CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-187

ADMINISTRATIVE DOCUMENTS

CONFIDENTIAL

PATENT INFORMATION AND ORIGINAL DECLARATION

PATENT INFORMATION

21 CFR §314.53 (c)(1)

(i) U.S. Patent No. 5,989,581

Expiration Date: April 8, 2018

(ii) Type of patent: product (all claims are directed to a "drug delivery system")

(iii) Name of patent owner: Akzo Nobel N.V.
Arnhem, Netherlands

(iv) Name of Agent: William Blackstone, Esq.
Akzo Nobel Patent Dept.
1300 Piccard Drive, Suite 206
Rockville, MD 20850-4373

ORIGINAL DECLARATION

21 CFR §314.53 (c) (2)

The undersigned declares that U.S. Patent No. 5,989,581 covers the formulation, composition and/or method of use of NuvaRing®. This product is the subject of this application for which approval is being sought.

Patrick J. Osinski
Vice President
Organon Inc.

EXCLUSIVITY SUMMARY for NDA # 21-187 SUPPL # _____

Trade Name -NuvaRing (etonogetsrel/ethinyl estradiol vaginal ring) Generic Name _____
Applicant Name Organon, Inc. HFD- 580
Approval Date _____

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain 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 an original NDA? YES/_X_/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /_X_/

      If yes, what type(SE1, SE2, etc.)? _____

   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 /_X_/ 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:

      _____

      _____

d) Did the applicant request exclusivity?

YES /_X_/ NO /___/

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

5 years

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

YES /___/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (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 /_X_/ NO /___/

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

NDA # 20-713 ethinyl estradiol

NDA # 20-071 ethinyl estradiol

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

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 /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(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 /_X_/ 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 9:**

_____

_____

(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 /_X_/

(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 /_X_/

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:

Investigation #1, Study # 068003

Investigation #2, Study # 34219

Investigation #3, Study # _____

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 /_X_/
Investigation #2	YES /___/	NO /_X_/
Investigation #3	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:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(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 /_X_/

Investigation #2 YES /___/ NO /_X_/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(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"):

Investigation #_1_, Study # 068003

Investigation #_2_, Study # 34219

Investigation #__, Study # _____

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 # [redacted] YES /_X__/ NO /___/ Explain: _____

_____

Investigation #2

IND # [redacted] YES /_X__/ 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 /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(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 /_X_/

If yes, explain: _____

_____

_____

_____ _____

Signature of Preparer Date

Title:_____

_____ _____

Signature of Office or Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

CLAIMED EXCLUSIVITY

21 CFR §314.50(j)(1) and (2)

Organon Inc. claims, and is entitled to, the marketing exclusivity set forth in 21 C.F.R. §314.108(b)(4) and provides the following additional information in support thereof.

21 CFR §314.50(j)(4)(i)

Organon Inc. hereby certifies, to the best of its knowledge, that NDA 21-187 contains clinical investigations which meets the definition of "new clinical investigation" set forth in 21 C.F.R. §314.108(a).

21 CFR §314.50(j)(4)(ii)

A list of all published studies and publicly available reports of clinical investigations known to Organon Inc. through a literature search that are relevant to the conditions for which Organon Inc. is seeking approval is provided in the Clinical Section of this NDA. Please see Vols. 145 and 146 of NDA 21-187 and to any INDs and NDAs as may be cross-referenced in support of NDA 21-187, all of which are incorporated herein by reference.

Organon Inc. hereby certifies that it has thoroughly searched the scientific literature and, to the best of its knowledge, the lists referenced above are complete and accurate. Organon Inc. further certifies that, in its opinion, these published studies and publicly available reports do not provide a sufficient basis for the approval of the conditions for which Organon Inc. is seeking approval without reference to the new clinical investigation(s) in NDA 21-187. The reason why the above referenced lists of published studies and reports are insufficient is that these studies and reports do not specifically evaluate the safety and efficacy of NuvaRing®, the product which is the subject of this application for which approval is being sought. To the best of its knowledge, Organon believes that there are no published studies or publicly available reports describing the safety and efficacy of NuvaRing®, the product which is the subject of this application for which approval is being sought. The new clinical investigation(s) referenced in NDA 21-187 provide(s) the necessary raw data, methodology and statistical analyses allowing for a conclusion that NuvaRing® is "safe for use" and "will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, [and] suggested in the proposed labeling thereof." See Section 505(d) (1) and (5) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. 355(d)(1) and (5).

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21 CFR §314.50(j)(4)(iii)

Organon Inc.'s Study Nos. 068003 , which is essential to the approval of NDA 21-187 and meets the definition of "new clinical investigation" set forth in 21 C.F.R. §314.108, was conducted under IND [redacted] Organon Inc. certifies that it was the sponsor named in the Form FDA-1571 for this IND [redacted] for Study No. 068003. Organon Inc.'s Study No. 34219, which is also "essential to the approval" of NDA 21-187 and meets the definition of "new clinical investigation" was sponsored and conducted by Organon Inc.'s affiliate N.V. Organon. Organon Inc.'s Study No. 34219, which was not required to be conducted under IND [redacted] should be considered to meet the requirement of being "conducted or sponsored by" Organon Inc. in that both Organon Inc. and N.V. Organon are under common ownership and control.

Patrick J. Osinski
Vice President
Organon Inc.

CERTIFICATION

Pursuant to Section 306(k)(1) of the Federal Food, Drug and Cosmetic Act, the undersigned certifies that Organon Inc. did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) [Section 306(a) or (b)], in connection with the New Drug Application for NuvaRing® (etonogestrel/ethinyl estradiol ring), NDA 21-187.

Albert P. Mayo
Executive Director
Regulatory Affairs

FDA Links Tracking Links Check Lists Searches Reports Help

PEDIATRIC PAGE (Complete for all original application and all efficacy supplements) View Word Document

NDA Number:	021187	**Trade Name:**	NUVARING(ESTRADIOL RING/ETHINYL/ESTONOGE
Supplement Number:	000	**Generic Name:**	ESTRADIOL RING/ETHINYL/ETONOGESTREL
Supplement Type:	N	**Dosage Form:**	
Regulatory Action:	OP	**COMIS Indication:**	PREVENTION OF PREGNANCY WHILE PROVIDING EXCELLENT MENSTRUAL CYCLE CONTROL IN WOMEN WHO ELECT CONTRACEPTIVES AS A METHOD OF CONTRACEPTION
Action Date:	12/28/00		

Indication # 1 contraception

Label Adequacy: Does Not Apply

Forumulation Needed: NO NEW FORMULATION is needed

Comments (if any): Safety and efficacy of NuvaRing have been established in women of reproductive age. Safety and Efficacy are expected to be the same for postpubertal adolescents under 16 years of age and older. Use of this product before menarche is not indicated.

	Lower Range	Upper Range	Status	Date
Tanner5	Adult		Waived	10/4/00

Comments: Safety and efficacy of NuvaRing have been established in women of reproductive age. Safety and Efficacy are expected to be the same for postpubertal adolescents under 16 years of age and older. Use of this product before menarche is not indicated.

This page was last edited on 12/4/00

/S/ 12/4/00

Signature Date

PEDIATRIC PAGE (Complete for all original application and all efficacy supplements)

View as Word Document

NDA Number:	021187	**Trade Name:**	NUVARING(ESTRADIOL RING/ETHINYL/ESTONOGE
Supplement Number:	000	**Generic Name:**	ESTRADIOL RING/ETHINYL/ETONOGESTREL
Supplement Type:	N	**Dosage Form:**	
Regulatory Action:	AE	**COMIS Indication:**	PREVENTION OF PREGNANCY IN WOMEN WHO ELECT TO USE THIS PRODUCT AS A METHOD OF CONTRACEPTION.
Action Date:	12/22/00		

Indication # 1 contraception

Label Adequacy: Does Not Apply

Formulation Needed: NO NEW FORMULATION is needed

Comments (if any): Safety and efficacy of NuvaRing have been established in women of reproductive age. Safety and Efficacy are expected to be the same for postpubertal adolescents under 16 years of age and older. Use of this product before menarche is not indicated.

Ranges for This Indication

Lower Range	Upper Range	Status	Date
Tanner5	Adult	Waived	10/4/00

Comments: Safety and efficacy of NuvaRing have been established in women of reproductive age. Safety and Efficacy are expected to be the same for postpubertal adolescents under 16 years of age and older. Use of this product before menarche is not indicated.

This page was last edited on 4/20/01

/S/

Signature

4/20/01

Date

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA Number: N 021187
Trade Name: NUVARING(ESTRADIOL RING/ETHINYL/ESTONOGE
Generic Name: ESTRADIOL RING/ETHINYL/ETONOGESTREL
Supplement Number. 000 **Supplement Type**: N
Dosage Form:
Regulatory Action: ~~AE~~ AP **Action Date**: ~~12/22/00~~ 10/3/01
COMIS Indication: PREVENTION OF PREGNANCY IN WOMEN WHO ELECT TO USE THIS PRODUCT AS A METHOD OF CONTRACEPTION.

Indication #1: contraception
Label Adequacy: Does not apply
Formulation Needed: No new formulation is needed
Comments (if any) Safety and efficacy of NuvaRing have been established in women of reproductive age. Safety and Efficacy are expected to be the same for postpubertal adolescents under 16 years of age and older. Use of this product before menarche is not indicated.

Lower Range	Upper Range	Status	Date
Tanner5	Adult	Waived	10/4/00

Comments: Safety and efficacy of NuvaRing have been established in women of reproductive age. Safety and Efficacy are expected to be the same for postpubertal adolescents under 16 years of age and older. Use of this product before menarche is not indicated.

This page was last edited on 9/19/01

Signature /S/ Date 9/19/01

DEC 22 2000

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 22, 2000

FROM: Florence Houn MD MPH /S/

SUBJECT: Office Director's Memo

TO: NDA 21,187 NuvaRing (etonogestrel/ethinyl estradiol ring)

This memo documents my concurrence with the recommendation of the Division of Reproductive and Urologic Drug Products to approve NuvaRing for pregnancy prevention in women who select this method; however, the professional and patient labeling remain under discussion between FDA and the manufacturer (Organon), so an approvable action will be taken.

This product is a new method of birth control. It is a flexible, vaginal ring that is inserted monthly and releases a third generation progestin and ethinyl estradiol (combination contraceptive). The efficacy of the product is documented in the medical reviews from the division and its contraceptive properties are comparable to other approved hormonal contraceptives. Safety issues surrounding this product are similar to other third generation progestin contraceptives--possible increased risk of venous thromboembolic events (VTE), to combined hormonal contraceptive products in general—bleeding pattern irregularities, and to a product that is used in the vagina—local irritation, expulsion, discomfort, etc. Remaining questions surrounding drug interaction with multiple-dose vaginal anti-fungal products, tampons, and pregnancy outcomes are to be addressed in phase 4 studies. Providing chemistry methods validation for a non-automated system will also be addressed post-marketing. Each of the post-marketing studies has specified timeframes to ensure commitments are being pursued.

My labeling comments were conveyed to the division. Most were clarifications. One issue that needs to be understood clearly by users is what additional contraceptive method is acceptable to use with this product during the first week. The earlier labeling and patient insert seem to imply any other barrier method is acceptable; however, the sponsor now has stated diaphragms would not be appropriate to use. This leaves the male condom, both with or without spermicide. If these are the only acceptable methods, then these clear choices should be stated. My view on the clinical trials section for contraceptives is if during the product's development special issues arise and need to be highlighted, these can be mentioned in the clinical trials section. For [redacted] the FDA was concerned that the bleeding pattern was more problematic than other methods and the data were presented for users. For this product, there are no particular issues that require a clinical trials section.

Finally, the patient insert is very important given this new method and its reliance on user compliance and technique. FDA was very careful in seeking multiple input from agency experts on communication to ensure the patient insert is understandable. Suggestions were made for pictures in the patient insert as well.

DEC 22 2000

Division Director Memorandum

NDA#:	**21-187**
Drug:	**NuvaRing® (etonogestrel/ethinyl estradiol vaginal ring)**
Indication:	**Prevention of pregnancy**
Dose:	**Daily in vitro release of 0.120 mg etonogestrel and 0.015 mg ethinyl estradiol**
Administration:	**Intravaginal ring placement daily for 21 days, followed by a ring-free interval of 7 days**
Formulation:	**Intravaginal ethylene vinylacetate ring containing 11.7 mg etonogestrel and 2.7 mg ethinyl estradiol**
Applicant:	**Organon, Inc.**
Date of submission:	**December 29, 1999**
Date of memorandum:	**December 22, 2000**

Background

NuvaRing® is a novel method of combined hormone delivery for contraception. It consists of a single-compartment, ethylene vinyl acetate ring containing 11.7 mg of etonogestrel (the active metabolite of the progestin, desogestrel) and 2.7 mg of ethinyl estradiol. NuvaRing® releases 0.120 mg of etonogestrel and 0.015 mg of ethinyl estradiol daily in *in vitro* testing. It was developed as an intravaginal contraceptive to be placed and remain in the vagina for 21 consecutive days followed by ring removal during the last 7 days of a 28-day menstrual cycle. The ring has an external diameter of 54 mm, comparable in size to a contraceptive diaphragm. It offers the advantages of avoidance of hepatic first-pass metabolism and avoidance of daily administration as required with oral contraceptives, the latter of which could be associated with improved user compliance.

Three phase 2 dose-finding studies (study 85012, 86016 and 34218) were conducted to determine the appropriate doses of etonogestrel and ethinyl estradiol for the to-be-marketed formulation of the product. Safety and efficacy of NuvaRing® were primarily evaluated in two, large-scale, phase 3 studies.

Contraceptive efficacy for NuvaRing® was demonstrated in two multi-center, randomized, open-label, noncomparative trials of thirteen cycles' duration (i.e., Study 68003 and Study 34219). Study 68003 was conducted in 47 centers in the United States and 1 center in Canada, while study 34219 was conducted in 53 centers in 11 European countries and Israel. Because the studies were of identical design, data for these studies were pooled for combined analysis.

Study 68003 enrolled a total of 1,210 women aged 18-41 years, 1,117 of who used NuvaRing® for at least 1 day and accounted for 11,188 cycles of exposure to NuvaRing®. Study 34219 enrolled a total of 1,182 women of the same age range, 1,145 of who used NuvaRing® for at least 1 day and accounted for 12,109 cycles of exposure to the product. A total of 2,262 participants enrolled in the two phase 3 studies used NuvaRing®, accounting for a total of 23,297 cycles of exposure to this drug product. A total of 1,501 participants completed thirteen cycles of NuvaRing® use.

Contraceptive effectiveness was based upon the occurrence of in-treatment pregnancy in the intent-to-treat evaluation group. A combined Pearl Index for the two studies of 1.23 was noted for all patients who used NuvaRing®. Since inclusion criteria permitted enrollment of women between the ages of 18-41 years, the total number of women between the ages of 18 and 34 who received NuvaRing® was also reviewed and determined to be 1,920, accounting for 19,053 total cycles of product use. The Pearl Index for women aged 18-34 who used NuvaRing® was 1.30 per 100 woman-years of use. Both Pearl Indices support the contraceptive effectiveness of this product.

Safety analyses for NuvaRing® focused on those issues unique to an intravaginal product (i.e., local effects such as irritation, inflammation and infection) as well as those associated with combined hormonal contraceptive products, particularly menstrual bleeding pattern alterations and venous thromboembolic events (VTEs). In addition, expulsion rates and product tolerability were evaluated in the trials conducted.

Bleeding pattern alterations associated with NuvaRing® use were assessed primarily from the two phase 3 trials in which daily bleeding diaries were completed by study participants. Although the sponsor sought to incorporate in the product label data on bleeding pattern alterations from three small-scale comparative trials of NuvaRing® versus an approved oral contraceptive, none of these trials was appropriately powered for superiority *a priori* and therefore comparative claims in the product label were not permitted. Non-comparative, descriptive statements regarding bleeding pattern alterations noted in the phase 3 trials with NuvaRing® were included in the warnings section of the product label.

Of note, a single venous thromboembolic event (VTE), namely a deep venous thrombosis (DVT) occurred in a 26 year old NuvaRing® user during her first cycle of product use. Several epidemiologic studies have reported that third generation oral contraceptive products including those containing desogestrel (the parent compound for etonogestrel) are associated with an approximate two-fold increase in risk for VTE when compared to second generation oral contraceptives. Other studies have not shown this two-fold increase in risk. Because of these findings, labeling for all FDA-approved desogestrel-containing hormonal contraceptive products was recently modified to include a summary statement regarding VTE risk with such products. Since etonogestrel is the active metabolite of desogestrel (one of the third-generation progestins that has been associated with an increased risk for VTE), the label for NuvaRing® will include the same text on VTE risk as that found in other FDA-approved desogestrel-containing contraceptive products.

Complete or partial expulsion of NuvaRing® was noted in 1.6% and 0.6%, respectively, of participants in six trials of NuvaRing®, and the majority of patients and their partners never or rarely felt NuvaRing® during intercourse.

The most common adverse events (AEs) leading to product discontinuation were device-related problems (occurring in 2.5% of users) and vaginal symptoms (occurring in 2.2% of users). Although vaginitis was the most commonly reported AE in the studies, occurring in 14.1% of 2,501 NuvaRing® users, a causal relationship between NuvaRing® use and vaginitis could not be definitively determined. Significant vaginal irritation was not noted on colposcopic examination in either the phase 3 studies or a separate local effects study (study 68004).

Twenty-two pregnancies were conceived following exposure to NuvaRing® during the two phase 3 clinical trials. Pregnancy outcome data was available for eleven of these pregnancies, three of which resulted in live births of health infants and eight of which ended in abortion. Outcomes for the remaining eleven pregnancies were unknown. Because complete pregnancy outcome data for all pregnancies occurring following NuvaRing® exposure in these clinical trials was not known, the sponsor was asked and agreed to a phase 4 commitment to obtain follow-up data on pregnancy outcome (including spontaneous abortion, septic abortion, premature delivery, stillbirth, live births, occurrence of congenital anomalies and duration of fetal exposure) for any pregnancies following NuvaRing® exposure that are spontaneously reported through postmarketing surveillance.

Key review issues from other review disciplines included the following:

Biopharmaceutics:

(1) the finding of an increase in serum etonogestrel and ethinyl estradiol AUC (17% and 16% increases, respectively) associated with single dose administration of an oil-based, intravaginal miconazole nitrate product in a small interaction study of NuvaRing® users.

These results were incorporated into the product label, and a phase 4 study was requested of and agreed to by the sponsor to investigate the effect of multiple dosing with oil-based, intravaginal miconazole nitrate products in NuvaRing® users.

(2) the possibility of drug-drug interactions and alterations in serum etonogestrel and ethinyl estradiol levels in NuvaRing® users taking concomitant anti-retroviral medications. Appropriate modifications in the product label to reflect these possible interactions were made.

(3) unacceptable *in vitro-in vivo* correlations (IVIVC) for etonogestrel and ethinyl estradiol. This was not an approvability issue, and a request for provision of internal or external validations for the proposed IVIVCs was made of the sponsor via a Discipline Review letter sent to the sponsor on December 15, 2000.

Chemistry:

During the current review cycle, one of the manufacturing sites that performed release and stability testing for NuvaRing® [redacted] received a "withhold" approval recommendation from the Office of Compliance. The sponsor was informed of this finding and subsequently withdrew this site from the NDA on November 14, 2000. As of December 15, 2000, all remaining manufacturing and testing facilities for NuvaRing® were found to be in compliance with cGMP. Thus, the application was approvable per the Chemistry review team.

Pharmacology/Toxicology:

Preclinical data provided in the application were found to be acceptable by the pharmacology/toxicology reviewer. The original version of the proposed label for NuvaRing® submitted by the sponsor did not include results from reproductive toxicity studies in rats and rabbits. Appropriate text in this regard was added by the pharmacology/toxicology review team after taking comments from the CAC and consulting toxicologist for ODE III into consideration.

Labeling:

Labeling for this product was modified from the original version submitted by the sponsor to incorporate important safety and unique use information for NuvaRing®. These modifications included (1) the addition of text on VTE risk associated with use of third generation hormonal contraceptive products; (2) inclusion of additional safety data (i.e., adverse event information) specific to use of NuvaRing®; (3) inclusion of results from the interaction study of NuvaRing® and oil-based intravaginal miconazole nitrate; (4) modifications in the text and format of the patient package insert to improve interpretability; and (5) recommendations for avoidance of product storage at temperatures above room temperature to reduce the likelihood of burst hormone release upon vaginal insertion of the product. Appropriate labeling revisions from all review disciplines were incorporated into the proposed final product label and patient package insert. On December 22, 2000, the sponsor notified the review division that they were unwilling

to accept the FDA's proposed version of the final product label and patient package insert; therefore, an approvable action will be taken during this review cycle.

As described in the primary and secondary clinical and chemistry reviews, four phase 4 commitments were requested of and agreed to by the sponsor in written correspondence dated December 13, 1000 and December 20, 2000:

(1) a pharmacokinetic/pharmacodynamic study to investigate the effect of multiple dosing with a commercially available oil-based, intravaginal miconazole nitrate product on serum etonogestrel and ethinyl estradiol concentrations and ovulation inhibition in NuvaRing® users. A draft protocol for this study will be submitted to the FDA within six months of NuvaRing® approval;
(2) a clinical study to evaluate the effects of tampon use on serum concentrations of etonogestrel and ethinyl estradiol in NuvaRing® users. A draft protocol for this study will also be submitted to the FDA within six months of NuvaRing® approval;
(3) for postmarketing safety reports of pregnancy following NuvaRing® exposure, the sponsor will attempt to obtain information on the outcome of all such pregnancies including live births, miscarriages (spontaneous abortions), septic abortions, premature births, occurrence of congenital anomalies and duration of fetal exposure to NuvaRing®.
(4) Within one year of NuvaRing® approval, the sponsor will provide FDA with a non-automated alternative for the *in vitro* release analytical method in order to validate the automated analytical method described in the application.

These phase 4 commitments will be finalized upon product approval.

Conclusions and Recommendations

I agree with assessments of the primary and secondary reviewers of all disciplines that data contained in the current NDA submission support the safety and effectiveness of NuvaRing® for marketing approval in the U.S. This application will be approvable pending resolution of and final agreement on labeling issues and postmarketing commitments by the sponsor.

/S/ 12/22/00

Susan S. Allen, MD, MPH
Director, HFD 580

Cc: NDA 21,187
HFD-580, Division File
HFD-103
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Division Director Memorandum

NDA#:	**21-187**
Drug:	**NuvaRing® (etonogestrel/ethinyl estradiol vaginal ring)**
Indication:	**Prevention of pregnancy**
Dose:	**Daily in vitro release of 0.120 mg etonogestrel and 0.015 mg ethinyl estradiol**
Administration:	**Intravaginal ring placement daily for 21 days, followed by a ring-free interval of 7 days**
Formulation:	**Intravaginal ethylene vinylacetate ring containing 11.7 mg etonogestrel and 2.7 mg ethinyl estradiol**
Applicant:	**Organon, Inc.**
Date of submission:	**February 28, 2001**
Date of memorandum:	**April 27, 2001**

Background

NuvaRing® is a novel method of combined hormone delivery for contraception. It consists of a single-compartment, ethylene vinyl acetate ring containing 11.7 mg of etonogestrel (the active metabolite of the progestin, desogestrel) and 2.7 mg of ethinyl estradiol. NuvaRing® releases 0.120 mg of etonogestrel and 0.015 mg of ethinyl estradiol daily in *in vitro* testing. It was developed as an intravaginal contraceptive to be placed and remain in the vagina for 21 consecutive days followed by ring removal during the last 7 days of a 28-day menstrual cycle. The ring has an external diameter of 54 mm, comparable in size to a contraceptive diaphragm. It offers the advantages of avoidance of hepatic first-pass metabolism, avoidance of daily administration as required with oral contraceptives, and comes as a one-size-fits-all device unlike a diaphragm that requires individual fitting. These characteristics could be associated with improved user compliance for this product.

The original new drug application (NDA) for NuvaRing® was submitted to the FDA on December 29, 1999. As described in the primary and secondary reviews and my tertiary review from the previous review cycle, the safety and contraceptive efficacy of NuvaRing® was demonstrated in two large, multi-center, phase 3 trials. Safety analyses previously performed for NuvaRing® focused on those issues unique to an intravaginal product (i.e., local effects such as irritation, inflammation and infection) as well as those associated with combined hormonal contraceptive products, particularly menstrual bleeding pattern alterations and venous thromboembolic events (VTEs).

During the previous review cycle, all review disciplines recommended modifications in the label for NuvaRing® in order to incorporate safety and unique use information into the product label and to facilitate interpretation of instructions for correct use of the product. Four phase 4 commitments were requested of and agreed to by the sponsor in written correspondence dated December 13, 1000 and December 20, 2000. They were:

(1) To conduct a pharmacokinetic/pharmacodynamic study to investigate the effect of multiple dosing with a commercially available oil-based, intravaginal miconazole nitrate product on serum etonogestrel and ethinyl estradiol concentrations and ovulation inhibition in NuvaRing® users. A draft protocol for this study will be submitted to the FDA within six months of NuvaRing® approval;
(2) To conduct a clinical study to evaluate the effects of tampon use on serum concentrations of etonogestrel and ethinyl estradiol in NuvaRing® users. A draft protocol for this study will also be submitted to the FDA within six months of NuvaRing® approval;
(3) For postmarketing safety reports of pregnancy following NuvaRing® exposure, the sponsor will attempt to obtain information on the outcome of all such pregnancies including live births, miscarriages (spontaneous abortions), septic abortions, premature births, occurrence of congenital anomalies and duration of fetal exposure to NuvaRing®.
(4) Within one year of NuvaRing® approval, the sponsor will provide FDA with a non-automated alternative for the *in vitro* release analytical method in order to validate the automated analytical method described in the application.

Approval of the application was recommended by all review disciplines during the previous review cycle. However, the sponsor notified the review division on December 22, 2000 that they were unwilling to accept the FDA's revisions to the final product label and patient package insert. Subsequently, an approvable letter was issued on December 22, 2000 for this application.

The current submission:

The current submission contains the sponsor's proposed version of the product label and patient package insert as well as a safety update that covers the period from 10/1/00

through 1/1/01. This submission includes safety data on 82 volunteers participating in an ongoing European trial of NuvaRing®.

Since the previous review cycle, NuvaRing® has received Marketing Authorization from the Dutch Medicines Evaluation Board, and approval of the product is being sought within the European Union. The product is not yet marketed in any country.

Clinical

As described in the primary clinical review dated April 27, 2001, no serious adverse events nor deaths were reported in the current safety update. Thus, information provided in this submission did not raise new safety concerns for this product that required significant modifications in the proposed labeling.

Chemistry

The chemistry review team recommended that (1) a statement regarding appropriate storage of the product (i.e., avoidance of exposure to direct sunlight or storage at temperatures above 86°) be included in both the product label and the patient package insert and (2) the established name for the product be changed from "etonogestrel/ethinyl estradiol ring" to "etonogestrel/ethinyl estradiol vaginal ring". These recommended changes were included in a version of the label sent to the sponsor on April 17, 2001. With the addition of the statement noted above to the final version of both documents and the modification in the established name for the product, the application would have been deemed acceptable by the chemistry review team.

Pharmacology/Toxicology

Preclinical data submitted during the previous review cycle was found acceptable by the pharmacology/toxicology review. Extensive revisions to the "Carcinogenesis, Mutagenesis and Impairment of Fertility" and the "Pregnancy" sections of the label were recommended by this review team during the last review cycle. No additional revisions to these sections were recommended during the current review cycle.

On April 25, 2001 the sponsor contacted the Pharmacology/Toxicology review team and stated that they did not agree with the FDA's proposed text for the "Carcinogenesis, Mutagenesis and Impairment of Fertility" section of the label. FDA reviewers informed the sponsor that inclusion of the specific text in that section of the label was recommended by the Carcinogenicity Assessment Committee (CAC) and could only be revised following submission and review of data to support such revisions. On April 26, 2001 the sponsor contacted the Division and stated their intent to submit additional preclinical data in support of revisions in the "Carcinogenesis, Mutagenesis and Impairment of Fertility" section of the label. However, they noted that they would be

unable to submit this data until after the goal date for the application (i.e., May 1, 2001). The sponsor therefore requested that an approvable action be taken on their application during the current review cycle.

Clinical Pharmacology and Biopharmaceutics

No new review issues were noted by this discipline during the current review cycle, and minor editorial modifications to the proposed label were included in the version of the label sent to the sponsor by the Division on April 17, 2001.

The sponsor's previous commitment to investigate the effect of multiple dosing with oil-based, intravaginal miconazole on serum etonogestrel and ethinyl estradiol concentrations and ovulation inhibition in NuvaRing® users will be included in the action letter for this application.

Labeling

Many of the Division's previously recommended modifications to the label for NuvaRing® were incorporated into the version of the label included in the current submission by the sponsor. However, the sponsor proposed to add text to the label and patient package insert related to (1) non-contraceptive benefits of combination hormonal products and (2) results from a small-scale, unblinded trial comparing lipid changes seen in 33 NuvaRing® users to those seen in 37 combination oral contraceptive users. Neither of these text additions was deemed appropriate by the review teams, and the proposed text was deleted from the product label.

Additional changes to the label and patient package insert during the current review cycle included (1) text describing bleeding pattern alterations in volunteers from the previously conducted US trial. Results from this study were added to the "Warnings" section of the label; (2) consistent wording regarding the types of contraceptive products deemed acceptable for use when additional contraception is required for NuvaRing® users; (3) statements that NuvaRing® use could interfere with the placement and position of contraceptive diaphragms; (4) statements regarding appropriate storage conditions for the product once purchased.

As noted above, the sponsor informed the Division on April 26, 2001 that they did not accept the Division's recommended changes to the "Carcinogenesis, Mutagenesis and Impairment of Fertility" section of the label. They also informed the Division that they would be unable to provide their comments to other sections of the FDA-revised label and patient package insert until after the goal date for the application.

Conclusions and Recommendations

I agree with the conclusions of the review teams for this application and recommend an approvable action for the current submission. This product could be approved pending agreement on final labeling for the product. The phase 4 commitments previously agreed to by the sponsor on December 13 and 20, 2000 will be included in the action letter for this application.

Susan S. Allen, MD, MPH
Director, HFD-580

Division Director Memorandum

NDA#:	**21-187**
Drug:	**NuvaRing® (etonogestrel/ethinyl estradiol vaginal ring)**
Indication:	**Prevention of pregnancy**
Dose:	**Daily in vitro release of 0.120 mg etonogestrel and 0.015 mg ethinyl estradiol**
Administration:	**Intravaginal ring placement daily for 21 days, followed by a ring-free interval of 7 days**
Formulation:	**Intravaginal ethylene vinylacetate ring containing 11.7 mg etonogestrel and 2.7 mg ethinyl estradiol**
Applicant:	**Organon, Inc.**
Date of submission:	**August 2, 2001**
Date of memorandum:	**September 28, 2001**

Background

This is the third review cycle for this product consisting of a single-compartment, ethylene vinylacetate ring containing ethinyl estradiol and etonogestrel (the active metabolite of the synthetic progestin, desogestrel) for intravaginal placement. By virtue of its design, NuvaRing® provides a unique delivery method for a combination hormonal contraceptive. It is to be placed and remain in the vagina for 21 consecutive days followed by ring removal during the last 7 days of a 28-day menstrual cycle. It offers the advantages of avoidance of first-pass metabolism and avoidance of daily administration, as required with oral contraceptives, and comes in a single size that does not require individual fitting by a health care provider.

An original new drug application (NDA) for this product was submitted to the FDA on December 29,1999 and received an approvable action by the Division on December 22, 2000 due to the sponsor's inability to complete their review of FDA-proposed labeling revisions prior to the original PDUFA goal date. The sponsor subsequently submitted a revised version of the proposed product label and patient package insert and a safety update on February 28, 2001. Based upon information contained in that submission, no new safety concerns were raised for the product. The sponsor was unable to reach agreement with the Agency on specific sections of the product label (e.g., the "Carcinogenesis, Mutagenesis and Impairment of Fertility", "Non-Contraceptive Health Benefits", and "Bleeding Irregularity" sections) and stated that they wished to submit additional preclinical data to support further revisions in the label. Because this

additional information could not be submitted until after the goal date for this submission, a second approvable action was taken on the application on April 27, 2001.

As described in my reviews dated December 22, 2000 and April 27, 2001 from the two previous review cycles, the safety and contraceptive efficacy of NuvaRing® was demonstrated in two large, multi-center, phase 3 trials. At the end of the first and second review cycles for this product, the sponsor agreed to four phase 4 commitments as described below:

(1) To conduct a pharmacokinetic/pharmacodynamic study to investigate the effect of multiple dosing with a commercially available oil-based, intravaginal miconazole nitrate product on serum etonogestrel and ethinyl estradiol concentrations and ovulation inhibition in NuvaRing® users. A draft protocol for this study will be submitted to the review division within six months of NuvaRing® approval;
(2) To conduct a clinical study to evaluate the effects of tampon use on serum concentrations of etonogestrel and ethinyl estradiol in NuvaRing® users. A draft protocol for this study will also be submitted to the review division within six months of NuvaRing® approval.
(3) For postmarketing safety reports of pregnancy following NuvaRing® exposure, the sponsor will attempt to obtain information on the outcome of all such pregnancies including live births, miscarriages (spontaneous abortions), septic abortions, premature births, occurrence of congenital anomalies and duration of fetal exposure to NuvaRing®.
(4) Within one year of NuvaRing® approval, the sponsor will provide FDA with a non-automated alternative for the *in vitro* release analytical method in order to validate the automated analytical method described in the application.

The Current Submission:

The current submission contains the sponsor's proposed version of the product label and patient package insert as well as a safety update that covers the period from January 1, 2001 through June 15, 2001. This submission includes safety data on 131 volunteers participating in an ongoing European trial to evaluate the effects of NuvaRing® on bone mineral density and endometrial histology.

Although NuvaRing® received Marketing Authorization from the Dutch Medicines Evaluation Board on February 14, 2001 it has not yet been marketed in any country.

Clinical

As described in the primary clinical review dated September 17, 2001 no serious adverse events or deaths were reported for the 102 volunteers using NuvaRing® in the ongoing European study. Thus, information provided in this submission did not raise new safety concerns for this product that required significant modifications to the proposed labeling.

On June 21, 2001 the sponsor submitted a proposed study to address the first two of the four phase 4 commitments listed above. The division provided comments on this protocol to the sponsor on July 10, 2001 and a final version of this protocol was submitted to the division on September 13, 2001. Per the primary and secondary reviewers, the design and goals of the study

were deemed acceptable for addressing the clinical and biopharmaceutics issues described in these two phase 4 commitments. During a teleconference on September 26, 2001 the sponsor was asked to revise the fourth phase 4 commitment listed above to incorporate the submission of a plan for collecting information on spontaneous reports of pregnancy occurring following NuvaRing® exposure. As of the date of this memorandum, written confirmation of the sponsor's agreement to revise these phase 4 commitments has not yet been received.

Pharmacology/Toxicology

During the review of the original NDA submission, the pharmacology/toxicology team recommended inclusion of text in the label that described findings of bronchoalveolar adenomas in female rats treated with 3-keto-desogestrel. As noted above, during the second review cycle for the application, the sponsor stated their intent to submit additional preclinical data in support of removal of this text. A re-read of the lung slides from the previously conducted rat studies was performed by consultant pathologists to the National Center for Toxicologic Research (NCTR) and submitted to the Division. Per the pharmacology/toxicology review team, this slide re-read did not indicate a treatment related carcinogenic effect of 3-keto-desogestrel in the rat lung and the sponsor's proposed removal of text in labeling describing such findings was supported. The pharmacology/toxicology review team made appropriate revisions to the label based upon this new information.

Clinical Pharmacology/Biopharmaceutics

No new review issues were noted by this discipline during the current review cycle, and the application was deemed acceptable for approval.

Chemistry

The sponsor made revisions to the chemistry section of the product label and the product container labeling as recommended by the review team during the previous review cycle. As described in the primary chemistry reviewer's memorandum dated September 5, 2001, the sponsor proposed that the product be approved with seven months storage at room temperature. During the first review cycle, the chemistry reviewer noted a 'burst effect' of drug product release after six months of storage at room temperature. This release was not thought to pose a clinically significant concern (see the Clinical Team Leader review dated December 22, 2000). During a teleconference on November 16, 2000, the sponsor proposed manufacturing changes for scaling up batch production of the product. Because the effects of such changes on the 'burst effect' were unknown, the chemistry reviewers stated that a prior approval supplement (PAS) containing six months of accelerated stability data would need to be submitted in support of the proposed manufacturing changes. This PAS would need to be followed by submission of an additional three months of stability data no later than two months into the PAS review.

During the current review cycle, the sponsor stated that they would be able to provide only the six months of accelerated stability data in the proposed PAS. They requested that a CBE submission to reduce the product expiry from seven to four months at room temperature be allowed following approval of the NDA. This would be followed by a PAS containing three months of accelerated stability data to support the proposed drug product manufacturing changes. Although the primary reviewing chemist agreed to these sponsor requests, the potential confusion for health care

providers, pharmacists and product users that could result from approving this product with seven months of expiry and subsequently reducing the expiry to four months at the time of CBE submission was not acceptable. Therefore, on September 26, 2001 the sponsor was asked to amend the application and the proposed labeling limiting product expiry at room temperature to four months. The sponsor agreed to this request during the teleconference and is expected to submit the requested amendment prior to the PDUFA goal date of October 3, 2001.

Labeling

Many of the Division's previously recommended modifications to the label for NuvaRing® were incorporated into the version of the label included in the current submission by the sponsor. The sponsor proposed to add text to the label and patient package insert related to (1) non-contraceptive benefits of combination hormonal products and (2) pooled bleeding pattern data from the two, large clinical trials. The sponsor also proposed removal of 'weight gain' from the list of the most common adverse events reported during the conduct of the phase 3 trials. None of these proposed revisions was acceptable to the clinical review team.

With regard to bleeding pattern alterations, because of differences in such patterns between the two phase 3 studies (with a much less favorable bleeding pattern noted in the US/Canadian study), pooling of the data for these studies was not acceptable. However, it was decided that the sponsor could either report bleeding pattern alterations for both trials separately or report only the results from US/Canadian study in the label. The sponsor chose to report results from both trials separately in the product label.

As of September 28, 2001 the proposed revisions to the label were acceptable to the review Division; however, final comments on the label from the Office of Drug Evaluation III will be needed prior to product approval.

Conclusions and Recommendations:

I agree with the conclusions of the review teams for this application and recommend that NuvaRing® be approved for US marketing provided full agreement on the product label is reached and acceptable revisions to the phase 4 commitments are received by the PDUFA goal date of October 3, 2001.

Susan S. Allen, MD, MPH
Director, Division of Reproductive and Urologic Drug Products

NuvaRing® Group Leader Review

OCT 6 2000

NDA:	21-187
Drug:	NuvaRing® (etonogestrel/ethinyl estradiol vaginal ring)
Dosage Form/Route:	Ethylene vinylacetate (EVA) ring, vaginal absorption, daily in vitro release rate of 0.120mg etonogestrel, 0.015mg ethinyl estradiol
Applicant:	Organon Inc.
Original Submission Date:	12-29-99
Reviewer:	Gerald Willett MD
Review Completed:	10-6-00

Summary

Based on the information reviewed to date, NuvaRing® (etonogestrel/ethinyl estradiol vaginal ring) is recommended for approval. I agree with the primary reviewers that the data contained in the NuvaRing® NDA supports safety and efficacy for the indication of prevention of pregnancy in women who elect to use this product as a method of contraception. Some additional information requested from the sponsor has arrived today in the electronic document room and will be reviewed. Outstanding issues will be noted in this review according to discipline.

A phase 4 clinical study assessing serum etonogestrel, serum ethinyl estradiol, and ovulation inhibition should be performed in women receiving multiple treatments of oil-based antimycotic vaginal preparations.

A phase 4 clinical study should be performed that addresses the impact of tampons on drug absorption. This should assess not only serum levels of etonogestrel and ethinyl estradiol and ovulation inhibition, but also tampon levels of these hormonal substances.

Background

Hormone releasing vaginal rings have been studied for both contraception and hormone replacement. Studies have been performed with estrogen-only rings, progestin-only rings and combination hormone rings. The estrogens studied have included estradiol, estrone and ethinyl estradiol. The progestational agents evaluated have included natural progesterone, chlormadinone acetate, norethisterone, nestorone, norethindrone acetate, norgestrel, levonorgestrel, and etonogestrel.

The development of a vaginal ring for contraception introduces a new, alternative delivery method for women. Though not as user-independent as intrauterine devices or

Norplant, the ring method does not require daily dosing, as do oral contraceptives. The ring is removed after 21 days of use and a new ring inserted 7 days later.

Clinical Efficacy and Safety

Contraceptive Efficacy

The dose finding studies (85012, 86016, and 34218) selected the to-be-marketed dose of etonogestrel and ethinyl estradiol based on ovulation inhibition and bleeding pattern. This approach and the final selected dosages are acceptable.

Two large clinical Phase 3 studies with adequate numbers of subjects, duration of use, acceptable pregnancy protection, and acceptable safety profile support approval of NuvaRing®. Study 68003 was conducted in 47 centers in the U.S. and one center in Canada. Study 34219 was conducted in 53 centers in 11 European countries and Israel.

In study 68003, a total of 1,117 subjects were exposed to NuvaRing® for a total of 11,188 cycles (858 woman years). The sponsor's Pearl Index for the intent-to-treat (ITT) population is 1.749. The Pearl Index established in the primary medical officer's review for the ITT population in this U.S./Canadian trial is 1.86. The reviewer's higher number is a result of the reclassification of subject 4321 as an in-treatment pregnancy. The per protocol use indices in this study were 0.910 (sponsor) and 1.452 (medical officer review). The higher per protocol index number in the medical officer's review is a result of the addition of three subjects (#1934, #4820, and #4321). If only under age 35 subjects are evaluated, the ITT Pearl Index is 1.879 (sponsor) and 2.017 (medical officer review) in the U.S./Canadian study.

In study 34219, a total of 1,145 subjects were exposed to NuvaRing® for a total of 12,109 cycles (928 woman years). The sponsor's Pearl Index for the ITT population is 0.646. The Pearl Index established in the medical officer's review for the ITT population in the European/ Israeli study is 0.644. The slightly lower number results from the reviewer calculating three more woman-years in the analysis. The per protocol use indices in this study were 0.396 (sponsor) and 0.525 (medical officer review) The higher per protocol index number in the medical officer's review is a result of the addition of subject 0524. If only under age 35 subjects are evaluated, the ITT Pearl Index is 0.650 (sponsor) and 0.648 (medical officer review) in the European/ Israeli study.

The reason for the differences in the efficacy results between the U.S./Canadian study and the European/Israeli study may be related to a number of factors. The Eupopean/Israeli study reported a higher number of switchers and OC as last contraceptive compared to the U.S./Canadian study (62% & 67% versus 41% & 37%). There was also a higher discontinuation rate of 41% in the U.S./Canadian study compared to 30% in the European/Israeli study. There may also be some cultural differences that result in improved compliance in the European/Israeli study, since Levlite™ (NDA 20-860) also showed a similar difference with a Pearl Index of 0.299 in its German study and 1.08 in its U.S. study.

Combining the under age 35 indices from 68003 and 34219 results in an ITT Pearl Index of 1.23 (sponsor) and 1.30 (medical officer's review). The Pearl Index for NuvaRing® varies from a low of 0.396 (per protocol, all ages, Europe/Israel) to 2.017 (ITT, less than 35, U.S./Canadian). The level of 2.017 is lower than that of Estrostep® (NDA 20-130). Approval of NuvaRing® should also recognize that this is a new method of contraception which may have distinct user advantages to some women; especially, in regard to less frequent dosing.

Bleeding Patterns

Irregular bleeding patterns have been identified with essentially all hormonal contraceptive products and intrauterine contraceptive devices. Mid-cycle spotting and the absence of withdrawal bleeding are two of the most common patterns identified. Unpredictable bleeding and concern over pregnancy when the withdrawal bleed does not occur makes a significant difference for women's acceptance of a contraceptive method. Most present contraceptive labels discuss irregular bleeding via class labeling in the side effect section. With new methods of contraception such as vaginal rings, patients and clinicians should be informed of the observed bleeding patterns.

The bleeding pattern data that appears to be the most appropriate to report from this NDA is derived from the two large clinical studies (68003 and 34219) where bleeding diaries were filled out daily by the study subjects. The ITT evaluable cycles from these two studies combined provides the following information on bleeding patterns per cycle:

Breakthrough bleeding/spotting episodes	(5.1%-7.9%)
Absence of withdrawal bleeding	(1.5%-2.9%)
Early withdrawal bleeding (usually spotting)	(5.6%-8.8%)
Continued withdrawal bleeding (usually spotting)	(19.5%-25.2%)
Intended bleeding pattern (period-only during ring-free time frame)	(59.9%-68.5%)

Additional bleeding pattern data requested from the sponsor will be reviewed and commented on in an addendum to the primary medical officer review. This additional information will focus on the long term patterns of bleeding, onset of withdrawal bleeding, and more specifics on percentages of altered bleeding. The primary medical officer review also contains more information on the definitions of the bleeding patterns.

The sponsor also studied bleeding patterns in the metabolic studies that were performed to evaluate the effect of NuvaRing on lipids, coagulation, and carbohydrates/adrenal/thyroid (34220, 34221, and 34222 respectively) These studies included a 0.15mg LNG/ 0.03mg EE oral contraceptive comparator. It is not felt that comparative bleeding pattern information from these smaller studies be included in the label (as the sponsor has proposed in a **Clinical Studies** section). Appropriately designed studies with statistical power and prior agency agreement on the appropriate comparator(s) would be needed to allow for labeling comparisons in regard to bleeding.