sudden blindness, partial or complete
- severe pain or pressure in your chest
- sudden, severe headache unlike your usual headaches

- weakness or numbness in an arm or leg, or trouble speaking
- yellowing of the skin or eyeballs

Other serious risks include:

- Toxic Shock Syndrome (TSS). Some of the symptoms are much the same as the flu, but they can become serious very quickly. Call your healthcare provider or get emergency treatment right away if you have the following symptoms:
  - sudden high fever
  - vomiting
  - diarrhea
  - a sunburn-like rash
  - muscle aches
  - dizziness
  - fainting or feeling faint when standing up
- liver problems, including liver tumors
- high blood pressure
- gallbladder problems
- accidental insertion into bladder
- symptoms of a problem called angioedema if you already have a family history of angioedema

The most common side effects of NuvaRing are:

- tissue irritation inside your vagina or on your cervix
- headache (including migraine)
- mood changes (including depression, especially if you had depression in the past). Call your healthcare provider immediately if you have any thoughts of harming yourself.
- NuvaRing problems, including the ring slipping out or causing discomfort
- nausea and vomiting
- vaginal discharge
- weight gain
- vaginal discomfort
- breast pain, discomfort, or tenderness
- painful menstrual periods
- abdominal pain
- acne
- less sexual desire

Some women have spotting or light bleeding during NuvaRing use. If these symptoms occur, do not stop using NuvaRing. The problem will usually go away. If it doesn't go away, check with your healthcare provider.

Other side effects seen with NuvaRing include allergic reaction, hives, and penis discomfort of the partner (such as irritation, rash, itching).

Less common side effects seen with combination hormonal birth control include:

- Blotchy darkening of your skin, especially on your face
- High blood sugar, especially in women who already have diabetes
- High fat (cholesterol, triglycerides) levels in the blood

Tell your healthcare provider about any side effect that bothers you or that does not go away. These are not all the possible side effects of NuvaRing. For more information, ask your healthcare provider or pharmacist. Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store NuvaRing and throw away used NuvaRings?

- Store NuvaRing at room temperature between 68°F to 77°F (20°C to 25°C).
- Store NuvaRing at room temperature for up to 4 months after you receive it. Throw NuvaRing away if the expiration date on the label has passed.
- Do not store NuvaRing above 86°F (30°C).
- Avoid direct sunlight
- Place the used NuvaRing in the re-closable foil pouch and properly throw it away in your household trash out of the reach of children and pets. Do not flush your used NuvaRing down the toilet.

Keep NuvaRing and all medicines out of the reach of children.

General information about the safe and effective use of NuvaRing

Medicines are sometimes prescribed for purposes other than those listed in the Patient Information. Do not use NuvaRing for a condition for which it was not prescribed. Do not give NuvaRing to other people. It may harm them.

This leaflet summarizes the most important information about NuvaRing. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about NuvaRing that is written for health professionals.

For more information, go to www.nuvaring.com or call 1-877-NUVARING (1-877-688-2746).

What are the ingredients in NuvaRing?

Active ingredients: etonogestrel and ethinyl estradiol

Inactive ingredients: ethylene vinylacetate copolymers (28% and 9% vinylacetate) and magnesium stearate.

NuvaRing is not made with natural rubber latex.

Do Hormonal Birth Control Methods Cause Cancer?

Hormonal birth control methods do not seem to cause breast cancer. However, if you have breast cancer now or have had it in the past, do not use hormonal birth control, including NuvaRing, because some breast cancers are sensitive to hormones.

Women who use hormonal birth control methods may have a slightly higher chance of getting cervical cancer. However, this may be due to other reasons such as having more sexual partners.

What should I know about my period when using NuvaRing?

When you use NuvaRing you may have bleeding and spotting between periods, called unplanned bleeding. Unplanned bleeding may vary from slight staining between menstrual periods to breakthrough bleeding, which is a flow much like a regular period. Unplanned bleeding occurs most often during the first few months of NuvaRing use, but may also occur after you have been using NuvaRing for some time. Such bleeding may be temporary and usually does not indicate any serious problems. It is important to continue using the ring on schedule. If the unplanned bleeding or spotting is heavy or lasts for more than a few days, you should discuss this with your healthcare provider.

What if I miss my regular scheduled period when using NuvaRing?

Some women miss periods on hormonal birth control, even when they are not pregnant. Consider the possibility that you may be pregnant if:

1. you miss a period and NuvaRing was out of the vagina for more than 3 hours during the 3 weeks (21 days) of ring use
2. you miss a period and waited longer than 1 week to insert a new ring
3. you have followed the instructions and you miss 2 periods in a row
4. you have left NuvaRing in place for longer than 4 weeks (28 days)

What if I want to become pregnant?

You may stop using NuvaRing whenever you wish. Consider a visit with your healthcare provider for a pre-pregnancy checkup before you stop using NuvaRing.

Instructions for Use

NuvaRing (NEW-vah-ring)
(etonogestrel/ethinyl estradiol vaginal ring)

Read these Instructions for Use before you start using NuvaRing and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your treatment.

How should I start using NuvaRing?

If you are not currently using hormonal birth control, you have 2 ways to start using NuvaRing. Choose the best way for you:

- **First Day Start:** Insert NuvaRing on the first day of your menstrual period. You will not need to use another birth control method since you are using NuvaRing on the first day of your menstrual period.
- **Day 2 to Day 5 Cycle Start:** You may choose to start NuvaRing on days 2 to 5 of your menstrual period. Make sure you also use an extra method of birth control (barrier method), such as male condoms with spermicide for the first 7 days of NuvaRing use in the first cycle.

If you are changing from a birth control pill or patch to NuvaRing:

If you have been using your birth control method correctly and are certain that you are not pregnant, you can change to NuvaRing any day. Do not start NuvaRing any later than the day you would start your next birth control pill or apply your patch.

If you are changing from a progestin-only birth control method, such as a minipill, implant or injection or from an intrauterine system (IUS):

- You may switch from a minipill on any day. Start using NuvaRing on the day that you would have taken your next minipill.
- You should switch from an implant or the IUS and start using NuvaRing on the day that you remove the implant or IUS
- You should switch from an injectable and start using NuvaRing on the day when your next injection would be due.

If you are changing from a minipill, implant or injection or from an intrauterine system (IUS), you should use an extra method of birth control, such as a male condom with spermicide during the first 7 days of using NuvaRing.

If you start using NuvaRing after an abortion or miscarriage:

- **Following a first trimester abortion or miscarriage:** You may start NuvaRing within 5 days following a first trimester abortion or miscarriage (the first 12 weeks of pregnancy). You do not need to use an additional birth control method.
- If you do not start NuvaRing within 5 days after a first trimester abortion or miscarriage, use a non-hormonal birth control method, such as male condoms and spermicide, while you wait for your period to start. Begin NuvaRing at the time of your next menstrual period. Count the first day of your menstrual period as "Day 1" and start NuvaRing one of the following 2 ways below.
    - **First Day Start:** Insert NuvaRing on the first day of your menstrual period. You will not need to use another birth control method since you are using NuvaRing on the first day of your menstrual period.
    - **Day 2 to Day 5 Cycle Start:** You may choose to start NuvaRing on Days 2 to 5 of your menstrual period. Make sure you also use an extra method of birth control (barrier method), such as male condoms with spermicide for the first 7 days of NuvaRing use in the first cycle.
- **Following a second trimester abortion or miscarriage:** You may start using NuvaRing no sooner than 4 weeks (28 days) after a second trimester abortion (**after** the first 12 weeks of pregnancy).

If you are starting NuvaRing after childbirth:

- You may start using NuvaRing no sooner than 4 weeks (28 days) after having a baby if you are not breastfeeding.
- If you have not gotten your menstrual period after childbirth, you should talk to your healthcare provider. You may need a pregnancy test to make sure you are not pregnant before you start using NuvaRing.
- Use another birth control method such as male condoms with spermicide for the first 7 days in addition to NuvaRing.

If you are breastfeeding you should not use NuvaRing. Use other birth control methods until you are no longer breastfeeding.

Step 1. Choose a position for insertion of NuvaRing.

- Choose the position that is comfortable for you. For example, lying down, squatting, or standing with 1 leg up **(See Figures A, B, and C)**.

Positions for NuvaRing insertion

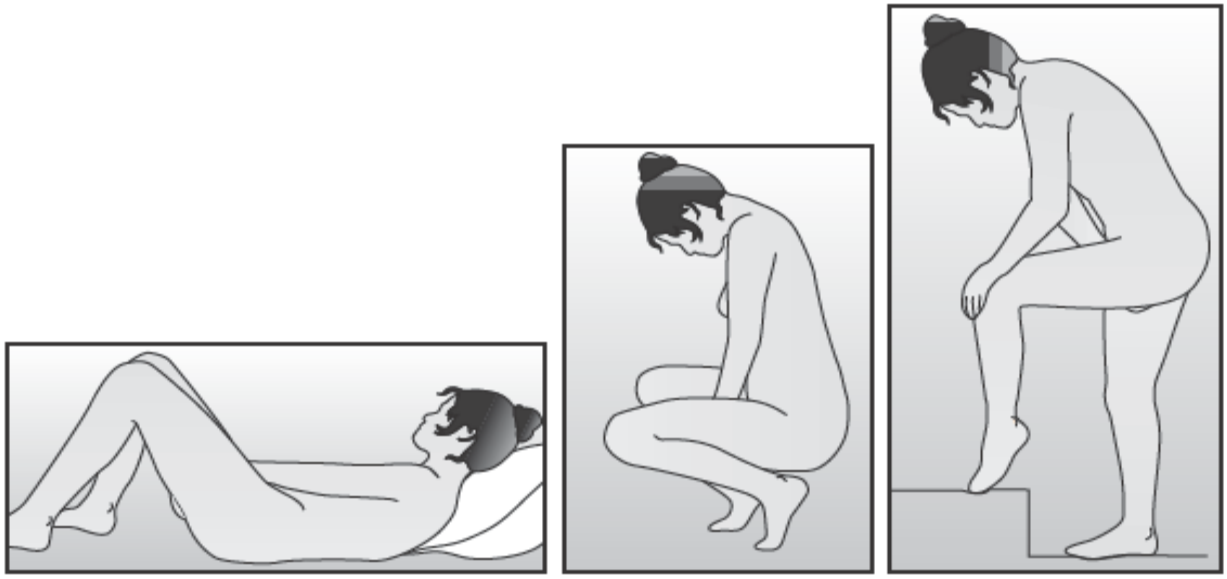


Figure A **Figure B** **Figure C**

Step 2. Open the pouch to remove your NuvaRing.

- Each NuvaRing comes in a re-sealable foil pouch.
- Wash and dry your hands before removing NuvaRing from the foil pouch.
- Open the foil pouch at either notch near the top.
- Keep the foil pouch so you can place your used NuvaRing in it before you throw it away in your household trash.

Step 3. Prepare NuvaRing for insertion.

- Hold NuvaRing between your thumb and index finger and press the sides of the ring together **(See Figures D and E)**.

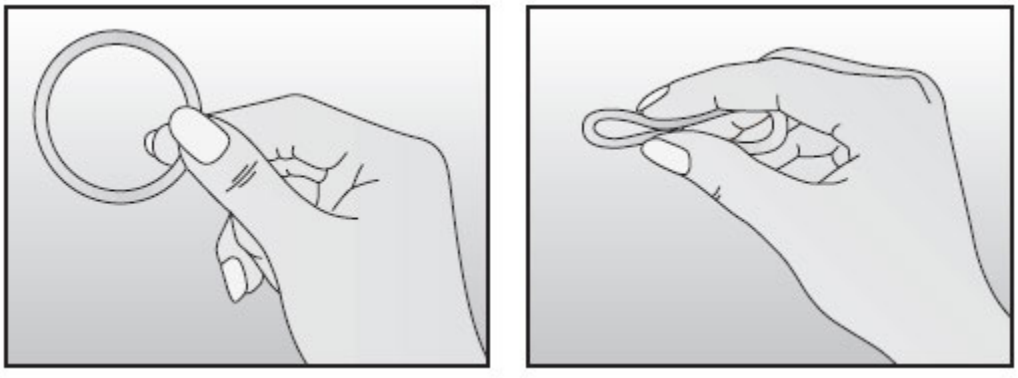
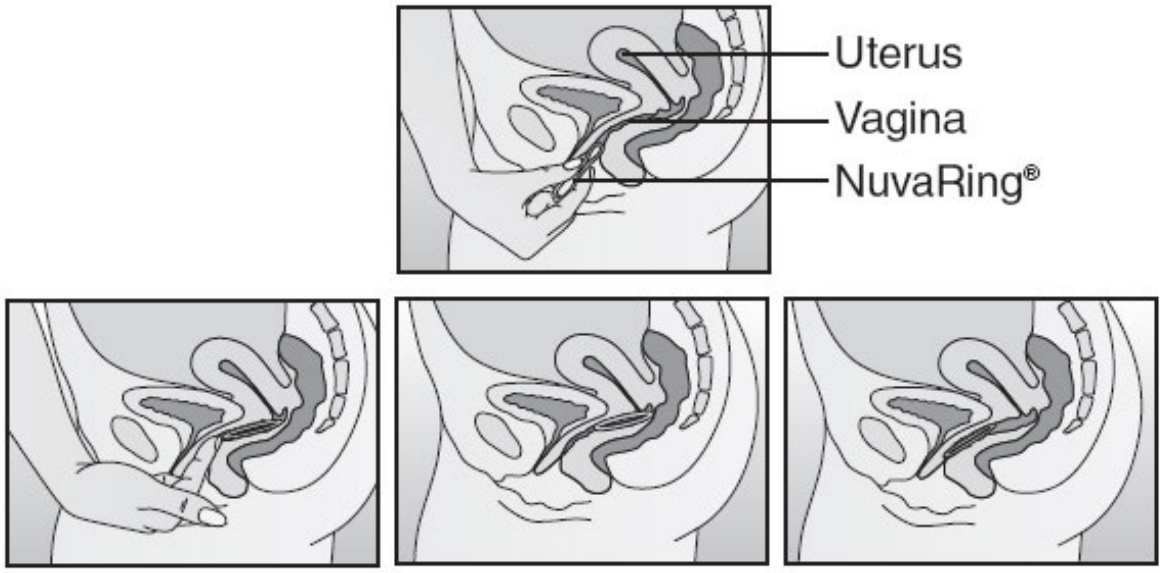


Figure D **Figure E**

Step 4. Insert NuvaRing into your vagina.

- Insert the folded NuvaRing into your vagina and gently push it further up into your vagina using your index finger **(See Figure F and G).**
- When you insert NuvaRing it may be in different positions in your vagina, but NuvaRing does not have to be in an exact position for it to work **(See Figure H and I).**
- NuvaRing may move around slightly within your vagina. This is normal. Although some women may be aware of NuvaRing in the vagina, most women do not feel it when it is in place.



Inserting NuvaRing (**Figure F, Figure G)** and positioning NuvaRing (**Figure H, Figure I)**

Note:

- If the NuvaRing feels uncomfortable, you may not have pushed the ring into your vagina far enough. Use your finger to gently push the NuvaRing as far as you can into your vagina. There is no danger of NuvaRing being pushed too far up in the vagina or getting lost **(See Figure G).**
- Some women have accidently inserted NuvaRing into their bladder. If you have pain during or after insertion and you cannot find NuvaRing in your vagina, call your healthcare provider right away.

Step 5. How do I remove NuvaRing?

- Wash and dry your hands.

- Choose the position that is most comfortable for you **(See Figures A, B, and C).**
- Put your index finger into your vagina and hook it through the NuvaRing. Gently pull downward and forward to remove the NuvaRing and pull it out **(See Figure J).**

Figure J

Step 6. Throw away the used NuvaRing.

- Place the used NuvaRing in the re-sealable foil pouch and put it in a trash can out of the reach of children and pets.
- Do not throw NuvaRing in the toilet.

What else should I know about using NuvaRing?

What If I leave NuvaRing in too long?

- If you leave NuvaRing in your vagina for up to 4 weeks (28 days) you will still be getting pregnancy protection. Remove your old NuvaRing for 1 week (7 days) and insert a new NuvaRing 1 week (7 days) later **(See Steps 1 through 4)**.
- If you leave NuvaRing in your vagina longer than 4 weeks (28 days), remove the ring and check to make sure you are not pregnant.

  If you are not pregnant, insert a new NuvaRing **(See Steps 1 through 4)**. You must use another birth control method, such as male condoms with spermicide, until the new NuvaRing has been used for 7 days in a row.

What should I do if my NuvaRing comes out of my vagina?

NuvaRing can slip or accidentally come out (expelled) of your vagina during sexual intercourse, bowel movements, use of tampons, or if it breaks.

- NuvaRing may break causing the ring to lose its shape. If the ring stays in your vagina this should not lower NuvaRing's effectiveness at preventing pregnancy.
    - If NuvaRing breaks and slips out of your vagina, throw the broken ring in your household trash out of the reach of children and pets.

- Insert a new NuvaRing **(See Steps 1 through 4).**

- You should pay attention when removing a tampon to be sure that your NuvaRing is not accidentally pulled out.
  - Be sure to insert NuvaRing before inserting a tampon.
  - If you accidentally pull out your NuvaRing while using tampons, rinse your NuvaRing in cool to lukewarm (not hot) water and insert it again right away**.**

- NuvaRing can be pushed out of (expelled from) your vagina during sexual intercourse or during a bowel movement.
  - If the expelled ring has been left out of your vagina for less than 3 hours, rinse the expelled NuvaRing in cool to lukewarm (not hot) water and insert it again right away.
  - If the expelled NuvaRing has been out of your vagina for more than 3 hours, insert a new NuvaRing as soon as you remember **(See Step 1 thru Step 4)**.
    - **During Weeks 1 and 2 after you have inserted your new NuvaRing,** you may not be protected from pregnancy. You should use another birth control method, such as male condoms with spermicide, until the ring has been in place for 7 days in a row.
    - **At the end of Week 3,** you should remove the NuvaRing and throw it away in your household trash away from children and pets and follow one of the two options below:

    Option 1. Insert a new ring right away to start your 21 Day NuvaRing use cycle. You may not have your regular period but you may have spotting or vaginal bleeding.

    Option 2. Insert a new ring no later than 7 days, from the time the previous ring was removed or expelled. During this time, you may have your period.

    Note: You should only choose to do option 2 if you used NuvaRing for 7 days in a row, prior to the day that your previous NuvaRing was accidently removed or expelled.

    With either option 1 or 2, you should use another birth control method such as male condoms with spermicides until the new NuvaRing has been used for 7 days in a row.

This Patient Information and Instructions for Use have been approved by the U.S. Food and Drug Administration.

Manufactured for: Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

Manufactured by: N.V. Organon, Oss, The Netherlands, a subsidiary of **Merck & Co., Inc.,** Whitehouse Station, NJ 08889, USA

U.S. Patent No. 5,989,581.

Revised: 10/2013

usppi-mk8342a-rng-1310r04

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21187/S021

CROSS DISCIPLINE TEAM LEADER 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:

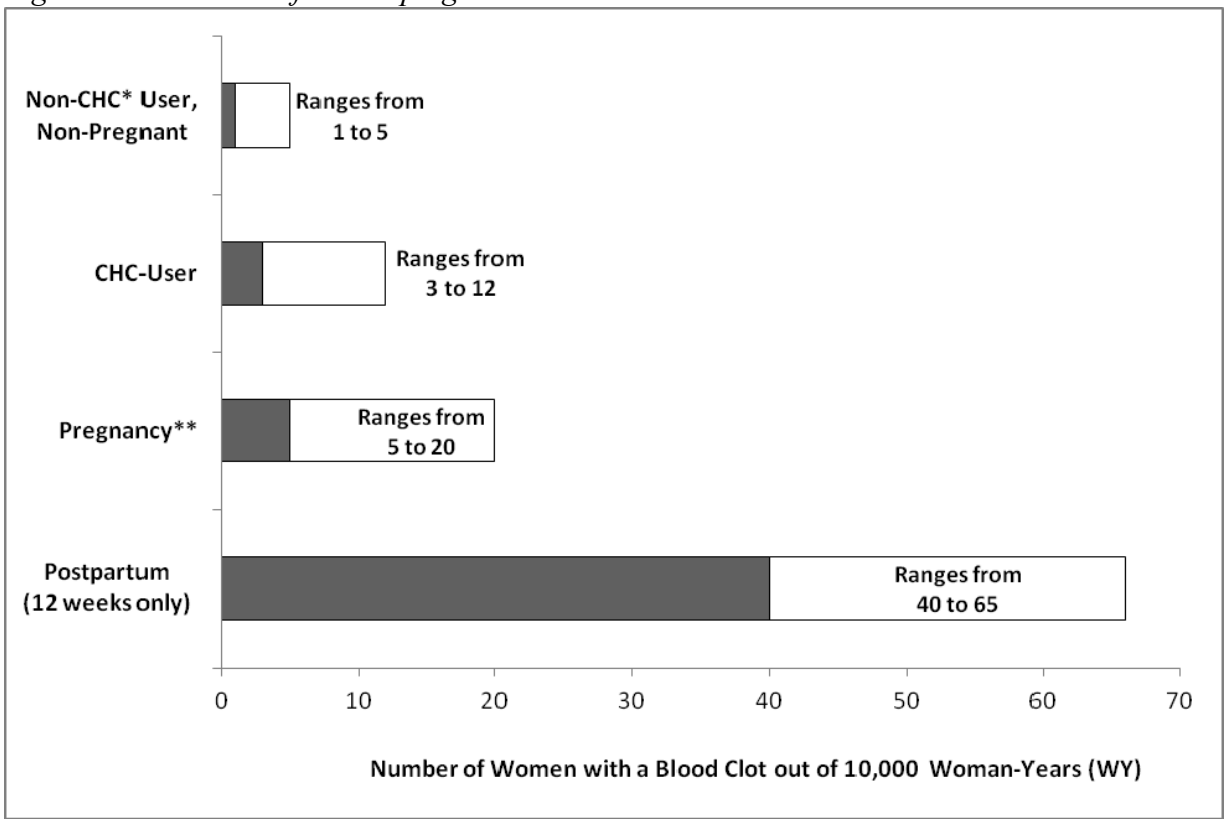
> *Stop [drug] if an arterial or venous thrombotic (VTE) event occurs. Although the use of COCs increases the risk of venous thromboembolism, pregnancy increases the risk of venous thromboembolism as much or more than the use of COCs. The risk of venous thromboembolism in women using COCs is 3 to 9 per 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 "In three large clinical trials of 13 cycles of NuvaRing use, pregnancy rates were between one and two per 100 women-years of use." 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	Adjusted incidence rate per 10,000 WY	HR: vs. All COCs HR (95% CI)	HR: vs. LNG/30 µg EE COCs 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

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/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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21187/S021

MEDICAL REVIEW(S)

CLINICAL REVIEW ADDENDUM

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.

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/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

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[1] that evaluated VTE risk and all-cause and cardiovascular mortality for 3 newer combination hormonal contraceptives

[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:

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://darrts.fda.gov:9602/darrts/viewEDR.do?suppDocId=8262273
4. Jessica Kim: Division of Biometrics VII, OB. Judy 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 (b) (4)

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 (b) (4) submitted to the Agency on December 20, 2012 should have been listed as anxiety (b) (4) 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), 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 (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:

- 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
Progestins of COCs			
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 (chlomadinoacetate)	NA	6.9	3.6
CPA (cyproteroacetate)	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) ($COC_{DSG/GSD}$), 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

    - 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/

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.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21187/S021

CHEMISTRY REVIEW(S)

1. Chemistry Review: 1	2. Division: HFD-580	NDA Number: 21187

3. Name and Address of Applicant:	4. Supplement(s): SLR PA
Organon USA Inc. One Merck Drive PO Box 100 Whitehouse Station, NJ 08889	**Number: S-021 (Efficacy)** **S-022 (SLR)** **Date(s):** 30-Aug-2012 (SDN 791) for S021 20-Dec-2012 (SDN 815) for S022
5. Name of Drug: NuvaRing	**6. Nonproprietary name:** Etonogestrel and ethinyl estradiol

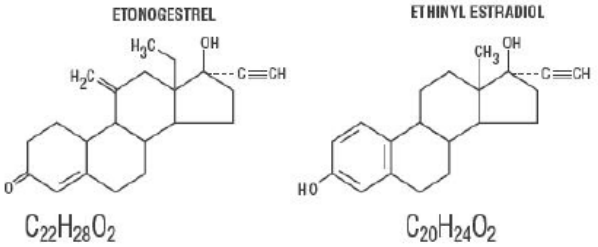
7.Supplement Provides for	8. Amendment(s):
Efficacy supplement to add results of the "Transatlantic Active Surveillance on Cardiovascular Safety of NuvaRing (TASC)" study and change approved label to Physicians Labeling Rule format.	SDN 817 dated 20-Dec-2012 SDN 827 dated 09-Jan-2013 SDN 845 dated 12-Mar-2013 SDN 877 dated 04-Sep-2013

9. Pharmacological Category:	10. How Dispensed:	11. Related Documents:
Progestin and estrogen	R_x	N/A

12. Dosage Form:	13. Potency:
Vaginal Ring	11.7 mg etonogestrel and 2.7 mg ethinyl estradiol which releases on average 0.120 mg/day of etonogestrel and 0.015 mg/day of ethinyl estradiol

14. Chemical Name and Structure:

etonogestrel (13-ethyl-17-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one)
ethinyl estradiol (19-nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol)



$C_{22}H_{28}O_2$ $C_{20}H_{24}O_2$

15. Comments

This supplements seek approval for addition of results from the "Transatlantic Active Surveillance on Cardiovascular Safety of NuvaRing (TASC)" study and to change the label to the PLR format. The label in PLR format is transferred from the approved label with minor editorial changes only. There are a few clarification comments that will be conveyed to the applicant when the label is sent by OND.

16. Conclusion:

This Supplement is recommended for approval from the CMC perspective, with the recommended changes made in the eRoom and captured in the Review Notes. As this is OND-managed, any correspondence with the applicant will come from OND.

17. Name:	Signature:	Date:
Donna F. Christner, Ph.D.		

18. Concurrence:	Signature:	Date:
Thomas F. Oliver, Ph.D.		

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/s/

DONNA F CHRISTNER
09/10/2013

THOMAS F OLIVER
09/10/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21187/S021

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW ADDENDUM

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 Pharmacology Primary Reviewer:	Chongwoo Yu, PhD
Clinical Pharmacology Secondary Reviewer:	Myong-Jin Kim, PharmD
OCP Division:	Division of Clinical Pharmacology 3 (DCP3)
OND Division:	Division of Bone, Reproductive, and Urologic Products (DBRUP)
Sponsor:	Merck Sharp & Dohme Corp.
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 Office of Clinical Pharmacology (OCP)'s final recommendation on Supplements 021 and 022 to NDA 021187.

In the original Clinical Pharmacology review of these supplements to NDA 021187 dated August 30, 2013 in DARRTS, it was stated that "*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.*"

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

1. Recommendation

The OCP/DCP3 finds NDA 021187 acceptable from the Clinical Pharmacology perspective.

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/s/

CHONGWOO YU
10/01/2013

MYONG JIN KIM
10/01/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21187/S021

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	October 2, 2013
To:	Hylton V. Joffe, M.D., Director **Division of Bone, Reproductive and Urologic Products (DBRUP)**
Through:	LaShawn Griffiths, RN, MSHS-PH, BSN Associate Director, Patient Labeling Team **Division of Medical Policy Programs (DMPP)** Robin Duer, RN, BSN, MBA Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Twanda Scales, RN, MSN/Ed. Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Carrie Newcomer, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert and Instructions for Use
Drug Name:	NuvaRing (etonogestrel/ethinyl estradiol vaginal ring)
Dosage Form and Route:	Vaginal Ring
Application Type/Number:	NDA 21-187
Supplement Number:	021, 022

1 INTRODUCTION

On August 30, 2012, Merck submitted for the Agency's review a New Drug Application (NDA) Efficacy Supplement (S-021) for NuvaRing (etonogestrel/ethinyl estradiol vaginal ring). NuvaRing is an estrogen/progestin combination hormonal contraceptive (CHC) for use by women to prevent pregnancy, and was originally approved on October 3, 2001.

Supplement 021 provides for the addition labeling information for NuvaRing based on results from the Applicant's study entitled "Transatlantic Active Surveillance on Cardiovascular Safety of NuvaRing (TASC)".

On December 20, 2012, Merck submitted for the Agency's review a Prior Approval Labeling Supplement (S-022) for NuvaRing (etonogestrel/ethinyl estradiol vaginal ring). Supplement 022 provides for the conversion of the NuvaRing labeling to Physician Labeling Rule (PLR) format. As requested by the Agency, S-022 also includes the addition of labeling information for NuvaRing based on results from the Applicant's TASC study included in S-021.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the DBRUP on August 27, 2013, and August 26, 2013, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for NuvaRing (etonogestrel/ethinyl estradiol vaginal ring).

2 MATERIAL REVIEWED

- Draft NuvaRing (etonogestrel/ethinyl estradiol vaginal ring) Patient Package Insert (PPI) and Instructions for Use (IFU) received on December 20, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on September 19, 2013
- Draft NuvaRing (etonogestrel/ethinyl estradiol vaginal ring) Patient Package Insert (PPI) and Instructions for Use (IFU) received on December 20, 2012, revised by the Review Division throughout the review cycle, and received by OPDP on September 23, 2013
- Draft NuvaRing (etonogestrel/ethinyl estradiol vaginal ring) Prescribing Information (PI) received on December 20, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on September 19, 2013
- Draft NuvaRing (etonogestrel/ethinyl estradiol vaginal ring) Prescribing Information (PI) received on December 20, 2012, revised by the Review Division throughout the review cycle, and received by OPDP on September 23, 2013
- Approved ORTHO EVRA (norelgestromin /ethinyl estradiol transdermal system) comparator labeling dated July 1, 2013
- FemRing (estradiol acetate vaginal ring) comparator labeling currently under FDA review and pending approval
- Guidance for Industry: Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms

— Recommended Prescribing Information for Health Care Providers and Patient Labeling dated November 2005

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI and IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI and IFU document using the Verdana font, size 11.

In our collaborative review of the PPI and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- rearranged information due to conversion of the PI to Physicians Labeling Rule (PLR) format
- removed unnecessary or redundant information
- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI and IFU are consistent with the approved comparator labeling where applicable

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI an IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

  Please let us know if you have any questions.

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/s/

TWANDA D SCALES
10/02/2013

CARRIE A NEWCOMER
10/02/2013

ROBIN E DUER
10/02/2013

LASHAWN M GRIFFITHS
10/02/2013

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title	**NuvaRing® (etonogestrel/ethinyl estradiol vaginal ring)**
Applicant	Merck, Sharp & Dohme Corp.
Application/Supplement Number	NDA 21187, supplement 21
Type of Application	Efficacy Supplement
Indication(s)	To prevent pregnancy
Established Pharmacologic Class[1]	Estrogen/Progestin
Office/Division	ODE III/DBRUP
Division Project Manager	Charlene Williamson
Date FDA Received Application	December 5, 2012
Goal Date	October 5, 2013
Date PI Received by SEALD	September 30, 2013
SEALD Review Date	October 1, 2013
SEALD Labeling Reviewer	Abimbola Adebowale
SEALD Division Director	Laurie Burke

PI = prescribing information

[1] The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements of Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO:** The PI **does not meet** the requirement for this item **(deficiency)**.
- **YES:** The PI **meets** the requirement for this item **(not a deficiency)**.
- **N/A** (not applicable): This item does not apply to the specific PI under review.

Highlights (HL)

GENERAL FORMAT

YES 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

YES 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been is granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period (for RPMs)**
  - *For efficacy supplements:* If a waiver was previously granted, select "**YES**" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "**NO**" in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of Cycle Period (for SEALD reviewers)**
  - The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

YES 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

YES 4. White space must be present before each major heading in HL.

Comment: *There is extra white space before the Warnings and Precautions heading in HL. Recommend removal of the extra white space.*

YES 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

YES 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a Boxed Warning is in the FPI

Selected Requirements of Prescribing Information

• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

Comment:

Product Title

YES 10. Product title in HL must be **bolded.**

Comment:

Initial U.S. Approval

YES 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded,** and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning

NO 12. All text must be **bolded**.

Comment: *Summary text in the Boxed Warning in HL is not bolded. Bold.*

YES 13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and

other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

YES 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." in *italics* and centered immediately beneath the heading.

Comment:

YES 15. Must be limited in length to 20 lines (this does not include the heading and statement "***See full prescribing information for complete boxed warning.***")

Comment:

YES 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

YES 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

YES 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

YES 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Dosage and Administration, Coronary Stenting (2.2) --- 3/2012".

Comment:

N/A 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

NO 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment: *The required statement in the Indications and Usage section of HL should read as "NuvaRing is an estrogen/progestin combination hormonal contraceptive (CHC) indicated for use by women to prevent pregnancy" instead of "* (b) (4) [redacted]

Dosage Forms and Strengths

Selected Requirements of Prescribing Information

N/A 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

YES 23. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known.

Comment:

YES 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

YES 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment: *There is no white space before the bolded adverse reactions verbatim reporting statement as per the PLR Labeling Implementation guidance (Appendix E). Recommend inserting white space before the statement.*

Patient Counseling Information Statement

YES 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide."**

Comment:

Revision Date

YES 27. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.

Comment: *In PLR format, this revision date at the end of HL replaces the "revision" date at the end of the PI and should not appear in both places. Recommend removal of the revision date at the end of the PI.*

Contents: Table of Contents (TOC)

GENERAL FORMAT

YES 28. A horizontal line must separate TOC from the FPI.

Comment: *Recommend inserting white space between the horizontal line and the FPI.*

YES 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS"**.

Comment:

NO 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment: *The following section heading and subheadings do not match in the TOC and FPI and must be matched:*

Subheading 2.2 in the TOC "When to Start NuvaRing" does not match subheading 2.2 in the FPI "How to Start Using NuvaRing."

Subheading 2.5 in the FPI "Use with Other Vaginal Products" is missing from the TOC.

Subheading 7.2 in the TOC "Effects of Combined Hormonal Contraceptives (CHCs) on Other Drugs" does not match subheading 7.2 in the FPI "Effects of CHCs on Other Drugs."

Subheading 12.2 "Pharmacodynamics" in the TOC is missing from the FPI.

Section heading 15 "REFERENCES" in the FPI is missing from the TOC.

YES 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

YES 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS"** must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

Selected Requirements of Prescribing Information

YES 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: *In the FPI, consider deleting the route of administration "FOR VAGINAL USE ONLY" from the Indications and Usage section and placing it under the Dosage and Administration section instead as per the Dosage and Administration Labeling guidance.*

YES 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

NO 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, "*[see Warnings and Precautions (5.2)]*".

Comment: *Under subsection 5.3, the cross reference "[see Use in Specific Populations (8.7)]" is not in italics. Italicize.*

In several sections and subsections (i.e., Boxed Warning, 2.2, 5.1, 8.6 and 12.3) in the FPI, the cross-reference is presented as "[See…]" instead of "[see…]."

YES 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

YES 42. All text is **bolded**.

Comment:

YES 43. Must have a heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

YES 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

N/A 45. If no Contraindications are known, this section must state "None".

Comment:

Adverse Reactions

YES 46. When clinical trials adverse reactions data is included (typically in the "Clinical Trials Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."

Comment:

YES 47. When postmarketing adverse reaction data is included (typically in the "Postmarketing Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Patient Counseling Information

NO 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

Selected Requirements of Prescribing Information

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Comment: *The statement at the beginning of Section 17 "See FDA-Approved Patient Labeling (Patient Information)" should read as "See FDA-approved patient labeling (Patient Information and Instructions for Use)" as shown above.*

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

/s/

ABIMBOLA O ADEBOWALE
10/01/2013

LAURIE B BURKE
10/01/2013

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: September 27, 2013

To: Charlene Williamson
Regulatory Project Manager
Division of Bone, Reproductive, and Urologic Products (DBRUP)

From: Carrie Newcomer, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA: 021187
NuvaRing (etonogestrel/ethinyl estradiol vaginal ring) (NuvaRing)

As requested in your consult dated August 26, 2013, OPDP has reviewed the draft labeling (package insert [PI]) for NuvaRing. OPDP's comments are based on the proposed, substantially complete, marked-up version of the draft PI provided to OPDP on September 23, 2013, via access to the DBRUP eRoom.

OPDP notes that the Division of Medical Policy Programs (DMPP) and OPDP will provide comments on the draft patient package insert (PPI) under separate cover.

OPDP's comments on the PI are provided directly in the attached copy of the labeling.

Thank you for your consult. If you have any questions, please contact Carrie Newcomer at 6-1233, or carrie.newcomer@fda.hhs.gov.

19 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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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/

CARRIE A NEWCOMER
09/27/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology: Review of Study Report

Date:	August 26, 2013
Reviewer(s):	Rita Ouellet-Hellstrom, PhD Division of Epidemiology II
Team Leader	CDR David Moeny, RPh, MPH, USPHS Division of Epidemiology II
Division Director	Judy Staffa, PhD, RPh Division of Epidemiology II
Subject	*Transatlantic Active Surveillance on Cardiovascular Safety of NuvaRing (TASC), Final Study Report*. By Jürgen Dinger August 9, 2012
Drug Name(s):	NuvaRing (etonogestrel)
Applicant/sponsor:	Organon USA, Inc.
NDA#	21-187
OSE RCM #:	2013-1575

TABLE OF CONTENTS

EXECUTIVE SUMMARY

NuvaRing (etonogestrel/ethinyl estradiol), a combined hormonal contraceptive (CHC), was approved for marketing on October 3, 2001.

As part of the approval, the Agency requested that the sponsor complete a safety epidemiologic study as a postmarketing commitment. The study, *Transatlantic Active Surveillance on Cardiovascular Safety of NuvaRing (TASC),* enrolled the first women in September 2007 and the last women in September 2009. Individual follow-up was up to 4 years. The Final Study Report reviewed is dated August 9, 2012.

Between NuvaRing's US market introduction in 2002 and 2011, several epidemiologic studies, including the FDA funded study, have been conducted and published.

The sponsor has submitted revised labeling. The Division of Bone, Reproductive, and Urologic Products (DBRUP) asked the Office of Surveillance and Epidemiology (OSE)'s Division of Epidemiology (DEPI) to review the final TASC study report submitted to the Agency on December 5, 2012, the proposed labeling relating to the risk of VTE in NDA 21-187, and to indicate if OSE/DEPI concurs with the proposed language in the revised label.

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.

OSE/DEPI has two recommendations specific to NuvaRing label information based on results of the TASC study and the FDA funded study.

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 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 for 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.

ABBREVIATIONS

AMI	Acute Myocardial Infarction
AT	as treated
ATE	Arterial thrombotic events
BMI	Body Mass Index
CHC	Combined Hormonal Contraceptive
CMA	Chlomadinoacetate
COC	Combined Oral Contraceptive
CPA	Cyproteroacetate
CVA	Cerebrovascular Accidents
DBRUP	Division of Bone, Reproductive, and Urologic Products
DEPI	Division of Epidemiology
DNG	Dinogest
DRSP	drospirenone
DSG	Desogestrel
DVT	Deep Venous Thrombosis
GSD	gestodene
HR	Hazard Ratio
ID	Identification number
IR	Incidence Rates
IRR	Incidence Rate Ratio
ITT	intention to treat
LNG	Levonorgestrel
NET	Norethisterone
NETA	Norethindrone
NG	Norgestrel
NGM	Norgestimate
OHC	Other hormonal contraceptives
OSE	Office of Surveillance and Epidemiology
PE	Pulmonary Embolism
PHI	Protected Health Information
SAE	Serious adverse event
SAP	Statistical analysis plan
TASC	Transatlantic Active Surveillance on Cardiovascular Safety of NuvaRing
US	United States
VTE	Venous thromboembolic events
WY	Women Years

1 INTRODUCTION

NuvaRing (etonogestrel/ethinyl estradiol), a combined hormonal contraceptive (CHC), was approved for marketing on October 3, 2001. It is a polymeric vaginal ring containing 11.7 mg etonogestrel and 2.7 mg ethinyl estradiol. The ring is inserted vaginally and remains in place continuously for three weeks, followed by a one-week ring-free interval.

As part of the approval, the Agency requested that the sponsor complete a safety epidemiologic study as a postmarketing commitment. The study, *Transatlantic Active Surveillance on Cardiovascular Safety of NuvaRing (TASC),* enrolled the first women in September 2007 and the last women in September 2009. Individual follow-up was up to 4 years. The Final Study Report reviewed is dated August 9, 2012.

Between NuvaRing's US market introduction in 2002 and 2011, several epidemiologic studies, including the FDA funded study, have been conducted and published. These studies included NuvaRing among other products evaluated. Prior to the 2011 advisory meetings that discussed the other combined hormonal contraceptive (CHC) products, results of the FDA study were posted on the FDA website at (http://www.fda.gov/downloads/Drugs/DrugSafety/UCM277384.pdf). The posted results included incidence rates and hazard ratios for venous thromboembolism (VTE), arterial thrombotic events (ATE), and mortality. The results for new users were later published[a].

The sponsor has submitted revised labeling that includes results from the TASC post-marketing safety surveillance study and those pertaining to NuvaRing from FDA-funded study on the incidence and relative risk of VTE. The Division of Bone, Reproductive, and Urologic Products (DBRUP) asked the Office of Surveillance and Epidemiology (OSE)'s Division of Epidemiology (DEPI) to review the final TASC study report submitted to the Agency on December 5, 2012, the proposed labeling relating to the risk of VTE in NDA 21-187, and to indicate if OSE/DEPI concurs with the proposed language in the revised label.

2 REVIEW METHODS AND MATERIALS

The following documents were reviewed:

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://darrts.fda.gov:9602/darrts/viewEDR.do?suppDocId=8262273 (Excerpt in Appendix 1).

[a] 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.

4. Jessica Kim: Division of Biometrics VII, Office of Biostatistics. Judy 26, 2013 Comments on the *Transatlantic Active Surveillance on Cardiovascular Safety of Nuvaring (TASC), Final Study Report. By Jürgen Dinger, August 9, 2012* (Appendix 3)

This review will evaluate the strengths and limitation of TASC and comment on whether the information in the revised label is supported by the study results.

3 REVIEW RESULTS

3.1 STUDY OVERVIEW

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 venous and arterial thrombotic and thromboembolic events (VTE and ATE). Reported serious adverse events were validated by contacting the diagnosing and treating physicians and by reviewing relevant source documents.

3.2 STUDY OBJECTIVES

The primary objective of the TASC study was to characterize and compare the VTE and ATE risks of short- and long-term use of NuvaRing with users of other combined oral contraceptives (COCs)

- Deep Venous Thrombosis (DVT)
- Pulmonary Embolism (PE)
- Acute Myocardial Infarction (AMI)
- Cerebrovascular Accidents (CVA)

Secondary objectives were to:

- Analyze the drug utilization pattern of NuvaRing and other COCs in a representative population of typical users
- Characterize the baseline risk (lifetime history of co-morbidity and duration of hormonal contraceptive use, risk markers, co-medication, socio-demographic and lifestyle data)
- Assess the compliance of NuvaRing users and users of other COCs
- Analyze the reasons for discontinuing the treatment

3.3 STUDY METHODS

3.3.1 Design

3.3.1.1 Study Type

This study was designed as a large, international, prospective, non-interventional, long-term cohort study. Women from Austria, France, Germany, Italy, Russia, and the United States participated in the study.

3.3.1.2 Population & Time Period

The cohorts consisted of new users of the NuvaRing or other combined oral contraceptives. For every NuvaRing user recruited, the physician recruited the next COC user who was willing to participate in the study. To provide standardized, comprehensive, reliable information on users of hormonal contraceptives, medical providers were free to prescribe as they would otherwise under routine medical conditions.

Recruitment started in Europe (Austria) in September 2007. The first US women were enrolled in late February 2008. Two years after the study commenced, enrollment of new study participants was completed in September 2009. Individual follow-up within the TASC study was up to 4 years beginning in September 2007 and continued without a break to September 2011. Loss-to-follow-up activities lasted till the end of March 2012.

3.3.1.3 Selection, Inclusion and Exclusion Criteria

Study participants included all women seeking a new prescription for a combined hormonal contraceptive (CHC) and who were willing to participate in the study. Other than requiring informed consent to participate in the study, no other specific inclusion or exclusion criteria were imposed due to the non-interference design. Once enrolled, a subject could discontinue use of study medication at any time or refuse to continue participation in the study.

3.3.1.4 Protected Health Information (PHI) Approvals

As noted in the report, the study was conducted in accordance with the ethical principles of the Declaration of Helsinki. The planning and conduct of the study was subject to the national laws and regulations of each participating countries. The primary ethical approval was provided by the ethical committee of the physicians' association in Berlin, Germany, home of the coordinating center. The study was registered in the public clinical trials database of the US National Library of Medicine under the registration number NCT00524 771.

3.3.2 Outcome & Exposure

3.3.2.1 Exposure

For this study, exposure was defined as first use of a CHC, either the NuvaRing or another COC. The study recruited women who were starters, switchers, or recurrent users. Starters were first-ever users of hormonal contraceptives. Switchers were users

who switched from one CHC to another CHC - e.g. from 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 another 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.

3.3.2.2 Outcome

For this study, the main clinical outcomes of interest for the short and long-term follow-up were venous thromboembolic and arterial thrombotic events (VTE and ATE) although information on other adverse events was also collected. The main clinical outcomes were

- Deep Venous Thrombosis (DVT)
- Pulmonary Embolism (PE)
- Acute Myocardial Infarction (AMI)
- Cerebrovascular Accidents (CVA)

Follow-up assessment was done using mailed questionnaire to each woman in the TASC study. These mailings were scheduled at 6, 12, 24, 36, and 48 months after study entry. The questionnaires included requests for information on personal health related events and name and address of the relevant physician (attending physician, physician responsible for the follow-up treatment after discharge from hospital, or primary care physician). In some cases, events were reported by the participant or by relatives, friends or attending physicians between the regular follow-up contacts. All reports were validated according to a predefined process, initially at the local field level. In case of unclear or missing information the women were contacted by telephone, e-mail or other means. For many events it was necessary to contact the diagnosing and/or treating physician for clarification and validation of the information received from the patient. This procedure was mandatory for all serious adverse drug reactions (including VTE and ATE).

Under routine medical conditions, diagnosis of a serious adverse event (SAE) is not always confirmed by a diagnostic method with high specificity. Therefore, SAEs were classified by the investigators as "confirmed" (definite and probable event) or "not confirmed". Details are provided in Section 3.6 of the Final Report.

3.3.3 Covariates

In the TASC study, baseline data were recorded on a self-administered questionnaire containing questions relating to participants' state of health and potential risk factors. Participants provided their medical history, and medication history including history of

COC use. The information given by the study participants was verified by their physicians. The documented information included:

- Baseline information: ID-number; date of birth; age at menarche; previous pregnancies; number of live births; age at the first live birth; hormonal contraceptive use [duration, switching, stopping, brand, time since last hormonal contraceptive use, previous adverse events (AEs) during COC-use (specified)]; brand name of hormonal contraceptive at study entry; reasons for prescription; smoking status and number of cigarettes per day; height & weight; medical conditions [hypertension, diabetes mellitus, high cholesterol, coronary heart disease, stroke, blood clots in the lung, deep venous thrombosis, cancer, surgery (specified), others (specified); risk factors for VTE (such as blood coagulation disorders; frequent long-haul flights, etc.]; family history of VTE and ATE; regular use of concomitant medication (specify); educational level.
- Follow-up information: ID-number; date of completion; new SAEs/AEs such as cardiovascular events (heart attack/MI. stroke, venous thromboembolism); other severe illnesses surgery ; hospitalizations ; AEs change of hormonal contraceptive use (stopped, switched, unchanged), reasons for stopping or switching; occurrence of pregnancy, delivery and potential problems during pregnancy and delivery; health problems of the newborn; pregnancy despite COC-use and potential reasons for contraceptive failure; changes in smoking status; weight changes; personal changes; name of treating physician or hospital to enable future contact (in case of AE/SAE occurrence).

In addition, participants provided their addresses and phone numbers, contact information of relatives or friends who could serve as a reserve contact person, and contact information for their primary care physician and gynecologist. In line with data privacy regulations, these data were kept separate from the analytical dataset.

3.3.4 Follow-up

Follow-up contact with each woman in the TASC study was scheduled at 6, 12, 24, 36, and 48 months after study entry. Questionnaires were mailed to the participating women. In some cases, events were reported by the participant or by relatives, friends, or attending physicians between the regular follow-ups.

To minimize loss to follow-up a multi-faceted, four-level follow-up process was established.

- Level 1 activities included mailing the follow-up questionnaire and - in case of no response – mailing of two reminder letters.
- Level 2 activities were initiated if level1 activities did not lead to a response. These included multiple attempts to telephone the woman, her friends, relatives, and gynecologist/primary care physician.
- Level 3 activities were initiated in parallel to level 2 activities. These included searches of national and international telephone and address directories as well as social networks.
- Level 4 activities included an official address search based on centralized or decentralized governmental administration files. Level 4 activity usually

provided information on a new address (or information that the respondent moved abroad or died).

The estimated loss to follow-up for the total study population was about 3%.

3.3.5 Sample Size/Power

The study proposed two analyses: 1) NuvaRing compared to other COCs and 2) NuvaRing compared to COCs that did not contain the progestin desogestrel (DSG) or gestodene (GSD). A third analysis was included due to the ongoing drospirenone (DRSP) controversy: NuvaRing compared to COCs that did not contain the progestin DSG, GSD or drospirenone (DRSP).

The Final Report notes that the study was sufficiently powered to exclude a twofold risk of VTE for NuvaRing users compared to COC_{all} users. The null hypothesis tested is that the hazard ratio (HR) for VTE is equal to or greater than 2. The alternative hypothesis is that HR for VTE less than 2. The report also notes that the study had sufficient power for the second analysis (NuvaRing vs COC_{op}: excluding COCs containing the progestins DSG and GSD), but not for the third ad-hoc analysis (NuvaRing vs. COC_{3p} (excluding COCs containing the progestins DSG, GSD, and DRSP).

For the ATE analysis, hazard ratios were calculated if a minimum of 5 confirmed events were available in each of the comparison groups. Based on this criterion, two ATE analyses were possible: NuvaRing compared to COC_{all} and NuvaRing compared to COC_{op} (all COCs that did not contain the progestin DSG or GSD.

Although the investigators evaluated risks of ATE and death in this population, the proposed sample size was selected to exclude a twofold risk for VTE in the combined cohort of US and European women and a threefold risk for ATE.

The study enrolled 33,295 women with a total 66,489 women-years (WY) of use. The investigators projected they would need more than 33,000 women with 70,000 to 90,000 WY based on an expected VTE incidence of 9.1 per 10,000 WY. According to the investigators' target, the expected power was 79% for 70,000 WYs, 84% for 80,000 WYs and 88% for 90,000 WYs. Actually with only 66,489 WYs accrued, the power was around 64.7% for the as treated analysis and 76% for the intent-to-treat analysis.

3.3.6 Statistical Analyses

The initial statistical analysis plan (SAP) proposed to analyze the data using two analytical methods: 1) the "as treated" (AT) population and 2) the "intention to treat" (ITT) population although the investigators note that the AT analysis is more appropriate to assess safety risk. Descriptive analyses and Cox Regression modeling were planned. The SAP was modified on November 15, 2010 to take into considerations concerns of the Safety Monitoring and Advisory Council that there is "strong evidence to suggest an increased risk of VTE each time COC use is recommenced after a period of discontinued use." The council requested that the investigators amend the statistical analysis plan by adding sub-analyses of recurrent use (starters, switchers and re-starters with and without gaps).

3.4 STUDY RESULTS

A total of 33,295 women with complete analyzable baseline records were enrolled in the study: 16,864 women used NuvaRing, 16,431 used COCs. Among the COC users, 2,620 used COCs containing DSG or 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 generally 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.

Ad hoc analyses comparing US and European women demonstrated more regional differences (Table 1). More US than European women were younger than 30 years of age (73% US vs. 61% EU), and used other medications (23% vs. 10%) especially psychotropic drugs (12% vs. 1%). US women also were more likely to be prescribed contraceptive products with estrogen (ethinyl estradiol (EE)) doses less than 30 ug. (57% vs. 41%). Except for endometriosis and other conditions where European women were more frequently prescribed hormonal contraceptives (3.4% vs. 1.7% and 6.0% vs. 4.6% respectively), US women were more likely to be prescribed a hormonal contraceptive for the following conditions: acne/PCOS (11% vs. 9%), premenstrual syndrome (13% vs. 5%) menstrual bleeding (10% vs. 9%), painful period (17% vs. 11%), and ovarian cysts (5% vs. 4%). Overall, the NuvaRing was prescribed less frequently than COCs for all of these other conditions.

Table1: Proportion of baseline characteristics for combined hormonal contraceptive users in the TASC Study, for all study subjects and by region.

Age (years)	US Women	European Women	All Women
< 30	72.5	60.9	67.0
30+	27.5	39.1	33.0
Other Medications	23.4	10.0	10.0
Psychotropics	11.8	1.4	1.4
Education			
>18 years	8.4	11.7	10.0
Reason for use			
Acne/PCOS	10.5	8.5	9.5
PMS	12.8	5.2	9.2
Bleeding	10.1	8.7	9.4
Painful period	16.6	10.9	13.7
Endometriosis	1.7	3.4	2.5
Ovarian cyst	4.6	3.9	4.3
Other	4.6	6.0	5.3
Ethinyl Estradiol dose			
< 30 ug	56.5	40.6	40.6
Loss to Follow-up	2.6	3.2	2.9

Over the 4 years of the study, loss-to-follow-up was minimal at 2.9% but was slightly lower in the US (2.6%) than in Europe (3.2%). Generally, duration of use in both regions was shorter (20 months Europe; 13 months US) for the NuvaRing than for the COCs (21 months Europe, 19 months US).

Although use of drospirenone (DRSP)- and levonorgestrel (LNG)-containing COCs were more frequently used in both regions, there was little overlap in the use of other progestin-containing products prescribed (Table 2).

Table2: Proportion (%) of combined oral contraceptives used in the TASC Study by progestin type, for all study subjects and by region

	US Women	European Women	All Women
Progestins of COCs			
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	--	1.4
Other	0.8	0.3	0.4
GSD (gestodene)	--	12.4	6.4
DNG (dinogest)	--	11.6	6.1
CMA (chlomadinoacetate)	--	6.9	3.6
CPA (cyproteroacetate)	--	5.6	2.9
N/A – not approved in the region			

Although this study collected information on and was able to adjust for BMI, family history of VTE/ATE, and smoking, very small baseline differences were noted between NuvaRing Users and other COCs users within region for BMI and family history. Observed but small differences were noted across treatment groups within each region mostly for smoking.

Venous Thromboembolic Events (VTE)

Over the study period, a total of 171 VTE events were reported and 57 (33%) were confirmed. The incidence rate per10,000 woman-years (WY) for NuvaRing, other COCs and COCs without desogestrel/gestodene is 8.3, 9.2, and 8.9 respectively, all with overlapping confidence intervals (Table 3).

The incidence rate (IR) was higher for the $COC_{DSG/GSD}$ sub-cohort than for any other sub-group suggesting that users of $COC_{DSG/GSD}$ may differ from women using the NuvaRing or those using COC_{op} or COC_{3p}.

Table 3: Incidence rates (IR) per 10,000 women-years (WY) for venous and arterial thrombotic and thromboembolic events (VTE/ATE) in NuvaRing and combined oral contraceptive (COC) sub-groups.

Sub-Group	VTE IR/10,000 WY		ATE IR/10,000 WY	
NuvaRing	8.3	(5.0-12.9)	2.2	(0.7-5.1)
COC	9.2	(6.0-13.5)	2.8	(1.2-5.6)
$COC_{DSG/GSD}$	10.6	(3.4-24.7)	4.2	(0.5-15.3)
COC_{op}	8.9	(5.5-13.6)	2.5	(0.9-5.5)
COC_{3p}	8.5	(4.5-14.6)		
No Use (discontinued use)	8.0	(4.1-14.4)	2.2	(0.5-6.4)
US	8.9			
Europe	8.5			

VTE= venous thromboembolic events; COC=combined oral contraceptive; WY= women-years; DSG = desogestrel; GSD = gestodene; COC_{op} = combined oral contraceptive containing progestins other than DSG and GSD; COC_{3p} = combined oral contraceptives containing progestins other than DSG, GSD, and drospirenone.

This is emphasized by the fact that the adjusted (age, BMI, duration of current use, family history of VTE) relative risk, summarized using the hazard ratio (HR) is not very different from the crude HRs although the 95% confidence intervals for the adjusted estimates were slightly narrower (Table 4). Although sub-cohort study results are presented in Table 4, the non-inferiority design of the study was not powered to assess differences for the sub-groups other than with COC_{op}.

Table 4: Crude and adjusted hazard ratio (HR) from the Cox regression analyses of VTE comparing NuvaRing to combined oral contraceptive (COC) cohort and sub-cohorts.

	VTE	WY	HR_{crude}	95% CI	HR_{adj}	95% CI
NuvaRing/COC	19/26	22,927/28,252	0.9	0.5-1.6	0.8	0.5-1.5
Sub-Cohort comparisons						
NuvaRing/COC_{op}	19/21	22,927/23,535	0.9	0.5-1.8	0.8	0.4-1.7
NuvaRing/ $COC_{DSG/GSD}$	19/5	22,927/4,717	0.8	0.2-2.7	0.7	0.3-2.3
NuvaRing/COC_{3p}	19/13	22,927/15,260	1.0*	0.5-2.1	--	--

VTE= venous thromboembolic events; COC=combined oral contraceptive; WY= women-years; CI = confidence intervals; adj = adjusted for age, BMI, duration of current use, family history of VTE; DSG = desogestrel; GSD = gestodene; COC_{op} = combined oral contraceptive containing progestins other than DSG and GSD; COC_{3p} = combined oral contraceptives containing progestins other than DSG, GSD, and drospirenone.

**Study not powered for this analysis*

Arterial Thrombotic Events (ATE)

There were 17 ATEs observed in the study: 6 acute myocardial infarctions (AMIs), 5 ischemic strokes, 5 transient ischemic strokes (TIAs) and 1 complete thrombosis of a peripheral artery.

Table 3 summarizes the incidence rates for ATE and Table 5 presents the results of the relative risk (HR) analysis in the COC sub-cohorts for ATE.

Again, the incidence rates were higher for the $COC_{DSG/GSD}$ sub-cohort (4.2/10,000 WY) compared to the NuvaRing (2.2/10,000 WY) and COC_{op} (2.5/10,000 WY) suggesting that users in DSG/GSD sub-cohort could be at higher risk of ATE as well either because of the contraceptive product used or prescribed the specific contraceptive product because of higher baseline risk factors. The products were frequently prescribed to women with menstrual problems.

The HR_{adj} comparing ATE risks in NuvaRing users with COC and COC_{op} users were 0.7 (95% CI – 0.2-2.3) and 0.8 (95% CI = 0.2-2.6) respectively (Table 5).

The report notes that the study was powered to assess no less than a threefold or higher risk of ATE between NuvaRing use compared to COC use.

Table 5: Crude and adjusted hazard ratio(HR) from the Cox regression analyses of ATE comparing NuvaRing to combined oral contraceptive (COC) cohort and sub-cohorts.

	ATE	WY	HR_{crude}	95% CI	HR_{adj}	95% CI
NuvaRing/COC	5/8	22,927/28,252	0.8	0.3-2.5	0.7	0.2-2.3
NuvaRing/COC_{op}	5/6	22,927/23,535	0.9	0.3-3.0	0.8	0.2-2.6

ATE= arterial thrombotic events; COC=combined oral contraceptive; CI = confidence intervals; adj = adjusted for age, BMI, smoking, treated hypertension; COC_{op} = combined oral contraceptives containing excluding the two progestin DSG and GSD.

3.5 STUDY CONCLUSIONS

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). Results from this study show that both the incidence and relative risks of VTE and ATE among NuvaRing users are similar to the risks observed for COC users. Based on sample size and study power, the study can determine that the VTE and ATE incidence rates are similar for the NuvaRing and COC cohorts. The study can rule out a two-fold increased risk of VTE and a threefold increased risk of ATE for NuvaRing users compared to COC users can be excluded. The study cannot conclude there is no risk between the groups, however.

Results from a priori defined sub-analyses that excluded desogestrel/gestodene-containing COCs and post-hoc defined sub-analyses that excluded desogestrel/gestodene/drospirenone-containing progestins were consistent with the results of the primary VTE analyses albeit the study was not powered for the ad-hoc analysis.

4 DISCUSSION

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, as designed, has many advantages that more recent administrative or claims-based contraceptive studies lack. The investigators enrolled approximately equal numbers of US and European women in a study using the same protocol and all centers were managed by the same coordinating center. This study, therefore, allowed a meaningful comparison of prescribing patterns and indication for use between the two regions that ultimately could confound risk estimates. Another major advantage of this study is the direct contact with users both at baseline and during the long follow-up. Although subject to recall bias on some elements, direct interviews are better able to capture lifetime history of contraceptive use, family history of VTE and ATE, and personal history of VTE than automated databases. Weight and height and smoking information can be measured at baseline and changes in status recorded during follow-up. During each follow-up contact, the women had the opportunity to report not only events of interest but any event, provide contact information of the treating medical provider, and give permission to the investigators to contact the medical providers if needed. The events were confirmed or ruled out by the treating physician(s).

Despite some variation, loss to follow-up was low across all countries and regions. Validation of reported events by the attending physicians as well as the availability on exact exposure information reduced the impact of information bias substantially.

Nonetheless, such a study is expensive and time consuming especially when used to assess rare outcomes. Therefore enrollment was targeted at ruling out no less than a twofold increased risk of VTE and a threefold increased risk of ATE. Although the results appear to show no difference in relative risk when NuvaRing is compared to any combined oral contraceptives, the study was actually designed to exclude a two-fold risk (that means the test group is not worse than the control group by no more than doubling of the VTE rate). This design is called a non-inferiority study. Therefore even if the upper confidence interval limit of the true relative risk of VTEs is less than 2 (or 3 for ATE), this does not necessarily mean that there is “no difference in relative risk”.

Regional differences among users are likely controlled to some extent by adjusting for BMI and smoking, two of the most important differences seen across the two regions. Nonetheless, remaining regional differences are observed (Table 6). Both incidence rate ratios and unadjusted hazards ratios were similar within region, but relative risks in the US regions were slightly lower than those in Europe. When adjusting for important VTE confounders (age, BMI, duration of current use, and family history of VTE), the hazard ratios were slightly lower, the 95% confidence intervals were narrower, but the regional differences remained, albeit all confidence intervals overlapped. Although the differences were quite small, the adjusted HRs for VTE changed more for European

women than for US women. It is possible that smoking[b] which is more common in European women than US women contributed to the slightly higher VTE risk estimates observed for Europeans.

Table 6: Incidence rates, incidence rate ratios and Hazard Ratios for confirmed venous thromboembolic events (VTE) by region (US and Europe)

	Incidence Rate (IR) pre 10,000 women-years				Hazard Ratios (HR)			
	NuvaRing	**COC**	**IRR**	**95% CI**	**HR $_{crude}$**	**95% CI**	**HR $_{adj*}$**	**95% CI**
Overall	8.3	9.2	0.9	0.5-1.7	0.9	0.5-1.6	0.8	0.5-1.5
US	7.5	10.3	0.7	0.3-1.9	0.7	0.3-1.8	0.7	0.3-1.7
Europe	8.8	8.2	1.1	0.4-2.6	1.1	0.5-2.4	1.0	0.5-2.3

adj: adjusted for age, BMI (body mass index0, current duration of use, and family history of VTE
CI: Confidence Intervals: COC: combined oral contraceptive

Results from this study show that both the incidence and relative risks of VTE and ATE among NuvaRing users were lower than a twofold risk for VTE (threefold for ATE) when compared to all COC users. Based on sample size and study power, the study can rule out a two-fold overall increased risk of VTE and a threefold overall increased risk of ATE for NuvaRing users compared to all COC users. This is a so-called non-inferiority study design. Even if the upper confidence interval limit of the true relative risk of VTEs is less than 2 (or less than 3 for ATE), this does not necessarily mean that there is "no difference in relative risk".

And although the investigators provided many sub-group and ad hoc analyses requested by the Safety Council and regulators, the study did not have the power to determine statistically significant risk differences for these subgroups.

5 PROPOSED LABEL CHANGE

Based on the results of this study and those of the FDA study posted on the FDA website (http://www.fda.gov/downloads/Drugs/DrugSafety/UCM277384.pdf), the sponsor proposes to include the epidemiologic summary information, excepted in Appendix 1, in the revised label.

Text preceding Figure 1 including Figure 1 in Appendix 1 reflect the standard language in the current label of several other hormonal products and OSE/DEPI has no additional comment for this section.

The following text is specific to the TASC study results.

A large prospective, observational study, the Transatlantic Active Surveillance on Cardiovascular Safety of NuvaRing (TASC), investigated the risk of VTE for new users, (b) (4) *in a population that is representative of routine clinical users. The women were followed for 24 to 48 months. The results showed a similar risk of VTE among NuvaRing users (VTE incidence 8.3 per 10,000 WY) and women using COCs (VTE incidence 9.2 per*

[b] *The covariates age, BMI, duration of current use, and family history of VTE were used to adjust relative risk estimates for VTE; the covariates age, BMI, **smoking**, and treated hypertension were used to adjust risk estimates for ATE.*

10,000 WY). [redacted] (b) (4)

[redacted] (b) (4)

A more appropriate statement based on the original study objectives would be:

For women using COCs, excluding desogestrel (DSG) and gestodene (GSD), VTE incidence was 8.9 per 10,000 WY.

More importantly, however, is the differences in information generated between the text leading to Table 1 in the label and the information presented in the table itself.

A retrospective cohort study using data from 4 health plans in the US (FDA-funded Study in Kaiser Permanente and Medicaid databases) showed [redacted] (b) (4)

The text should be revised to provide incidence rate information for comparable groups in both studies given that comparable groups are available.

As written, the text presents incidence rates for the

TASC study
- a. NuvaRing: 8.3 per10,000 WY
- b. COCs (all): 9.2 per 10,000 WY

[redacted] (b) (4)

Incidence rates for comparable groups would include the following

TASC study
- a. NuvaRing: 8.3 per10,000 WY
- b. COCs (all): 9.2 per 10,000 WY
- c. COCs (excluding DSG, GSD) 8.9 per 10,000 WY

FDA study:
- a. NuvaRing: 11.4 per10,000 WY
- b. Other COCs: 8.2 per 10,000 WY
- c. LNG 9.2 per 10,000 WY

In comparison, *a retrospective cohort study using data from 4 health plans in the US (FDA-funded Study in Kaiser Permanente and Medicaid databases) showed VTE incidence for new users of NuvaRing of 11.4 events per 10,000 WY,* 8.2 events per 10,000 WY for new users of other COCs available during the course of the study, and similar incidence rates *for new users of levonorgestrel (LNG)-containing COCs of 9.2 events per 10,000 WY.*

6 RECOMMENDATIONS

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.

OSE/DEPI has two recommendations specific to NuvaRing label information based on the results of the TASC study and the FDA funded study.

1. The TASC study was powered to assess no less than a twofold risk of VTE for NuvaRing when compared to all COCs and to COCs that do not contain the progestins desogestrel (DSG) and gestodene GSD. (b) (4) OSE/DEPI recommends including the incidence rates and Hazard Ratio risk estimates for the comparisons initially proposed by and powered for the study.
    a. VTE incidence rate for COC without (DSG and GSD): 8.9 per 10,000 WY in the text (b) (4)
    b. HR_{adj} 0.8 (0.4-1.7) in Table 1 instead of (b) (4) when comparing with COCs that exclude DSG and GSD
2. The second recommendation is to align the VTE incidence rate information for the FDA funded study to those presented for the TASC study. As written, the text presents incidence rates for the

    TASC study
    a. NuvaRing: 8.3 per10,000 WY
    b. COCs (all): 9.2 per 10,000 WY

    (b) (4)

    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. OSE/DEPI recommends using the following comparisons for the incidence rates in the text preceding Table 1:

    TASC study
    a. NuvaRing: 8.3 per10,000 WY
    b. COCs (all): 9.2 per 10,000 WY
    c. COCs (excluding DSG, GSD) 8.9 per 10,000 WY

    FDA study:
    a. NuvaRing: 11.4 per10,000 WY
    b. Other COCs: 8.2 per 10,000 WY
    c. LNG 9.2 per 10,000 WY

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4 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

APPENDIX 3: DBVII TASC REPORT

DBVII Tasc Study Report

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

/s/

RITA P OUELLET-HELLSTROM
08/27/2013

DAVID G MOENY
08/27/2013

JUDY A STAFFA
08/27/2013

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: 21187 /S-021

Application Type: Efficacy Supplement with Clinical Data (SE-8)

Name of Drug: NuvaRing® (etonogestrel/ethinyl estradiol) vaginal ring

Applicant: Organon USA, Inc.

Submission Date: December 5, 2012

Receipt Date: December 5, 2012

Regulatory History and Applicant's Main Proposals

On August 30, 2012, Organon USA, Inc. submitted a Prior Approval Supplement to update the NuvaRing labeling based on the results of the "*Transatlantic Active Surveillance on Cardiovascular Safety of Nuvaring®*" and the FDA-funded study entitled, "*Combined Hormonal Contraceptives and the Risk of Cardiovascular Disease Endpoints."*

On October 31, 2012, an Unacceptable for Filing Letter, requesting a User Fee, and a request for Physician's Labeling Rule (PLR) labeling for the prior approval supplement submitted on August 30, 2012.

The Sponsor submitted a User Fee on December 5, 2012, and the PLR labeling on December 20, 2012.

Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in **Word format** by **March 11, 2013**. The resubmitted PI will be used for further labeling review.

Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

YES 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

YES 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been is granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period (for RPMs)**
  - *For efficacy supplements:* If a waiver was previously granted, select "**YES**" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "**NO**" in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of Cycle Period (for SEALD reviewers)**
  - The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

YES 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

NO 4. White space must be present before each major heading in HL.

Comment: *White space is not present before each major heading in the Highlights sections*

YES 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

YES 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a Boxed Warning is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

NO 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

Comment: *Name of drug product is not in Upper Case.*

Product Title

YES 10. Product title in HL must be **bolded.**

Comment:

Initial U.S. Approval

YES 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded,** and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Selected Requirements of Prescribing Information (SRPI)

Boxed Warning

NO 12. All text must be **bolded**.

Comment: *All text is not bolded*

YES 13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

YES 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." centered immediately beneath the heading.

Comment:

YES 15. Must be limited in length to 20 lines (this does not include the heading and statement "***See full prescribing information for complete boxed warning.***")

Comment:

YES 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

YES 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

YES 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

YES 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Dosage and Administration, Coronary Stenting (2.2) --- 3/2012".

Comment:

N/A 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

YES 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)]."

Comment:

Dosage Forms and Strengths

YES 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

YES 23. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known.

Comment:

YES 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

YES 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement

YES 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide."**

Comment:

Revision Date

NO 27. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.

Comment: *Revision date is missing*

Contents: Table of Contents (TOC)

GENERAL FORMAT

YES 28. A horizontal line must separate TOC from the FPI.

Comment:

YES 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS"**.

Comment:

YES 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

NO 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

YES 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS"** must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

YES 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

YES 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

YES 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

YES 42. All text is **bolded**.

Comment:

YES 43. Must have a heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

YES 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

N/A 45. If no Contraindications are known, this section must state "None".

Comment:

Adverse Reactions

NO 46. When clinical trials adverse reactions data is included (typically in the "Clinical Trials Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."

Comment: *Statement is not verbatim - missing the word "clinical"*

YES 47. When postmarketing adverse reaction data is included (typically in the "Postmarketing Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Patient Counseling Information

YES 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Comment:

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

/s/

ZETA-MAE C WILLIAMSON
01/23/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21187/S021

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 21187 SUPPL # 021 HFD #

Trade Name NuvaRing

Generic Name etonogestrel/ethinyl estradiol

Applicant Name Organon USA, Inc.

Approval Date, If Known October 4, 2013

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

SE - 8

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

Add new information to the labeling for NuvaRing based on the findings of two epidemiologic studies that evaluated the risk of venous thromboembolic events compared to other combination hormonal contraceptives.

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA

#(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#	21187	NuvaRing
NDA#	21529	Implanon
NDA#	21529	Nexplanon

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical

investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or

sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Transatlantic Active Surveillance on Cardiovascular Safety of NuvaRing (TASC), AND an FDA-funded Study: *Recent combined hormonal contraceptives (CHCs) and the risk of thromboembolism and other cardiovascular events in new users*.

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the

effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Transatlantic Active Surveillance on Cardiovascular Safety of NuvaRing (TASC), AND an FDA-funded Study: *Recent combined hormonal contraceptives (CHCs) and the risk of thromboembolism and other cardiovascular events in new users*.

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # YES ☐ ! NO ☐
! Explain:

Investigation #2

IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☒
Explain:	! Explain: The study was supervised by an independent Safety Monitoring and Advisory Council that had full authority over the study (including study protocol, protocol amendments, data analysis, and stopping the study). The funder (Organon) had no access to the source data and did not participate in designing or analyzing the study

Investigation #2	!
	!
YES ☐	! NO ☒
Explain:	! Explain: FDA Funded Study (OSE)

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Charlene Williamson
Title: Regulatory Project Manager
Date: November 4, 2013

Name of Office/Division Director signing form: Audrey Gassman, M.D.
Title: Deputy Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

ZETA-MAE C WILLIAMSON
11/22/2013

AUDREY L GASSMAN
11/22/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**Division of Clinical Pharmacology 3** **Office of Clinical Pharmacology** **Tracking/Action Sheet for Formal/Informal Consults**

From: **Chongwoo Yu, Ph.D.**			**To: DOCUMENT ROOM (LOG-IN and LOG-OUT)** **Please log-in this consult and review action for the specified IND/NDA submission**	
DATE: 8/9/2013	IND No.: Serial No.:	NDA No.: 021187 Suppl. No.: 021, 022	DATE OF DOCUMENT 8/30/2012 (s-021; SDN 791) 12/20/2012 (s-022; SDN 815) 3/12/2013 (s-021; SDN 845)	
NAME OF DRUG **NuvaRing® (11.7 mg etonogestrel/2.7 mg ethinyl estradiol vaginal ring)**	PRIORITY CONSIDERATION		Date of informal/Formal Consult:	

NAME OF THE SPONSOR: Merck Sharp & Dohme Corp.

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE

☐ PRE-IND	☐ DISSOLUTION/IN-VITRO RELEASE	☐ FINAL PRINTED LABELING
☐ ANIMAL to HUMAN SCALING	☐ BIOAVAILABILITY STUDIES	☒ LABELING REVISION
☐ IN-VITRO METABOLISM	☐ IN-VIVO WAIVER REQUEST	☐ CORRESPONDENCE
☐ PROTOCOL	☐ SUPAC RELATED	☐ DRUG ADVERTISING
☐ PHASE II PROTOCOL	☐ CMC RELATED	☐ ADVERSE REACTION REPORT
☐ PHASE III PROTOCOL	☐ PROGRESS REPORT	☐ ANNUAL REPORTS
☐ DOSING REGIMEN CONSULT	☐ SCIENTIFIC INVESTIGATIONS	☐ FAX SUBMISSION
☐ PK/PD- POPPK ISSUES	☐ MEETING PACKAGE ( )	☒ OTHER *(SPECIFY BELOW):*
☐ PHASE IV RELATED		[Efficacy supplement]

REVIEW ACTION

☐ NAI (No action indicated)	☐ Oral communication with	☒ Formal Review/Memo (attached)
☐ E-mail comments to:	Name: [ ]	☐ See comments below
☐Medical ☐Chemist ☐Pharm-Tox	☐ Comments communicated in	☐ See submission cover letter
☐Micro ☐Pharmacometrics ☐Others	meeting/Telecon. see meeting minutes	☐ OTHER *(SPECIFY BELOW)*:
(Check as appropriate and attach e-mail)	dated: [ ]	[ ]

REVIEW COMMENT(S)

☐ **NEED TO BE COMMUNICATED TO THE SPONSOR** ☐ **HAVE BEEN COMMUNICATED TO THE SPONSOR**

INDICATION: Prevention of pregnancy

OBJECTIVE: Efficacy supplement (s-021) and prior approval labeling supplement (s-022)

BACKGROUND: Sponsor submitted an efficacy supplement (s-021) and a prior approval labeling supplement (s-022) to New Drug Application (NDA) 021187 (originally approved on October 3, 2001) for NuvaRing® (11.7 mg etonogestrel/2.7 mg ethinyl estradiol [EE] vaginal ring) on August 30, 2012 and December 20, 2012, respectively. One NuvaRing® should be inserted in the vagina and remain in place continuously for 3 weeks followed by a 1 week ring-free interval.

Efficacy Supplement (s-021)

On September 7, 2007, the Agency requested the Sponsor to conduct a U.S. epidemiological study to evaluate the risk of serious thrombotic and thromboembolic events for NuvaRing® users compared to users of a low dose combination oral contraceptive (COC) product. In the submission dated August 30, 2013, the Sponsor submitted the final report of the clinical study entitled, "Transatlantic Active Surveillance on Cardiovascular Safety of NuvaRing® (TASC)." The Sponsor also provided their proposed edits to the NuvaRing® product label based on the study results of the TASC study in this supplement. Subsequently, the Sponsor submitted a revision on March 12, 2013, with proposed labeling updates for NuvaRing® based on the TASC study in a physician labeling rule (PLR) format.

Reviewer's Comment: *There was no new Clinical Pharmacology information submitted in issues in the efficacy supplement (i.e., TASC study). Therefore, this review only pertains to the PLR conversion.*

Prior Approval Labeling Supplement (s-022)

The Sponsor submitted a prior approval labeling supplement (s-022) on December 20, 2012. The purpose of this supplement is to convert the product label that was approved on April 20, 2008 into a PLR format.

Reviewer's Comment: *The Division of Bone, Reproductive, and Urologic Products (DBRUP) plans to take an action on S-021 and S-022 at the same time. Therefore, this review will cover both supplements together based on the latest draft product label submitted by the Sponsor on March 12, 2013.*

Sponsor's Proposed Changes to the Product Labeling

The Sponsor proposed the following edits to the Clinical Pharmacology related sections of the product label. ~~Strikethroughs~~ are used for deletion and double underlines are used for addition to reflect the edits to the Sponsor's proposal. Please note that the parts showed below are limited to those that have edits but do not necessarily represent the entire respective Sections.

Full Prescription Information Contents

Reviewer's Comment: *Sponsor needs to add the following Sections in the contents listing:*
12.2 Pharmacodynamics

Full Prescription Information

7 DRUG INTERACTIONS

Consult the labeling of all concurrently-used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.

7.1 Effects of Other Drugs on Combined Hormonal Contraceptives (CHCs)

(b) (4)

[redacted]

Reviewer's Comment: *Edits were made to be consistent with the recently updated Drug Interactions class labeling (i.e., NDA 204654 Lo Minastrin Fe; approved on July 24, 2013) language for hormonal contraceptives.*

8 USE IN SPECIFIC POPULATIONS

(b) (4)

Reviewer's Comment: *Edits were made to be consistent with other products in the drug class. The Race subsection has been deleted as there was no additional meaningful information.*

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

(b) (4)

(b) (4)

Reviewer's Comment: *Deleted to avoid redundancy as no additional information compared to Section 8 Use in Specific Populations was added.*

(b) (4)

Reviewer's Comment: *Minor edits were made for clarity and to delete unnecessary contents.*

Recommendation:
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.

SIGNATURE OF REVIEWER: _____	Date _____
SIGNATURE OF TEAM LEADER: _____	Date _____
CC.: DCP3; TL: Kim; DD: Bashaw	**Project Manager:**_____ **Date** _____

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

/s/

CHONGWOO YU
08/30/2013

MYONG JIN KIM
08/30/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR PATIENT LABELING REVIEW CONSULTATION

TO: **CDER-DMPP-PatientLabelingTeam**		FROM: Division of Bone, Reproductive and Urologic Products Attn: Charlene Williamson	
REQUEST DATE: August 26, 2013	NDA/BLA NO.: NDA 21187/S-021 & S-022	TYPE OF DOCUMENTS: Labeling Supplement and PLR Conversion	
NAME OF DRUG: NuvaRing	PRIORITY CONSIDERATION: Priority	CLASSIFICATION OF DRUG: Non-oral contraceptive	DESIRED COMPLETION DATE (Generally 2 Weeks after receiving substantially complete labeling)
SPONSOR: Merck, Sharpe & Dohme		PDUFA Date: October 5, 2013	

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
☒ PATIENT PACKAGE INSERT (PPI)
☐ MEDICATION GUIDE
☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
☐ ORIGINAL NDA/BLA
☒ EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☐ LABELING SUPPLEMENT
☐ MANUFACTURING (CMC) SUPPLEMENT
☒ PLR CONVERSION

REASON FOR LABELING CONSULT
☐ INITIAL PROPOSED LABELING
☒ LABELING REVISION

EDR link to submission: http://darrts.fda.gov:9602/darrts/viewEDR.do?suppDocId=8455622

Please Note: DMPP uses substantially complete labeling, which has already been marked up by the CDER Review Team, when reviewing MedGuides, IFUs, and PPIs. Once the substantially complete labeling is received, DMPP will complete its review within 14 calendar days. Please provide a copy of the sponsor's proposed patient labeling in Word format.

COMMENTS/SPECIAL INSTRUCTIONS:

Labeling Meetings: TBD

Please review Patient Labeling for S-021 – Updated based on FDA-Funded Study and S-022 – PLR Conversion

SIGNATURE OF REQUESTER
Charlene Williamson

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) ☐ eMAIL (BLAs Only) ☐ DARRTS

Version: 12/9/2011

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/s/

ZETA-MAE C WILLIAMSON
08/26/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION** ****Please send immediately following the Filing/Planning meeting****

TO: **CDER-DDMAC-RPM** **Attn: Carrie Newcomer**			FROM: **Division of Bone, Reproductive and Urologic Prods** **Attn: Charlene Williamson**
REQUEST DATE August 26, 2013	IND NO.	NDA/BLA NO. 21187/S-021	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)

NAME OF DRUG NuvaRing	PRIORITY CONSIDERATION Priority	CLASSIFICATION OF DRUG Non-oral contraceptive	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)

NAME OF FIRM: Merck, Sharpe, & Dohme	PDUFA Date: October 5, 2013

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
☒ PACKAGE INSERT (PI)
☒ PATIENT PACKAGE INSERT (PPI)
☐ CARTON/CONTAINER LABELING
☐ MEDICATION GUIDE
☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
☐ ORIGINAL NDA/BLA
☐ IND
☐ EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☐ LABELING SUPPLEMENT
☐ PLR CONVERSION

REASON FOR LABELING CONSULT
☐ INITIAL PROPOSED LABELING
☐ LABELING REVISION

EDR link to submission: http://darrts.fda.gov:9602/darrts/viewEDR.do?suppDocId=8455622
Please review Nuvaring S-021 – PI and PPI based on a FDA-funded Study and S-022 - PLR Conversion. This is a labeling supplement with clinical data.

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

COMMENTS/SPECIAL INSTRUCTIONS:

Labeling Meetings: To Be Scheduled Shorlty

SIGNATURE OF REQUESTER Charlene Williamson

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check all that apply) ☐ eMAIL ☐ DARRTS ☐ HAND

06/18/2013

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/s/

ZETA-MAE C WILLIAMSON
08/26/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Mail: OSE
Attn: Marcus Cato

FROM: **Division of Bone, Reproductive and Urologic Products - Attn: Charlene Williamson**

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
July 5, 2013		21187	Labeling Supplement	December 5, 2012

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
NuvaRing® (etonogestrel /ethinyl estradiol vaginal ring)	**Priority**	Contraceptive	August 16, 2013

NAME OF FIRM: Merck, Sharpe & Dohme Corp.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: *The Sponsor has submitted revised labeling based upon the final study report from the TASC post-marketing safety surveillance study and the FDA-funded study on risk of VTE with hormonal contraception. Please review the final study report of TASC, submitted on December 5, 2012.*

Please review the proposed labeling relating to the risk of VTE in NDA 21-187 and indicate if you concur with the proposed language, or detail any recommended revisions.
EDR Link: http://darrts.fda.gov:9602/darrts/viewEDR.do?suppDocId=8262273

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check all that apply) ☐ MAIL ☐ DARRTS ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

06/18/2013

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/s/

ZETA-MAE C WILLIAMSON
07/04/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 21187/S-021

ACKNOWLEDGEMENT --
PRIOR APPROVAL SUPPLEMENT

Organon USA Inc.
Attention: Ripal Shah, Pharm.D.,
Regulatory Liaison, Global Regulatory Affairs
One Merck Drive
P.O. Box 100
Whitehouse Station, NJ 08889

Dear Dr. Shah:

We have received your Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 21187

SUPPLEMENT NUMBER: 021

PRODUCT NAME: NuvaRing® (etonogestrel/ethinyl estradiol) Vaginal Ring

DATE OF SUBMISSION: August 30, 2012

DATE OF RECEIPT: August 30, 2012

This supplemental application proposes the following changes to the labeling based on the results of the "*Transatlantic Active Surveillance on Cardiovascular Safety of Nuvaring®*" and the FDA-funded study entitled, "*Combined Hormonal Contraceptives and the Risk of Cardiovascular Disease Endpoints.*"

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on October 30, 2012, in accordance with 21 CFR 314.101(a).

If the application is filed, the goal date will be February 30, 2013.

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at

http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3).

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have questions, call me at (301) 796-1025.

Sincerely,

{See appended electronic signature page}

Z. Charlene Williamson
Regulatory Project Manager
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

ZETA-MAE C WILLIAMSON
10/26/2012