

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

021187Orig1s021s022

**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

Explain:

!

!

! NO

! 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

Explain:

!

!

! NO

! 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

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/s/

ZETA-MAE C WILLIAMSON
11/22/2013

AUDREY L GASSMAN
11/22/2013



NDA 21187/S-022

**ACKNOWLEDGEMENT --
PRIOR APPROVAL SUPPLEMENT**

Merck Sharp & Dohme Corp.
Attention: Ripal Shah, Pharm.D.
Regulatory Liaison, Global Regulatory Affairs
2015 Galloping Hill Road, Mail Stop: 3175
Kenilworth, NJ 07033

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: 022
PRODUCT NAME: NuvaRing® (etonogestrel/ethinyl estradiol vaginal ring)
DATE OF SUBMISSION: December 19, 2012
DATE OF RECEIPT: December 20, 2012

This supplemental application proposes updating the labeling for NuvaRing® to the Physician Labeling Rule (PLR).

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 February 18, 2013, in accordance with 21 CFR 314.101(a). If the application is filed, the goal date will be June 20, 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
03/20/2013

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

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

REVIEW ACTION

- | | | |
|---|---|---|
| <input type="checkbox"/> NAI (No action indicated) | <input type="checkbox"/> Oral communication with | <input checked="" type="checkbox"/> Formal Review/Memo (attached) |
| <input type="checkbox"/> E-mail comments to: | Name: [] | <input type="checkbox"/> See comments below |
| <input type="checkbox"/> Medical <input type="checkbox"/> Chemist <input type="checkbox"/> Pharm-Tox | <input type="checkbox"/> Comments communicated in | <input type="checkbox"/> See submission cover letter |
| <input type="checkbox"/> Micro <input type="checkbox"/> Pharmacometrics <input type="checkbox"/> Others | meeting/Telecon. see meeting minutes | <input type="checkbox"/> OTHER (<i>SPECIFY BELOW</i>): |
| (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 content]

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** _____

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/s/

CHONGWOO YU
08/30/2013

MYONG JIN KIM
08/30/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		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) <input checked="" type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE(IFU)		TYPE OF APPLICATION/SUBMISSION <input type="checkbox"/> ORIGINAL NDA/BLA <input checked="" type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> MANUFACTURING (CMC) SUPPLEMENT <input checked="" type="checkbox"/> PLR CONVERSION		REASON FOR LABELING CONSULT <input type="checkbox"/> INITIAL PROPOSED LABELING <input checked="" type="checkbox"/> LABELING REVISION	
EDR link to submission: http://darrrts.fda.gov:9602/darrrts/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) <input type="checkbox"/> eMAIL (BLAs Only) <input type="checkbox"/> 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) <input checked="" type="checkbox"/> PACKAGE INSERT (PI) <input checked="" type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input type="checkbox"/> CARTON/CONTAINER LABELING <input type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE(IFU)		TYPE OF APPLICATION/SUBMISSION <input type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	
REASON FOR LABELING CONSULT <input type="checkbox"/> INITIAL PROPOSED LABELING <input type="checkbox"/> 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 Shortly			
SIGNATURE OF REQUESTER Charlene Williamson			
SIGNATURE OF RECEIVER		METHOD OF DELIVERY (Check all that apply) <input type="checkbox"/> eMAIL <input type="checkbox"/> DARRTS <input type="checkbox"/> HAND	

06/18/2013

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/s/

ZETA-MAE C WILLIAMSON
08/26/2013

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/s/

ZETA-MAE C WILLIAMSON
07/04/2013



NDA 021187/S-021

**PRIOR APPROVAL SUPPLEMENT
USER FEES RECEIVED**

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 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for NuvaRing® (etonogestrel/ethinyl estradiol) Vaginal Ring.

You were notified in our letter dated October 31, 2012, that your supplemental application was not accepted for filing due to non-payment of fees. This is to inform you that the Agency has received all required fees and your application has been accepted as of December 5, 2012.

This supplemental application proposes the following changes to the labeling based on the following studies, "*Transatlantic Active Surveillance on Cardiovascular Safety of NuvaRing*" (TASC) and the FDA-funded study, "*Combined Hormonal Contraceptives and the Risk of Cardiovascular Disease Endpoints.*"

Unless we notify you within 60 days of the above date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 3, 2013 in accordance with 21 CFR 314.101(a).

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). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at:

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/ct/SignificantAmendmentstotheFDCAAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm>. Additional information regarding Title VIII of FDAAA is available at: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information for registering your clinical trials is available at the Protocol Registration System website <http://prsinfo.clinicaltrials.gov/>.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to NDA 21187/S-021 submitted on August 30, 2012, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

The application number cited above should be included 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

If you have any 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
12/19/2012



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



NDA 21187/S-021

UNACCEPTABLE FOR FILING

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 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: NuvaRing[®] (etonogestrel/ethinyl estradiol) Vaginal Ring

NDA Number: 21187

Supplement Number: 021

Date of Application: August 30, 2012

Date of Receipt: August 30, 2012

This supplemental application proposes the following changes to the labeling based on the following studies, "Transatlantic Active Surveillance on Cardiovascular Safety of NuvaRing" (TASC) and the FDA-funded study, "Combined Hormonal Contraceptives and the Risk of Cardiovascular Disease Endpoints."

We have not received the appropriate user fee for this application. An application is considered incomplete and cannot be accepted for filing until all fees owed have been paid. Therefore, this application is not accepted for filing. We will not begin a review of this application's adequacy for filing until FDA has been notified that the appropriate fee has been paid. Additionally, submit draft labeling in PLR format as a prior approval efficacy supplement to this application. Payment should be submitted to the following address:

Food and Drug Administration
P.O. Box 979107
St. Louis, MO 63197-9000

Checks sent by courier should be addressed to:

U.S. Bank
Attention: Government Lockbox 979107
1005 Convention Plaza
St. Louis, MO 63101

When submitting payment for an application fee, include the User Fee I.D. Number, the Application number, and a copy of the user fee coversheet (Form 3397) with your application fee payment. When submitting payment for previously unpaid product and establishment fees, please include the Invoice Number(s) for the unpaid fees and the summary portion of the invoice(s) with your payment. The FDA P.O. Box number (P.O. Box 979107) should be included on any check you submit.

Please cite the NDA 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

If you wish to send payment by wire transfer, or if you have any other user fee questions, please call Bev Friedman or Mike Jones at 301-796-3602.

Additionally,

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

Sincerely,

{See appended electronic signature page}

Z. Charlene Williamson
Regulatory Health 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
10/31/2012