

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-187

CHEMISTRY REVIEW(S)

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS - HFD-580
Review of Chemistry, Manufacturing and Controls

NDA #: 21-187

CHEMISTRY REVIEW #: 4

DATE REVIEWED: 05-SEP-2001

| <u>SUBMISSION TYPE</u> | <u>DOCUMENT DATE</u> | <u>CDER DATE</u> | <u>ASSIGNED DATE</u> |
|-------------------------------|-----------------------------|-------------------------|-----------------------------|
| Original | 28-DEC-99 | 28-DEC-99 | 07-JAN-00 |
| Amendment | 02-AUG-01 | 03-AUG-01 | |

NAME & ADDRESS OF SPONSOR: Organon Inc.
375 Mt. Pleasant
West Orange, NJ 07052

DRUG PRODUCT NAME:

Proprietary: NuvaRing
Nonproprietary/Established/USAN: Etonogestrel/Ethinyl estradiol
Code Name/#: Org 37681
Chem.Type/Ther.Class: IS

PARMACOLOGICAL CATEGORY/INDICATION: Progestin, estrogen/Prevention of pregnancy
DOSAGE FORM: Insert, Extended Release [Ring]
STRENGTHS: 0.120 mg/0.015 mg per day
ROUTE OF ADMINISTRATION: Vaginal
DISPENSED: Rx OTC
SPECIAL PRODUCTS: Yes No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

- a. Etonogestrel: 13-ethyl-17-hydroxy-11-methylene-18,19-dinor-17 α -pregn-4-en-20-yn-3-one
C₂₂H₂₈O₂
MW 324.46
- b. Ethinyl estradiol: 19-nor-17 α -pregna-1,3,5(10)-trien-20-yne-3,17-diol
C₂₀H₂₄O₂
MW 296.41

See Chemistry Review #1 for structural formulas.

RELATED DOCUMENTS:

None

SUPPORTING DOCUMENTS:

See Chemistry Review #2.

PATENT STATUS:

See Chemistry Review #1.

CONSULTS:

See Chemistry Review #2.

REMARKS/COMMENTS:

The August 2, 2001 amendment contains responses to the Agency's April 27, 2001 Approvable Letter.

NDA #21-187

Sponsor: Organon Inc.

Drug: Nuvaring
(etonogestrel/ethinyl estradiol ring)

CONCLUSIONS & RECOMMENDATIONS:

This NDA may be approved from a Chemistry, Manufacturing and Controls point of view.

cc:

Orig. NDA #21-187
HFD-580/Division File
HFD-580/JMercier
HFD-580/MRhee/DLin
HFD-820/EDuffy

David T. Lin, Ph.D.
Review Chemist

R/D Init by:

Addendum to Summary of Chemistry Review of NDA 21-187
(Second Review Cycle), Nuvaring

A. Drug Product:

1) Labeling:

The sponsor agreed via an e-mail on April 26, 2001, to make changes as requested from this review cycle, however, the sponsor proposed to overlabel the sachet with the newly changed information for the first 3 months after approval.

This proposal is acceptable and it will be formally reviewed when the sponsor submits an amendment for the next review cycle.

C. Conclusion and Recommendation:

From chemistry, manufacturing, and controls point of view, as the primary reviewer recommends, this NDA is **approvable** pending formal review of these labeling issues.

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader
For the Division of reproductive and Urologic Drug Products
DNDC II, Office of New Drug Chemistry

Memorandum

To: NDA 21-187, Nuvaring (etonogestrel/ethinyl estradiol vaginal ring)
Through: Moo-Jhong Rhee, Ph.D.
From: David Lin, Ph.D.
Date: April 27, 2001
Re: Addendum to Chemistry Review #3

The sponsor has tentatively agreed to the CMC labeling comments (addition of "Vaginal" to the established name and revision of the storage statement) made in Chemistry Review #3. This agreement was made through a proposal submitted as an email attachment. The sponsor will agree to the changes if they are allowed to overlabel their printed sachet and carton labels with the FDA's proposed wording. This overlabeling will be done via a manual operation with peel-proof stickers containing the correct wording. The sponsor will use labels with the correct wording within 3 months of approval. The sponsor's proposal is acceptable. **However, since the sponsor's agreement was not officially submitted as an amendment to the NDA, the CMC recommendation is still Approvable. When the sponsor's agreement is submitted as an amendment in the next review cycle, the NDA may be Approved.**

cc:
Orig. NDA #21-187
HFD-580/Division File
HFD-580/JMercier
HFD-580/MRhee/DLin

Memorandum

To: NDA 21-187, Nuvaring (etonogestrel/ethinyl estradiol vaginal ring)
Through: Moo-Jhong Rhee, Ph.D.
From: David Lin, Ph.D.
Date: April 17, 2001
Re: Chemistry Review #3 (2/28/01 Amendment to 12/22/00 Approvable Letter)

Since the last CMC review (#2) during the first review cycle, the sponsor has corrected the chemical name for etonogestrel. However, there are still three pending labeling issues. The first issue concerns OPDRA's recommendation that the established name be revised from "etonogestrel/ethinyl estradiol ring" to "etonogestrel/ethinyl estradiol vaginal ring". This comment was previously conveyed to the sponsor during the December 22, 2000 teleconference, but was not addressed in the sponsor's February 28, 2001 amendment. The second issue is the inclusion in the Physician Package Insert and the Patient Package Insert the "storing above 86°F (30°C)" phrase to the following statement, "avoid direct sunlight or storing above 86°F (30°C)". Although the storage condition is currently written as "Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F)", this additional phrase is important because of the unknown clinical significance of the "burst effect", the initial high release of hormones, that occurs when this product is initially stored at refrigerated conditions followed by storage above room temperature conditions 25°C (77°F). The third issue relates to the second labeling issue and concerns the addition of the statement, "Avoid storing above 86°F (30°C)", to the sachet and carton labels.

From a CMC point of view, this NDA may be approved pending satisfactory resolution of the labeling issues.

cc:
Orig. NDA #21-187
HFD-580/Division File
HFD-580/JMercier
HFD-580/MRhee/DLin

DEC 22 2000

Memorandum

To: NDA 21-187, Nuvaring (etonogestrel/ethinyl estradiol vaginal ring)

Through: Moo-Jhong Rhee, Ph.D.

From: David Lin, Ph.D.

Date: December 22, 2000

Re: Addendum to Chemistry Review #2

/S/

/S/

12/22/00

re 12/22/00

OPDRA has proposed the established name for this drug product should be "etonogestrel/ethinyl estradiol vaginal ring" instead of "etonogestrel/ethinyl estradiol ring". This recommendation was conveyed to the sponsor during the 12/22/00 telecon, with the explanation that this would maintain consistency with currently approved drug products which contain the route of administration in the established name. Examples include Estring (estradiol vaginal ring), transdermal products and intrauterine device drug products. In addition to this issue concerning the established name, there are other pending clinical labeling issues with the sponsor's proposed physician insert. **Therefore, the issue of the established name will be addressed after the sponsor has satisfactorily responded to this labeling issue and the other clinical labeling issues.**

cc:

Orig. NDA #21-187

HFD-580/Division File

HFD-580/JMercier

HFD-580/MRhee/DLin

DEC 21 2000

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS - HFD-580
Review of Chemistry, Manufacturing and Controls

NDA #: 21-187

CHEMISTRY REVIEW #: 2

DATE REVIEWED: 21-DEC-2000

| <u>SUBMISSION TYPE</u> | <u>DOCUMENT DATE</u> | <u>CDER DATE</u> | <u>ASSIGNED DATE</u> |
|------------------------|----------------------|------------------|----------------------|
| Original | 28-DEC-99 | 28-DEC-99 | 07-JAN-00 |
| Amendment | 06-OCT-00 | 10-OCT-00 | 10-OCT-00 |
| Amendment | 06-OCT-00 | 10-OCT-00 | 10-OCT-00 |
| Amendment | 19-OCT-00 | 20-OCT-00 | |
| Amendment | 24-OCT-00 | 25-OCT-00 | |
| Amendment | 14-NOV-00 | 15-NOV-00 | 16-NOV-00 |
| Amendment | 13-DEC-00 | 18-DEC-00 | |
| Amendment | 14-DEC-00 | 21-DEC-00 | |

NAME & ADDRESS OF SPONSOR:

Organon Inc.
375 Mt. Pleasant
West Orange, NJ 07052

DRUG PRODUCT NAME:

Proprietary: NuvaRing
Nonproprietary/Established/USAN: Etonogestrel/Ethinyl estradiol
Code Name/#: Org 37681
Chem.Type/Ther.Class: 1S

PHARMACOLOGICAL CATEGORY/INDICATION: Progestin, estrogen/Prevention of pregnancy
DOSAGE FORM: Insert, Extended Release [Ring]
STRENGTHS: 0.120 mg/0.015 mg per day
ROUTE OF ADMINISTRATION: Vaginal
DISPENSED: Rx OTC
SPECIAL PRODUCTS: Yes No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

- a. Etonogestrel: 13-ethyl-17-hydroxy-11-methylene-18,19-dinor-17 α -pregn-4-en-20-yn-3-one
C₂₂H₂₈O₂
MW 324.46
- b. Ethinyl estradiol: 19-nor-17 α -pregna-1,3,5(10)-trien-20-yne-3,17-diol
C₂₀H₂₄O₂
MW 296.41

See Chemistry Review #1 for structural formulas.

RELATED DOCUMENTS:

None

PATENT STATUS:

See Chemistry Review #1.

CONSULTS:

1. The Division of Biopharmaceutics has been consulted for the in-vitro release specifications.
2. The overall EER recommendation from the Office of Compliance is acceptable (see Appendix A).

- 3. The proposed trademark, NuvaRing, has been consulted to OPDRA and determined to be acceptable (see Appendix B). The general labeling comments in section II of the OPDRA review (dated 10/11/00) have been addressed by the sponsor (see Labeling Section).

REMARKS/COMMENTS:

The October 6, 2000 amendment contains responses to the Agency's September 20, 2000 Information Request Letter.

The October 19, 2000 amendment contains a letter of authorization to allow the DMF holder for DMF to cross-reference "leachables" testing data and biological reactivity test data from this NDA.

The October 24, 2000 amendment contains an updated ethinyl estradiol assay and related substances

The November 14, 2000 amendment contains clarification of the sponsor's responses in the 10/6/00 amendment.

The December 13, 2000 amendment contains a Phase IV commitment to develop a non-automated alternate for the in vitro release analytical method; to be provided within one year from the date of the Agency's action.

The December 14, 2000 amendment contains the final agreed upon in-vitro release specifications and acceptance criteria.

CONCLUSIONS & RECOMMENDATIONS:

This NDA may be approved from a Chemistry, Manufacturing and Controls point of view.

cc:
Orig. NDA #21-187
HFD-580/Division File
HFD-580/JMercier
HFD-580/MRhee/DLin
HFD-820/JGibbs/SKoepeke

12/21/00
DSL
David T. Lin, Ph.D.
Review Chemist

R/D Init by: *DSL* *12/21/00*

Marcia

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS - HFD-580
Review of Chemistry, Manufacturing and Controls

NDA #: 21-187

CHEMISTRY REVIEW #: 1

DATE REVIEWED: 15-SEP-2000

| <u>SUBMISSION TYPE</u> | <u>DOCUMENT DATE</u> | <u>CDER DATE</u> | <u>ASSIGNED DATE</u> |
|------------------------|----------------------|------------------|----------------------|
| Original | 28-DEC-99 | 28-DEC-99 | 07-JAN-00 |
| Amendment | 08-MAR-00 | 09-MAR-00 | |
| Amendment | 01-JUN-00 | 02-MAR-00 | |
| Amendment | 11-AUG-00 | 12-AUG-00 | |
| Amendment | 29-AUG-00 | 30-AUG-00 | |

NAME & ADDRESS OF SPONSOR: Organon Inc.
375 Mt. Pleasant
West Orange, NJ 07052

DRUG PRODUCT NAME:

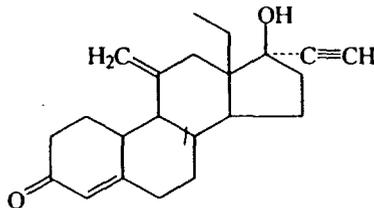
Proprietary: NuvaRing
Nonproprietary/Established/USAN: Etonogestrel/Ethinyl estradiol
Code Name/#: Org 37681
Chem.Type/Ther.Class: 1S

PHARMACOLOGICAL CATEGORY/INDICATION: Progestin, estrogen/Prevention of pregnancy
DOSAGE FORM: Insert, Extended Release [Ring]
STRENGTHS: 0.120 mg/0.015 mg per day
ROUTE OF ADMINISTRATION: Vaginal
DISPENSED: Rx OTC
SPECIAL PRODUCTS: Yes No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

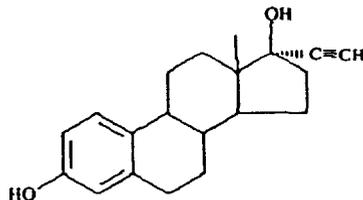
a. Etonogestrel: 13-ethyl-17-hydroxy-11-methylene-18,19-dinor-17 α -pregn-4-en-20-yn-3-one

C₂₂H₂₈O₂
MW 324.46



b. Ethinyl estradiol: 19-nor-17 α -pregna-1,3,5(10)-trien-20-yne-3,17-diol

C₂₀H₂₄O₂
MW 296.41



SUPPORTING DOCUMENTS:

| Type/Number | Subject | Holder | Status | Review Date | Letter Date |
|--------------------------|---------|--------|--------|-------------|-------------|
| [Redacted Table Content] | | | | | |

RELATED DOCUMENTS:

none

PATENT STATUS:

| Patent No. | Type | Expiration | Patent Owner |
|------------|--|------------|-----------------|
| 5,989,581 | Product (directed to a drug delivery system) | 4/8/2018 | Akzo Nobel N.V. |

CONSULTS:

1. The Division of Biopharmaceutics has been consulted for the in-vitro release specifications.
2. The EER was sent to Compliance on February 4, 2000 (the overall recommendation is pending; see Appendix A).
3. The proposed trademark, NuvaRing, has been consulted to OPDRA. The final recommendation is pending.

REMARKS/COMMENTS:

NuvaRing® (Org 37681) is a Combined Contraceptive Vaginal Ring, which releases 120 µg etonogestrel (Org 3236) and 15 µg ethinyl estradiol (Org 224) daily for use as a contraceptive. It is a transparent, colorless to almost colorless ring with an outer diameter of 54 mm and a cross-sectional diameter of 4 mm. Each cycle consists of a three (3) consecutive week period followed by a one week ring-free period. The ring is manufactured by ring-closure of 157 mm of skin-core fiber. Its core consists of Evatane® 28-25 (ethylene vinylacetate copolymer with 28% vinyl acetate) loaded with etonogestrel and ethinyl estradiol. The skin is made of Evatane® 1020 VN3 (ethylene vinylacetate copolymer with 9% vinyl acetate). The Evatane® materials are supplied by the manufacturer, [Redacted] NuvaRing® is manufactured by N.V. Organon, Oss, The Netherlands. The proposed commercial batch size is 32 kg (approximately 15,000 rings). The rings will be packaged for commercial sale in reclosable aluminum laminate sachets by N.V.

Organon, Oss, The Netherlands. The sachetted rings are over-packaged into pre-printed folding cartons with patient labeling inserts by Organon Inc., Allentown, Pennsylvania. The main advantages of the vaginal ring compared to oral contraceptives are the more constant steroid levels built up in comparison with oral formulations, the avoidance of the hepatic first-pass effects and the potential for a better patient compliance.

The March 8, 2000 amendment contains additional information for the Methods Validation Package.

The June 1, 2000 amendment contains comparative in-vitro release profiles and accelerated stability data on process validation batches.

The August 11, 2000 amendment contains clarification of the ethinyl estradiol test methods, clarification of the in-vitro release values presented in the NDA, addition information on the previous in-vitro release test method, and addition information on the in-vitro release test method apparatus.

The August 29, 2000 amendment contains additional primary stability data.

CONCLUSIONS & RECOMMENDATIONS:

This NDA is approvable pending satisfactory resolution of the issues delineated in the draft letter.

cc:

- Orig. NDA #21-187
- HFD-580/Division File
- HFD-580/JMercier
- HFD-580/MRhee/DLin
- HFD-820/JGibbs/SKoepeke

R/D Init by:

DSL 7/18/00

DSL 9/15/00

David T. Lin, Ph.D.
Review Chemist