

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

021187Orig1s021s022

OTHER REVIEW(S)

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

PATIENT LABELING REVIEW

Date: October 2, 2013

To: Hylton V. Joffe, M.D., Director
Division of Bone, Reproductive and Urologic Products (DBRUP)

Through: LaShawn Griffiths, RN, MSHS-PH, BSN
Associate Director, Patient Labeling Team
Division of Medical Policy Programs (DMPP)

Robin Duer, RN, BSN, MBA
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

From: Twanda Scales, RN, MSN/Ed.
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

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

Subject: Review of Patient Labeling: Patient Package Insert and Instructions for Use

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

Dosage Form and Route: Vaginal Ring

Application Type/Number: NDA 21-187

Supplement Number: 021, 022

1 INTRODUCTION

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

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

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

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

2 MATERIAL REVIEWED

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

3 REVIEW METHODS

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

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

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

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

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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/s/

TWANDA D SCALES
10/02/2013

CARRIE A NEWCOMER
10/02/2013

ROBIN E DUER
10/02/2013

LASHAWN M GRIFFITHS
10/02/2013

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

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

PI = prescribing information

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

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

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

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

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

Selected Requirements of Prescribing Information

Highlights (HL)

GENERAL FORMAT

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

Comment:

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

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

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

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

Comment:

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

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

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

Comment:

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

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

Selected Requirements of Prescribing Information

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

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

Comment:

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

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

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

Comment:

Highlights Limitation Statement

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

Comment:

Product Title

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

Comment:

Initial U.S. Approval

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

Comment:

Boxed Warning

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

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

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

Selected Requirements of Prescribing Information

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

Comment:

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

Comment:

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

Comment:

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

Comment:

Recent Major Changes (RMC)

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

Comment:

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

Comment:

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

Comment:

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

Comment:

Indications and Usage

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

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

Dosage Forms and Strengths

Selected Requirements of Prescribing Information

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

Comment:

Contraindications

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

Comment:

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

Comment:

Adverse Reactions

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

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

Patient Counseling Information Statement

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

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

- “**See 17 for PATIENT COUNSELING INFORMATION**”

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

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

Comment:

Revision Date

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

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

Contents: Table of Contents (TOC)

GENERAL FORMAT

Selected Requirements of Prescribing Information

- YES** 28. A horizontal line must separate TOC from the FPI.
Comment: *Recommend inserting white space between the horizontal line and the FPI.*
- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.
Comment:
- NO** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.
Comment: *The following section heading and subheadings do not match in the TOC and FPI and must be matched:*
Subheading 2.2 in the TOC “(b)(4)” does not match subheading 2.2 in the FPI “How to Start Using NuvaRing.”
Subheading 2.5 in the FPI “Use with Other Vaginal Products” is missing from the TOC.
Subheading 7.2 in the TOC “(b)(4)” does not match subheading 7.2 in the FPI “Effects of CHCs on Other Drugs.”
Subheading (b)(4) in the TOC is missing from the FPI.
Section heading 15 “REFERENCES” in the FPI is missing from the TOC.
- YES** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.
Comment:
- YES** 32. All section headings must be **bolded** and in UPPER CASE.
Comment:
- YES** 33. All subsection headings must be indented, not bolded, and in title case.
Comment:
- YES** 34. When a section or subsection is omitted, the numbering does not change.
Comment:
- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”
Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.
Comment:
- YES** 37. All section and subsection headings and numbers must be **bolded**.
Comment:

Selected Requirements of Prescribing Information

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

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

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

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

Comment:

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

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

Selected Requirements of Prescribing Information

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

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

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

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

Comment:

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

Comment:

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

Comment:

Contraindications

- N/A** 45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

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

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

Comment:

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

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

Comment:

Patient Counseling Information

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

Selected Requirements of Prescribing Information

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

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

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/s/

ABIMBOLA O ADEBOWALE
10/01/2013

LAURIE B BURKE
10/01/2013

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

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

Memorandum

Date: September 27, 2013

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

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

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

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

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

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

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

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

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/s/

CARRIE A NEWCOMER
09/27/2013

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

Epidemiology: Review of Study Report

Date: August 26, 2013

Reviewer(s): Rita Ouellet-Hellstrom, PhD
Division of Epidemiology II

Team Leader CDR David Moeny, RPh, MPH, USPHS
Division of Epidemiology II

Division Director Judy Staffa, PhD, RPh
Division of Epidemiology II

Subject *Transatlantic Active Surveillance on Cardiovascular Safety of NuvaRing (TASC), Final Study Report.* By Jürgen Dinger
August 9, 2012

Drug Name(s): NuvaRing (etonogestrel)

Applicant/sponsor: Organon USA, Inc.

NDA# 21-187

OSE RCM #: 2013-1575

TABLE OF CONTENTS

EXECUTIVE SUMMARY	2
ABBREVIATIONS	3
1 INTRODUCTION	4
2 REVIEW METHODS AND MATERIALS	4
3 REVIEW RESULTS	5
3.1 Study Overview	5
3.2 Study Objectives	5
3.3 Study Methods	6
3.3.1 Design	6
3.3.2 Outcome & Exposure	6
3.3.3 Covariates	7
3.3.4 Follow-up	8
3.3.5 Sample Size/Power	9
3.3.6 Statistical Analyses	9
3.4 Study Results	10
3.5 Study Conclusions	13
4 DISCUSSION	14
5 PROPOSED LABEL CHANGE	15
6 RECOMMENDATIONS	17
APPENDIX 1 – Epidemiology Excerpt in Proposed Label	18
APPENDIX 2: Study Summary	21
APPENDIX 3: DBVII TASC Report	22

EXECUTIVE SUMMARY

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

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

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

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

The epidemiologic information proposed for the revised NuvaRing PLR label is generally acceptable and follows the format of the information included in the label of other contraceptive products with labels revised recently.

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

First, the TASC study was powered to assess no less than a twofold risk of VTE for NuvaRing when compared to all other oral contraceptives (COCs) and to COCs that do not contain the progestins desogestrel (DSG) and gestodene GSD. Although VTE risks for NuvaRing were compared to COCs that excluded DSG, GSD and drospirenone (DRSP), the latter was an ad hoc comparison for which this study lacked power to do. OSE/DEPI recommends including the incidence rates and hazard ratio risk estimates for the comparison initially proposed and powered for the study.

The second recommendation is to align the VTE incidence rate (IR) information for the FDA funded study to those presented for the TASC study (for NuvaRing, other COCs) rather than limiting incidence rates to NuvaRing and to levonorgestrel-containing COCs for the FDA study. The IR for other COCs is available for this study as well. Although the differences are minor, the text in the label that presents incidence information should compare the incidence rates of comparable groups for the two studies since the information is available.

ABBREVIATIONS

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

1 INTRODUCTION

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

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

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

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

2 REVIEW METHODS AND MATERIALS

The following documents were reviewed:

1. *Transatlantic Active Surveillance on Cardiovascular Safety of NuvaRing (TASC). Final Study Report.* Jürgen Dinger, August 9, 2012.
2. Dinger J and Pineda A. *Risk of Venous Thromboembolism in Users of an Etonogestrel/Ethinyl estradiol Containing Vaginal Ring. Final Results from the TASC Study.* Slides 2012.
3. Proposed PLR label (01-proposed-wrm-uspi-mk8342amg-plr-tasc.pdf); EDR Link: <http://dartrts.fda.gov:9602/dartrts/viewEDR.do?suppDocId=8262273> (Excerpt in Appendix 1).

^a Sidney S, Cheetham TC, Connell FA, Ouellet-Hellstrom R, Graham DJ, Davis D, Sorel M, Quesenberry Jr. CP, Cooper WO. *Recent combined hormonal contraceptives (CHCs) and the risk of thromboembolism and other cardiovascular events in new users.* *Contraception.* 2013; 87:93-100.

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

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

3 REVIEW RESULTS

3.1 STUDY OVERVIEW

The *Transatlantic Active Surveillance on Cardiovascular Safety of NuvaRing* (TASC) study was a large, four-year multinational, prospective, observational active surveillance study of new hormonal contraceptive NuvaRing users compared to users of other marketed combined oral contraceptives (COCs). The study recruited 33,295 women on these treatments in routine clinical practice settings between September 2007 and September 2009. Women were followed for 24 to 48 months depending on when they were recruited. The study was started in Europe (Austria) in September 2007. The first US women were enrolled in late February 2008. Women from Austria, France, Germany, Italy, Russia and the United States participated in the study.

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

3.2 STUDY OBJECTIVES

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

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

Secondary objectives were to:

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

3.3 STUDY METHODS

3.3.1 Design

3.3.1.1 Study Type

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

3.3.1.2 Population & Time Period

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

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

3.3.1.3 Selection, Inclusion and Exclusion Criteria

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

3.3.1.4 Protected Health Information (PHI) Approvals

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

3.3.2 Outcome & Exposure

3.3.2.1 Exposure

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

who switched from one CHC to another CHC - e.g. from COC to NuvaRing or from a norgestimate-containing COC to a levonorgestrel containing COC- without an intake break or with an intake break of less than 4 weeks. Recurrent users were women who restarted contraceptive use with NuvaRing or another COC after an intake break of at least 4 weeks.

Two additional exposure cohorts were developed during the long follow-up of this study as some women changed their contraceptive method to other hormonal contraceptives (OHC) or completely stopped using hormonal contraception during the follow up period ('no-use' cohorts).

Study subjects who discontinued the study medication continued to be followed over the course of the study provided that they did not withdraw consent. Reason(s) for treatment discontinuation was obtained during follow-up.

3.3.2.2 Outcome

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

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

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

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

3.3.3 Covariates

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

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

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

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

3.3.4 Follow-up

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

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

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

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

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

3.3.5 Sample Size/Power

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

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

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

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

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

3.3.6 Statistical Analyses

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

3.4 STUDY RESULTS

A total of 33,295 women with complete analyzable baseline records were enrolled in the study: 16,864 women used NuvaRing, 16,431 used COCs. Among the COC users, 2,620 used COCs containing DSG or GSD (COC_{DSG/GSD}), and 13,811 used COCs containing other progestins (COC_{op}). Of the 33,295 women, 17,381 (52.2%) were from the US and 15,914 (47.8%) were European, mostly from Germany and Russia (78% of Europeans). In general, US women were generally heavier (BMI ~ 26-27) than European women (BMI ~22-23) and more European women smoked (30%) than US women (15%), but within each region there was no difference by treatment.

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

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

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

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

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

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

	US Women	European Women	All Women
Progestins of COCs			
DRSP (drospirenone)	25.4	32.9	29.3
NGM (norgestimate)	23.1	1.1	11.7
NETA (norethindrone)	21.7	N/A	10.5
LNG (levonorgestrel)	12.0	15.2	13.7
NET (norethisterone)	8.0	N/A	3.9
DSG (desogestrel)	6.2	14.0	10.3
NG (norgestrel)	2.8	--	1.4
Other	0.8	0.3	0.4
GSD (gestodene)	--	12.4	6.4
DNG (dinogest)	--	11.6	6.1
CMA (chlomadinacetate)	--	6.9	3.6
CPA (cyproteroaacetate)	--	5.6	2.9
N/A – not approved in the region			

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

Venous Thromboembolic Events (VTE)

Over the study period, a total of 171 VTE events were reported and 57 (33%) were confirmed. The incidence rate per 10,000 woman-years (WY) for NuvaRing, other COCs and COCs without desogestrel/gestodene is 8.3, 9.2, and 8.9 respectively, all with overlapping confidence intervals (Table 3).

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

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

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

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

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

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

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

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

*Study not powered for this analysis

Arterial Thrombotic Events (ATE)

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

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

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

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

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

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

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

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

3.5 STUDY CONCLUSIONS

The *Transatlantic Active Surveillance on Cardiovascular Safety of NuvaRing* (TASC) study was a large, four-year multinational, prospective, observational active surveillance study of new hormonal contraceptive NuvaRing users compared to users of other marketed combined oral contraceptives (COCs). Results from this study show that both the incidence and relative risks of VTE and ATE among NuvaRing users are similar to the risks observed for COC users. Based on sample size and study power, the study can determine that the VTE and ATE incidence rates are similar for the NuvaRing and COC cohorts. The study can rule out a two-fold increased risk of VTE and a threefold increased risk of ATE for NuvaRing users compared to COC users can be excluded. The study cannot conclude there is no risk between the groups, however.

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

4 DISCUSSION

The *Transatlantic Active Surveillance on Cardiovascular Safety of NuvaRing* (TASC) study was a large, four-year multinational, prospective, observational active surveillance study of new hormonal contraceptive NuvaRing users compared to users of other marketed combined oral contraceptives (COCs).

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

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

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

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

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

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

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

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

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

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

5 PROPOSED LABEL CHANGE

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

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

The following text is specific to the TASC study results.

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

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

10,000 WY). For women using COCs, (b) (4) desogestrel (DSG), gestodene (GSD) (b) (4)

Although the study did compare the incidence of VTE between NuvaRing with COCs not containing DSG/GSD/DRSP based on the recommendation of the Study Council, the study was only powered to assess no less than a twofold risk when comparing NuvaRing to COCs that excluded DSG/GSD products only. Furthermore, over 29% of the COC users were prescribed a DRSP product (n= 8,275) in addition to the 4,717 DSG/GSD users. Removing DSG, GSD, and DRSP users excludes nearly half of the original comparison cohort. A more appropriate statement based on the original study objectives would be:

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

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

A retrospective cohort study using data from 4 health plans in the US (FDA-funded Study in Kaiser Permanente and Medicaid databases) showed a VTE incidence for new users of NuvaRing (b) (4) 11.4 events per 10,000 WY (b) (4) for new users of a levonorgestrel (LNG)-containing COC of 9.2 events per 10,000 WY.

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

As written, the text presents incidence rates for the

TASC study

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

(b) (4)

Incidence rates for comparable groups would include the following

TASC study

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

FDA study:

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

In comparison, a retrospective cohort study using data from 4 health plans in the US (FDA-funded Study in Kaiser Permanente and Medicaid databases) showed VTE incidence for new users of NuvaRing (b) (4) 11.4 events per 10,000 WY, (b) (4)

6 RECOMMENDATIONS

The epidemiologic information proposed for the revised NuvaRing PLR label is generally acceptable and follows the format of the information included in the label of other contraceptive products with recently revised labels.

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

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

TASC study

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

(b) (4)

Although the differences are minor, the text in the label that presents incidence information should compare the incidence rates of comparable groups for the two studies since the information is available. OSE/DEPI recommends using the following comparisons for the incidence rates in the text preceding Table 1:

TASC study

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

FDA study:

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

APPENDIX 1 – EPIDEMIOLOGY EXCERPT IN PROPOSED LABEL

The following warnings and precautions are principally based on experience in women using combination oral contraceptives and are also considered applicable to NuvaRing.

5.1 Thromboembolic Disorders and Other Vascular Problems

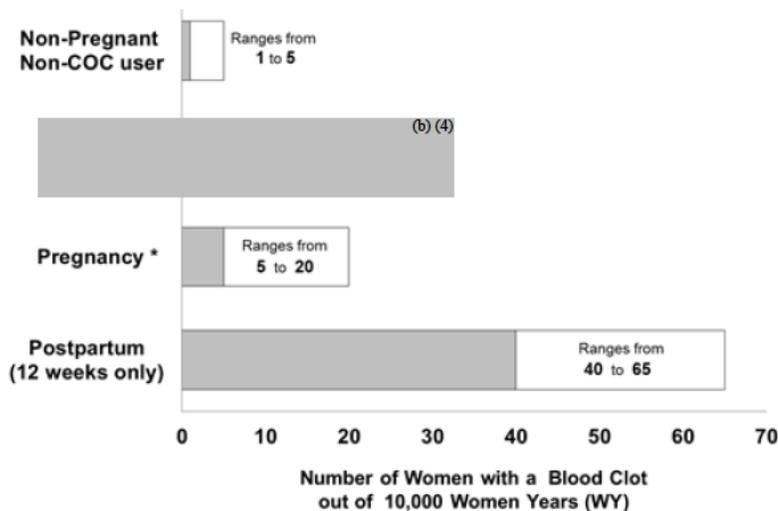
Stop NuvaRing use if an arterial or venous thrombotic event occurs.

The use of combined oral contraceptives (COCs) increases the risk of venous thromboembolism (VTE).



Figure 1 shows the risk of developing a VTE for women who are not pregnant and do not use oral contraceptives, for women who use oral contraceptives, for pregnant women, and for women in the postpartum period. To put the risk of developing a VTE into perspective: If 10,000 women who are not pregnant and do not use oral contraceptives are followed for one year, between 1 and 5 of these women will develop a VTE.

Figure 1: Likelihood of Developing a VTE



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

In studies required or sponsored by regulatory agencies, NuvaRing users had a risk of VTE similar to COC users (see Table 1 for adjusted hazard ratios). A large prospective, observational study, the Transatlantic Active Surveillance on Cardiovascular Safety of

NuvaRing (TASC), investigated the risk of VTE for new users, (b) (4) NuvaRing and COCs in a population that is representative of routine clinical users. The women were followed for 24 to 48 months. The results showed a similar risk of VTE among NuvaRing users (VTE incidence 8.3 per 10,000 WY) and women using COCs (VTE incidence 9.2 per 10,000 WY). For women using COCs, (b) (4) desogestrel (DSG), gestodene (GSD) (b) (4) VTE incidence was (b) (4) per 10,000 WY.

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

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

Epidemiologic Study (Author, Year of Publication) Population Studied	Comparator Product(s)	Hazard Ratios (HR) (95% CI)
TASC (Dinger, 2012) Initiators, including new users, switchers and restarters	All COCs available during the course of the study * COCs available excluding DSG-, GSD-, (b) (4) containing OCs	HR†: 0.8 (0.5-1.5) HR†: 0 (b) (4) (0.4- (b) (4))
FDA-funded Study in Kaiser Permanente and Medicaid databases (Sidney, 2011) First use of a combined hormonal contraceptive (CHC) during the study period	COCs available during the course of the study‡ LNG/0.03 mg ethinyl estradiol	HR§: 1 (b) (4) ((b) (4)) HR§: (b) (4) ((b) (4))

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

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

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

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

(b) (4)

Several epidemiology studies indicate that third generation oral contraceptives, including those containing desogestrel (etonogestrel, the progestin in NuvaRing, is the biologically active metabolite of desogestrel), ^{(b) (4)} associated with a higher risk of venous thromboembolism than ^{(b) (4)} oral contraceptives. In general, these studies indicate an approximate two-fold increased risk, which corresponds to an additional one to two cases of venous thromboembolism per 10,000 women-years of use. However, data from ^{(b) (4)} studies have not shown this two-fold increase in risk.

(b) (4)

APPENDIX 2: STUDY SUMMARY

Table 1 – Transatlantic Active Surveillance on Cardiovascular Safety of NuvaRing (TASC) Study

	Study																
1.1 Objectives	Primary: Absolute & Relative Risk of VTE & ATE Secondary: Utilization Patterns																
1.2.1 Design																	
1.2.1.1 Type	Large, international, prospective, non-interventional, long-term cohort study.																
1.2.1.2 Data Source	Personal baseline interviews at prescribing visit and mail follow-up of contraceptive initiators in Europe and the US.																
1.2.1.3 Time Period	2007 to 2011																
1.2.1.4 Criterion (Selection) Standards	NuvaRing & combined oral contraceptive (COC) initiators from Austria France, Germany, Italy, Russia, and the United States.																
1.2.1.5 Protected Health Information	Approval provided by the ethical committee of the physicians' association in Berlin, Germany, home of the coordinating center & of each participating countries																
1.2.2 Setting	Regular clinical visits and mail questionnaires																
1.2.3 Exposure	Initiation of NuvaRing or other COCs																
1.2.4 Outcome(s)	VTE (PE, DVT), ATE (AMI, CVA)																
1.2.5 Covariates	DOB, menstrual hx, pregnancies, BMI, smoking hx, family & personal hx VTE & ATE, cancer, surgery, concomitant meds, education, travel, medical conditions																
1.2.6 Sample Size	33,295 women enrolled																
1.2.7 Statistical Analyses	Incidence rates & Cox Proportional Regression																
1.2.8 Study Results (if relevant)	<p>Incidence Rates per 10,000 WY</p> <table style="margin-left: 20px;"> <thead> <tr> <th></th> <th style="text-align: center;">VTE</th> <th style="text-align: center;">ATE</th> </tr> </thead> <tbody> <tr> <td>NuvaRing</td> <td style="text-align: center;">8.3 (5.0-12.9)</td> <td style="text-align: center;">2.2 (0.7-5.1)</td> </tr> <tr> <td>COCs</td> <td style="text-align: center;">9.2 (6.0-13.5)</td> <td style="text-align: center;">2.8 (1.2-5.6)</td> </tr> <tr> <td>COC_{op}</td> <td style="text-align: center;">8.9 (5.5-13.6)</td> <td style="text-align: center;">2.5 (0.9-5.5)</td> </tr> </tbody> </table> <p>Hazard Ratios (adjusted for age, BMI, duration of current use, family history of VTE)</p> <table style="margin-left: 20px;"> <tbody> <tr> <td>NuvaRing vs. COC:</td> <td style="text-align: center;">0.8 (0.5-1.5)</td> </tr> <tr> <td>NuvaRing vs. COC_{op}</td> <td style="text-align: center;">0.8 (0.4-1.7)</td> </tr> </tbody> </table>		VTE	ATE	NuvaRing	8.3 (5.0-12.9)	2.2 (0.7-5.1)	COCs	9.2 (6.0-13.5)	2.8 (1.2-5.6)	COC _{op}	8.9 (5.5-13.6)	2.5 (0.9-5.5)	NuvaRing vs. COC:	0.8 (0.5-1.5)	NuvaRing vs. COC _{op}	0.8 (0.4-1.7)
	VTE	ATE															
NuvaRing	8.3 (5.0-12.9)	2.2 (0.7-5.1)															
COCs	9.2 (6.0-13.5)	2.8 (1.2-5.6)															
COC _{op}	8.9 (5.5-13.6)	2.5 (0.9-5.5)															
NuvaRing vs. COC:	0.8 (0.5-1.5)																
NuvaRing vs. COC _{op}	0.8 (0.4-1.7)																
ATE: arterial thrombotic events; VTE: venous thromboembolic events; PE: pulmonary embolism; DVT: deep vein thrombosis; hx: history; BMI: body mass index (height & weight); AMI: acute myocardial infarction; CVA: cerebrovascular accidents																	

APPENDIX 3: DBVII TASC REPORT



DBVII Tasc Study
Report

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

/s/

RITA P OUELLET-HELLSTROM
08/27/2013

DAVID G MOENY
08/27/2013

JUDY A STAFFA
08/27/2013

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

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

Application: 21187 /S-021

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

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

Applicant: Organon USA, Inc.

Submission Date: December 5, 2012

Receipt Date: December 5, 2012

Regulatory History and Applicant's Main Proposals

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

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

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

Review of the Prescribing Information (PI)

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

Conclusions/Recommendations

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

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

Selected Requirements of Prescribing Information (SRPI)

Appendix

Selected Requirements of Prescribing Information (SRPI)

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

Highlights (HL)

GENERAL FORMAT

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

Comment:

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

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

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

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

Comment:

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

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

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

Selected Requirements of Prescribing Information (SRPI)

Comment:

YES

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

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

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

Comment:

YES

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

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES

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

Comment:

Highlights Limitation Statement

NO

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

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

Product Title

YES

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

Comment:

Initial U.S. Approval

YES

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

Comment:

Selected Requirements of Prescribing Information (SRPI)

Boxed Warning

- NO** 12. All text must be **bolded**.
Comment: All text is not bolded
- YES** 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).
Comment:
- YES** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.
Comment:
- YES** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)
Comment:
- YES** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).
Comment:

Recent Major Changes (RMC)

- YES** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
Comment:
- YES** 18. Must be listed in the same order in HL as they appear in FPI.
Comment:
- YES** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.
Comment:
- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).
Comment:

Indications and Usage

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

Dosage Forms and Strengths

Selected Requirements of Prescribing Information (SRPI)

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

Comment:

Contraindications

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

Comment:

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

Comment:

Adverse Reactions

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

Comment:

Patient Counseling Information Statement

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

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

- “**See 17 for PATIENT COUNSELING INFORMATION**”

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

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

Comment:

Revision Date

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

Comment: *Revision date is missing*

Contents: Table of Contents (TOC)

GENERAL FORMAT

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

Comment:

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

Comment:

Selected Requirements of Prescribing Information (SRPI)

- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.
Comment:
- NO** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.
Comment:
- YES** 32. All section headings must be **bolded** and in UPPER CASE.
Comment:
- YES** 33. All subsection headings must be indented, not bolded, and in title case.
Comment:
- YES** 34. When a section or subsection is omitted, the numbering does not change.
Comment:
- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”
Comment:
-

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.
Comment:
- YES** 37. All section and subsection headings and numbers must be **bolded**.
Comment:
- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

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

Selected Requirements of Prescribing Information (SRPI)

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

Comment:

YES

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

Comment:

YES

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

Comment:

YES

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

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

YES

42. All text is **bolded**.

Comment:

YES

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

Comment:

YES

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

Comment:

Contraindications

N/A

45. If no Contraindications are known, this section must state “None”.

Selected Requirements of Prescribing Information (SRPI)

Comment:

Adverse Reactions

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

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

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

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

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

Comment:

Patient Counseling Information

- YES** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment:

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

/s/

ZETA-MAE C WILLIAMSON
01/23/2013