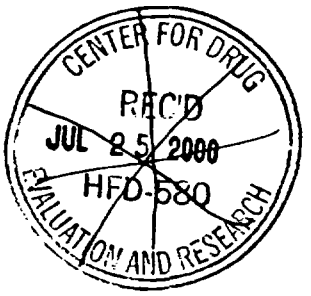
AKZO NOBEL

Organon Inc.

July 24, 2000

CONFIDENTIAL

Dr. Karl Lin
Division of Biometrics II
Center for Drug Evaluation and Research (HFD-715)
Office of Biostatistics
Document Control Room 10B06
5600 Fishers Lane
Rockville, Maryland 20857



NDA No. 21-187
NuvaRing® (etonogestrel / ethinyl estradiol ring)
DESK COPY
(24 Month Oncogenicity Study)

Dear Dr. Lin:

Reference is made to our New Drug Application (No. 21-187) for NuvaRing® (etonogestrel / ethinyl estradiol ring) which was submitted on December 28, 1999. Reference is also made to the telephone conversation between yourself and Mr. Edward Nellis (Organon Inc.) on Friday (July 21, 2000).

As agreed during the aforementioned telephone conversation, Organon is providing you with a desk copy of our "24 Month Oncogenicity Study of Org 3236 in the Rat via Subcutaneous Implants" which is identified by the Organon Report Number SDGRR# 4412, and which is enclosed herein. This report was copied directly from the NuvaRing NDA (Volumes 45-52) and represents a true copy of the study report as provided in the original NDA.

We are also in the process of evaluating your request for electronic (SAS) datasets for this study. As indicated by Mr. Nellis during the July 21st telephone conversation, these datasets are not currently available in electronic form, and we had previously been granted a waiver by the Agency with regard to this requirement. However, in an effort to facilitate your review we will try to accommodate your needs to the extent possible (although we cannot make any definite commitment regarding submission of electronic datasets at this time). Upon completion of our evaluation we will let you know if it will be possible for Organon to provide this information in electronic form (i.e. as SAS datasets).

Organon

Please note that Organon Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of 18 U.S.C. and Title 21 of the Code of Federal Regulations.

Should you have any questions or comments concerning this submission, please contact Mr. Edward Nellis at (973) 325-4904.

Sincerely,

Edwina Muir
Associate Director, Regulatory Affairs

EN/cjw

Enclosures

Submitted via Federal Express Airbill No. 810474969293

cc: [redacted]
w/o enclosures
via Federal Express Airbill No. 810494769308

Dr. Krishan Raheja (FDA/CDER/DRUDP)
w/o enclosures
Via Federal Express Airbill No. 810494769319

AKZO NOBEL

Confidential

Organon Inc.

July 6, 2000

ORIGINAL

Susan Allen, M.D. Acting Director
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation II
Document Control Room 17B45
5600 Fishers Lane
Rockville, Maryland 20857

ORIG AMENDMENT

BM

NDA No. 21-187
NuvaRing® (etonogestrel/ethinyl estradiol ring)
Clinical Amendment

Dear Dr. Allen:

Reference is made to our New Drug Application for NuvaRing® (etonogestrel/ethinyl estradiol ring), submitted on December 28, 1999. Reference is also made to the telephone conversation between the undersigned and Ms. Jenine Best on June 29, 2000 during which Ms. Best was informed that **Organon has reanalyzed the data from study 068003**.

During a clinical quality assurance audit of study 068003, it was discovered that, in some of the later months of this study, the first ring day was incorrectly represented in the database. Subsequent to this discovery, a complete reanalysis of study 068003, as well as the Integrated Summary of Effectiveness (ISE) data, were carried out. The reanalysis has resulted in necessary correction to various tables related to compliance, contraceptive efficacy, and cycle control in the clinical trial report 068003, as well as the ISE. In addition, there was a minor effect on the data in the NuvaRing® Physician and Patient Package Insert.

This reanalysis does not affect the safety data presented in NDA 21-187.

At this time, Organon is submitting a **summary document** which describes the above referenced changes. We propose that the package insert not be amended at this time, and that any changes to the efficacy data (as presented in the package insert) will be made during the final labeling discussions with the Agency.

Organon

This NDA submission is provided in paper (1 volume) and electronic format. Electronic files are supplied on 1 CD-ROM (total file size is approximately 467 KB). The CD-ROM was checked for viruses using McAfee Vshield Version 4.0.3. The CD-ROM is being provided under separate cover, directly to the Electronic Document Room.

Organon Inc.
[illegible]
[illegible]
[illegible]
USA
Tel: (973) [illegible]
Fax: (973) [illegible]

0001

Please note that Organon Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of 18 U.S.C. and Title 21 of the Code of Federal Regulations.

Should you have any questions or comments regarding this submission, please contact Edward Nellis, Assistant Manager of Regulatory Affairs at (973) 325-4904.

Sincerely,

Edwina L. Muir
Director, Regulatory Affairs

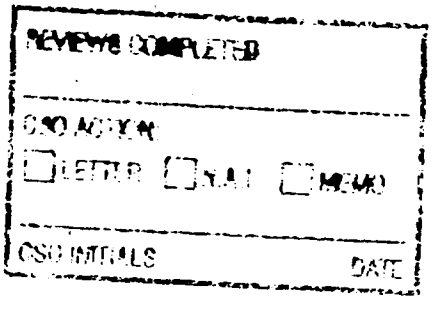
ELM/hpm

Attachment
Form FDA 356h

Review Copies:

Medical Review Copy: Volume 1
Statistical Review Copy: Volume 1

Submitted via Federal Express No. 8197 5503 4791



CD-ROM to:

Electronic Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852

Submitted via Federal Express No. 8197 5503 4806

AKZO NOBEL

Organon Inc.

June 9, 2000

ORIGINAL

CONFIDENTIAL

Electronic Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852

ORIG AMENDMENT

BZ

NDA No. 21-187
NuvaRing® (etonogestrel/ethinyl estradiol ring)
REPLACEMENT ELECTRONIC MEDIA
(for April 21, 2000 NDA Amendment)

Dear Sir / Madam:

Reference is made to our New Drug Application for NuvaRing® (etonogestrel/ethinyl estradiol ring), which was originally submitted on December 28, 1999. Further reference is made to our April 21, 2000 NDA Amendment which provided Organon responses to Reviewers' requests for additional NuvaRing® documentation. The April 21st amendment was provided in both paper and electronic format (1 CD-ROM).

Subsequent to the filing of the aforementioned amendment, it has been determined that there were certain deficiencies in the electronic files which were provided with the April 21st submission. These deficiencies involve the indexing files and hyperlinking on the CD-ROM. **At this time we are therefore providing a Replacement CD-ROM which incorporates the appropriate indexing files and which includes functional hyperlinking. Apart from the added indexing files and hyperlinking, the information content of the enclosed CD-ROM is identical to the CD-ROM provided with the April 21, 2000 submission.**

The enclosed CD-ROM (28MB) was checked for viruses using McAfee Vshield (version 4.0.3).

Please note that Organon Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of 18 U.S.C. and Title 21 of the Code of Federal Regulations.

Should you have any questions or comments concerning this submission, please contact the undersigned at (973) 325-4540.

Sincerely,

Edwina Muir
Director, Regulatory Affairs

Enclosure

Submitted via Federal Express Airbill No. 810494769709

Organon

ORIGINAL **CONFIDENTIAL**

June 1, 2000

AKZO NOBEL

Organon Inc.

Susan Allen, M.D. Acting Director
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation II
Document Control Room 17B45
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 21-187
NuvaRing® (etonogestrel/ethinyl estradiol ring)
Chemistry, Manufacturing & Controls Amendment ORIG AMENDMI

BC

Dear Dr. Allen:

Reference is made to our New Drug Application for NuvaRing® (etonogestrel/ethinyl estradiol ring), submitted on December 28, 1999. Reference is also made to the Pre-NDA meeting of July 7, 1999 during which Organon agreed to provide additional CMC information during the NDA review.

At this time, we are providing the following information, as agreed during the July 1999 meeting:

1. Comparative in-vitro release profiles between the registration/clinical batches [redacted] and the to-be-marketed batches
2. Three month accelerated stability data on process validation batches
3. Stability protocol for process validation batches

This NDA submission is provided in paper (1 volume) and electronic format. Electronic files are supplied on 1 CD-ROM (total file size is approximately 610 KB). The CD-ROM was checked for viruses using McAfee Vshield Version 4.0.3. The CD-ROM is being provided under separate cover, directly to the Electronic Document Room.

In accordance with 21 CFR 314.70(a), an identical field copy of this Chemistry, Manufacturing and Controls amendment has been prepared for simultaneous submission to the District Office of the FDA in North Brunswick, New Jersey.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Organon

Organon Inc
375 Mt Pleasant Av
New Jersey 07052
USA
Tel (973) 325-450
Fax (973) 325-456

0001

CONFIDENTIAL

Please note that Organon Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of 18 U.S.C. and Title 21 of the Code of Federal Regulations.

Should you have any questions or comments regarding this submission, please contact the undersigned at (973) 325-4540.

Sincerely,

Edwina L. Muir
Associate Director, Regulatory Affairs

ELM/

Attachment
Form FDA 356h

Review Copy:
Chemistry Review Copy: Volume 1
Submitted via Federal Express No. 808590822207

Copy to:
District Office, Volume 1
Food and Drug Administration
120 North Center Drive, Bldg. C
North Brunswick, NJ 08902

Federal Express No. 808590822218

CD-ROM to:
Electronic Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852

Federal Express No. 808590822229

AKZO NOBEL

Organon Inc.

May 16, 2000

CONFIDENTIAL

Jeanine Best, Regulatory Project Manager
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation II
Document Control Room 17B45
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 21-187
NuvaRing® (etonogestrel / ethinyl estradiol ring)
REPLACEMENT COPIES

Dear Ms. Best:

Reference is made to our New Drug Application (No. 21-187) for NuvaRing® (etonogestrel / ethinyl estradiol ring) which was submitted on December 28, 1999. Reference is also made to the May 12, 2000 telephone conversation between yourself and Mr. Edward Nellis (Regulatory Affairs Department, Organon Inc). During the telephone conversation you had requested SAS Datasets for the NuvaRing Efficacy Studies. These datasets were previously submitted to the Agency on April 14, 2000 along with certain other documentation (as requested by FDA). Attached please find a duplicated copy of the April 14th submission which contains the following documentation:

- Original April 14, 2000 Cover letter
- Attachment 1- Placebo Rings*
- Attachment 2- Product Information Inserts (MS Word files, 2 diskettes)
- Attachment 3- SAS Datasets for PK/PD Studies 34218, 34225, 34226 (one CD-ROM disk)
- Attachment 4- SAS Datasets for Efficacy Studies 34219, 068003, 068004 (one CD-ROM disk)

* Please note that Placebo Rings (Attachment 1, above) are NOT provided in the current (May 16, 2000) submission. If additional placebo rings are needed, please contact the undersigned (or Mr. Edward Nellis, Organon Regulatory Affairs Department), to arrange for these samples to be provided under separate cover.

Organon

Please note that Organon Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of 18 U.S.C. and Title 21 of the Code of Federal Regulations.

Organon Inc
375 Mt. Pleasant Av.
West Orange
New Jersey 07052
USA
Tel: (973) 325-4500
Fax: (973) 325-4565

CONFIDENTIAL

Should you have any questions or comments concerning this submission, please contact the undersigned at (973) 325-4540; or Mr. Edward Nellis at (973) 325-4904.

Sincerely,

(for)

Edwina Muir
Associate Director, Regulatory Affairs

ELM/cjw

Enclosures

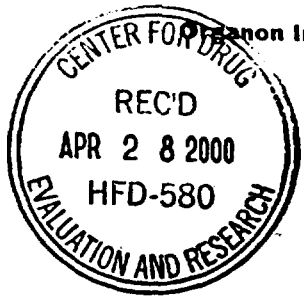
Submitted via Federal Express Airbill No. 810494769179

CONFIDENTIAL

AKZO NOBEL

April 27, 2000

Organon Inc.



Susan Allen, M.D. Acting Director
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation II
Document Control Room 17B45
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 21-187
NuvaRing® (etonogestrel/ethinyl estradiol ring)
120 Day Safety Update
Labeling Amendment

Dear Dr. Allen:

Reference is made to our New Drug Application for NuvaRing® (etonogestrel/ethinyl estradiol ring), submitted on December 28, 1999. In accordance with 21 CFR 314.50(d)(5)(vi)(a), we herewith submit an update to the safety information provided in the original NDA. The final study report for Protocol 068004 is also being submitted at this time.

In addition, we are also submitting revised container (sachet) labeling for the trade, clinic and professional sample packages. Please note that these changes were sent to the Division via e-mail on April 3, 2000 for a preliminary review by the Chemist. Feedback from David Lin indicated that these changes were acceptable.

This NDA submission is provided in paper (7 volumes) and electronic format. Electronic files are supplied on 1 CD-ROM (total file size is approximately 34 MB). The CD-ROM was checked for viruses using McAfee Vshield Version 4.0.3. As in the original NDA, domain files and patient profiles are provided for Study 068004, in place of SAS transport files.

Please note that Organon Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of 18 U.S.C. and Title 21 of the Code of Federal Regulations.

Should you have any questions or comments regarding this submission, please contact the undersigned at (973) 325-4540.

Sincerely,

Edwina L. Muir
Associate Director, Regulatory Affairs

Organon

ELM/
Attachments
Form FDA 356h
Volume 1 – chemistry review copy
Volumes 1 thru 7 – clinical review copy
Volumes 2 thru 7 – statisical review copy

Submitted via Federal Express No 819754455912

0001

Organon Inc.
375 Mt. Pleasant
West Orange
New Jersey 0705
USA
Tel: (973) 325-4
Fax: (973)-325-4

ORIGINAL

CONFIDENTIAL

April 27, 2000

AKZO NOBEL

Organon Inc.

Electronic Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852

SU / BL

NDA No. 21-187
NuvaRing® (etonogestrel/ethinyl estradiol ring)
120 Day Safety Update
Labeling Amendment

Dear Sir/Madam:

Reference is made to our New Drug Application for NuvaRing® (etonogestrel/ethinyl estradiol ring), submitted on December 28, 1999. At this time, we are submitted the 120 Day Safety Update and a labeling amendment, in the form of an electronic and paper submission. The paper copy has been sent to the Division Document Room, HFD-580.

Electronic files are supplied on 1 CD-ROM (total file size is 34 MB). The CD-ROM was checked for viruses using McAfee Vshield Version 4.0.3.

Please note that Organon Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of 18 U.S.C. and Title 21 of the Code of Federal Regulations.

Should you have any questions or comments regarding this submission, please contact the undersigned at (973) 325-4540.

Sincerely,

Edwina L. Muir
Associate Director, Regulatory Affairs

ELM/

Attachment
Form FDA 356h

Submitted via Federal Express No 8197 5445 5923

Organon

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

Organon Inc
375 Mt. Pleasant Avenue
West Orange
New Jersey 07052
USA
Tel: (973) 325-4500
Fax: (973)-325-4589

AKZO NOBEL

Organon Inc.

April 24, 2000

ORIGINAL **CONFIDENTIAL**

Ms. Jennifer Mercier
Regulatory Project Manager
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation II
Document Control Room 17B45
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 21-187
NuvaRing® (etonogestrel/
ethinyl estradiol ring)
Replacement Copies
(for 4/21/2000 NDA Amendment/Vol. 4)

NC

Dear Ms. Mercier:

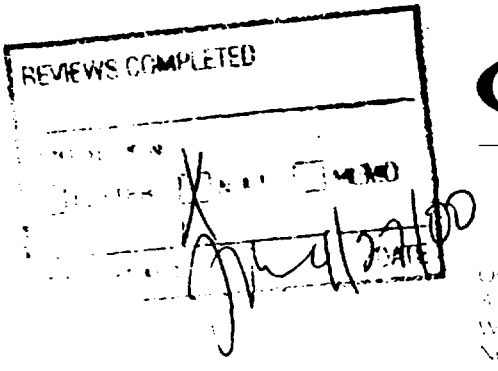
As requested during your April 24, 2000 telephone conversation with Mr. Edward Nellis (Regulatory Affairs Department, Organon Inc.,), enclosed you will find one archival copy (and one clinical section copy) of "Volume 4" from our April 21, 2000 NDA Amendment.

Please note that Organon Inc. regards this submission and all correspondences related thereto as confidential, trade secret and proprietary information and hereby claims protection from disclosure under the applicable sections of 18 U.S.C. and 21 CFR.

Should you have any questions or need further information, please do not hesitate to contact the undersigned at (973) 325-4540.

Sincerely,

Edwina L. Muir
Associate Director, Regulatory Affairs



Organon

EN/cjw

Enclosures

Submitted in Duplicate
via Federal Express Airbill No. 810494769742

CONFIDENTIAL

April 21, 2000

AKZO NOBEL

Organon Inc.

Susan Allen, M.D. Acting Director
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation II
Document Control Room 17B45
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 21-187
NuvaRing® (etonogestrel/ethinyl estradiol ring)
Response to Reviewers' Requests

Dear Dr. Allen:

Reference is made to our New Drug Application for NuvaRing® (etonogestrel/ethinyl estradiol ring), submitted on December 28, 1999. Reference is also made to the February 24, 2000 telephone conversation between Ms. Jennifer Mercier of your Division and the undersigned, during which Ms. Mercier indicated that NDA No. 21-187 had been filed by FDA, and that the reviewers requested some information/clarification. Further reference is made to the March 3, 2000 email from Ms. Mercier clarifying the previous statistical request, and providing additional requests from the Biopharmaceutics reviewer.

Clarifications of site number system and status of studies 068004 and 34224 were provided verbally to Ms. Mercier on February 24, 2000. Desk copies of the requested placebo rings, datasets and package insert on diskette have been provided on April 14, 2000.

At this time, the remaining February 24th and March 3rd requests from reviewers are being addressed:

Biopharm:

Comment 1: The validity of whether the clinically-tested formulation is identical to the to-be marketed formulation needs to be confirmed based on the cover letter stating that changes to the [redacted] occurred.

Response: The clinical formulation of the NuvaRing is identical to the to-be-marketed formulation. Detailed information can be found in the section labeled **Investigational Formulation.**

Organon

Organon Inc
375 Mt. Pleasant Avenue
West Orange
New Jersey 07052
USA
tel: (973) 325-4500
fax: (973) 325-4589

CONFIDENTIAL

Comment 2: Since ENG is s new molecular entity and only information on in vitro human hepatic microsomes study was provided in the original NDA, information on human mass balance of ENG, on specific human enzymes/pathways that metabolizes ENG, and on the induction or inhibition potential of humans should be submitted as private reports or published literature.

Response: Information on metabolism of etonogestrel can be found in the section labeled **Etonogestrel Metabolism.**

Comment 3: Proposed in vitro release method was mentioned in the Human PK/BA summary. However, details of the method such as content of release media and method conditions were absent. No proposed specifications for the in vitro release of ENG and EE were stated.

Response: The requested information was included in the Chemistry, Manufacturing and Controls section of the original NDA. For ease of review, it is also being provided in the section labeled **In-vitro Release Test.**

Clinical

Comment 4: Please analyze efficacy data for women up to age 35.

Response: Analysis of the efficacy data for women under 35 years has been performed, and the data are provided in the section labeled **Efficacy by Age**.

This NDA submission is provided in paper (4 volumes) and electronic format. Electronic files are supplied on 1 CD-ROM (total file size is approximately 28 MB). The CD-ROM was checked for viruses using McAfee Vshield Version 4.0.3.

Please note that Organon Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of 18 U.S.C. and Title 21 of the Code of Federal Regulations.

Should you have any questions or comments regarding this submission, please contact the undersigned at (973) 325-4540.

Sincerely,

Edwina L. Muir
Associate Director, Regulatory Affairs

ELM/

Attachment
Form FDA 356h

Submitted via Federal Express No 808590822192

AKZO NOBEL

CONFIDENTIAL

Organon Inc.

March 16, 2000

NEW CORRES

Roy Blay, Ph.D.
Office of Medical Policy
Division of Scientific Investigations
GCPB 1, HFD-46
7520 Standish Place
Rockville, MD 20855

NDA No. 21-187
NuvaRing® (etonogestrel/ethinyl estradiol ring)
Protocol 068003 Site Information Request

Dear Dr. Blay:

N C

Reference is made to our New Drug Application for NuvaRing® (etonogestrel/ethinyl estradiol ring), submitted on December 28, 1999. Reference is also made to the March 3, 2000 telephone conversation during which you requested information in preparation for the clinical study site inspections at the following locations:

068003, site 19 [redacted]
068003, site 43
068003, site 47

* Please note that Dr. Serna was replaced by Dr. Robert Nett as Principal Investigator of this site.

The following information is provided, as per your request:

A. Volume 1 (one copy) containing "Monitoring Survey Information"

Protocol number
Site number and Names of investigators (for above 3 sites)
Address of each site
Name, address and type of monitoring organization that monitored each site
Name of monitor who visited and date(s) of visits
Were original subject (medical) records reviewed? Yes/No
Copy of monitoring SOP

Organon

Organon Inc
375 Mt Pleasant Avenue
West Orange
New Jersey 07052
USA
Tel (973) 325-4500
Fax (973) 325-4589

B. Volumes 2-4 (one volume for each site) to include the following information:

Protocol with cover letter(s) for amendment(s)
Blank CRF
Form 1572
Study start and end dates for each site
Data Listings:
- A.1 Disposition
- A.2 Discontinuations
- A.3 Protocol Violations
- A.4 Deviations from In/Exclusion Criteria
- A.5 Primary Efficacy
- A.6 Beta hCG
- A.7 Adverse Events
- A.8 Concomitant Medications
- A.9 Clinically Significant Abnormal Laboratory Values

A randomly selected completed CRF
(for a subject who completed the entire study)

Please note that Organon Inc. considers this NDA application and all correspondence related thereto as confidential, proprietary, trade secret information and hereby claims protection from disclosure under the applicable sections of 18 U.S.C. and Title 21 of the Code of Federal Regulations.

Should you have any questions or comments regarding this submission, please contact the undersigned at (973) 325-4540.

Sincerely,

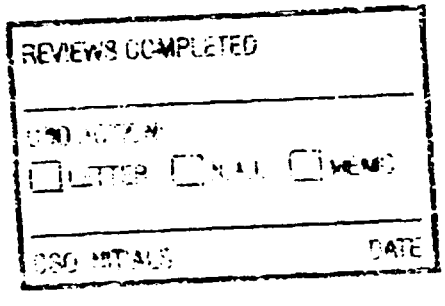
(for)

Edwina L. Muir
Associate Director, Regulatory Affairs

ELM/bl

Attachments

Submitted via Federal Express No. 810494766283



Cover letter only to: NDA No. 21-187
Susan Allen, M.D. Acting Director
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation II
Document Control Room 17B45
5600 Fishers Lane
Rockville, Maryland 20857

AKZO NOBEL

CONFIDENTIAL

Organon Inc.

March 8, 2000

ORIGINAL

Susan Allen, M.D., Acting Director
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation II
Document Control Room 17B45
5600 Fishers Lane
Rockville, Maryland 20857

B C

ORIG AMENDMENT

NDA No. 21-187
NuvaRing® (etonogestrel / ethinyl estradiol ring)
NDA AMENDMENT

Dear Dr. Allen:

Reference is made to our New Drug Application (NDA No. 21-187) for (NuvaRing®, Combined Contraceptive Vaginal Ring) which was originally submitted on December 28, 1999. In particular, please refer to the "Note To Reviewer" in volume 1.13 (page 0003) of the CMC section.

The Food and Drug Regulations (21 CFR Part 314.50[e][2][i]) require that "complete results of the applicant's tests on each sample" be submitted in the new drug application. The "samples" being referred to here are the drug substance and drug product samples which will be submitted (upon request) to the FDA Laboratories to validate Organon's analytical methods. At the time of the original NDA submission, the drug product samples were still undergoing analysis at N.V.Organon, and the necessary laboratory documentation (including the certificate of analysis) was not available for inclusion in the submission. This documentation is now available and is enclosed herein. This NDA submission is provided in paper (1 volume) and electronic format. Electronic files are supplied on 1 CD-ROM (total file size is approximately 2830 KB). CD-ROMs were checked for viruses using McAfee VShield Version 4.0.3.

In accordance with 21 CFR Part 314.60(c), an identical field copy of this amendment has been filed with our local FDA District Office in North Brunswick, New Jersey.

Organon

Organon Inc
375 Mt Pleasant A
West Orange
New Jersey 07052
USA
Tel (973) 325-45
Fax (973)-325-45

0001

CONFIDENTIAL

Please note that Organon Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of 18 U.S.C. and Title 21 of the Code of Federal Regulations.

Should you have any questions or comments concerning this document, please contact the undersigned at (973) 325-4540.

Sincerely,

Edwina Muir
Associate Director
Regulatory Affairs

Enclosure
FDA Form 356h
Archival Copy (+) 3 CMC Review Copies Submitted
via Federal Express Airbill No. 810494766490

AKZO NOBEL

CONFIDENTIAL

Organon Inc.

January 4, 2000

NEW CORRESP
NC

ORIGINAL

Jennifer Mercier, Project Manager
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation II
Document Control Room 17B45
5600 Fishers Lane
Rockville, Maryland 20857

NDA 21-187
NuvaRing® (etonogestrel/ethinyl estradiol ring)
Desk Copies

Dear Ms. Mercier:

Reference is made to our original New Drug Application for NuvaRing® (etonogestrel/ethinyl estradiol ring), NDA No. 21-187, submitted on December 28, 1999.

As requested, enclosed please find three of each of the following volumes:

Volume 1.1 - Overall Index
Volumes 1.136-1.138 - Integrated Summary of Effectiveness Data
Volumes 1.139-1.143 - Integrated Summary of Safety Information

Should you have any questions regarding the attached, please contact the undersigned at (973) 325-4540.

Sincerely,

Edwina L. Muir
Associate Director, Regulatory Affairs

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☒ N.A.I. ☐ MEMO
CSO INITIALS DATE 1/10/00

ELM/

Attachment

Organon

Submitted via Federal Express No. 810494767897

Organon Inc
375 Mt. Pleasant Avenue
West Orange
New Jersey 07052
USA
Tel.: (973) 325-4500
Fax: (973)-325-4589

December 28, 1999

AKZO NOBEL

Organon Inc.

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, Maryland 20852

ORIGINAL

CONFIDENTIAL

NDA 21-187
NuvaRing® (etonogestrel/ethinyl estradiol ring)
Original New Drug Application

Dear Sir/Madam:

Pursuant to Section 505(b) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.50, we hereby submit an original New Drug Application for NuvaRing® (etonogestrel/ethinyl estradiol ring) for the indication of contraception. NuvaRing® provides 0.120 mg etonogestrel and 0.015 mg ethinyl estradiol daily, for a period of 21 days, followed by a 7 day ring-free period.

Etonogestrel (17α)-13-ethyl-17-hydroxy-11-methylene-18,19-dinorpregn-4-en-20-yn-3-one) and ethinyl estradiol (19-nor-17α-pregna-1,3,5(10)-trien-20-yne-3, 17-diol) are formulated for use as a combination hormonal contraceptive ring.

In addition, pursuant to 21 CFR 314.55(c)(2), we hereby request a full waiver of the requirements for adequate data to assess the safety and effectiveness of NuvaRing® for the claimed indication in all pediatric subpopulations.

We also reference communications between the Division of Reproductive and Urologic Drug Products (DRUDP) and Organon Inc. with respect to the following agreements:

Pre-IND discussions on July 18 and May 15, 1991

- FDA stated that no additional studies, other than a 2-year rat carcinogenicity study with etonogestrel by the parenteral route would be necessary to complete the toxicology package for the NDA.

Teleconferences September 21, 1998, and December 2, 1998

- A larger than anticipated number of pregnancies had been reported for the US study 068003 as compared to the non-US study 34219. Both phase III protocols were essentially identical. It was concluded that a Pearl Index (as a barometer of efficacy) above two (2.0) would require an explanation but should not be a barrier to approval.

Organon

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Organon Inc.
375 Mt. Pleasant Avenue
West Orange
New Jersey 07052
USA
Tel.: (973) 325-4500
Fax: (973)-325-4589

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Confirmation by CDER's Electronic Submissions Coordinator on May 7, 1999

- An electronic submission in December 1999 containing domain profile CRTs in bookmarked PDF format would not result in a refusal to file the NDA and would be accepted for the archival copy in lieu of paper.

Letter from Organon dated May 26, 1999, conversation with FDA August 12, 1999

- Proposal to deviate from the January 1999 Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - General Considerations*, and its recommendations for fonts for the Human PK and Bioavailability (Item 6), Clinical (Item 8) and Statistical (Item 10, 11, 12) sections of our NDA was deemed acceptable to the Division.
- This NDA submission is provided in paper (149 volumes) and electronic format. Electronic files are supplied on 4 CD-ROMS (total file size is 1.4 GB). CD-ROMs were checked for viruses using McAfee VShield Version 4.0.3. Domain files (data listings) are provided for Studies 068003, , 068004, 34218, 34219, 34220, 34221, 34222, 34225 and 34226. Patient profiles (CRTs) are provided for Studies 068003, 068004, 34219, 34220, 34221 and 34222. CRFs are provided for all subjects with narratives in Studies 068003, 068004, 34219, 34220, 34221, 34222 and 34226.

Pre-NDA Meeting on July 7, 1999 to discuss various CMC issues

- Proposed pre-NDA submission manufacturing changes such as change in supplier of a packaging material [redacted] a change in the core EVA [redacted] site and the primary packaging site, and changes in the manufacture [redacted] assembly, and packaging of the product were discussed. The Agency concluded that these changes [redacted] were "Level 3" changes requiring a biostudy, however FDA indicated that iv-vivo/in-vitro correlation is reviewable and that it may support the use of the in-vitro release test for the purposes of demonstrating bioequivalence.
- The Agency concurred with the proposed studies and documentation to be submitted to justify the proposed manufacturing changes and agreed that the in-vitro release specifications may be acceptable for routine batch release and control.
- The Agency also concurred with the proposed finished product stability protocol and agreed that it would be acceptable for establishing product stability at either room temperature or at 5°C.
- The Agency agreed to the proposed etonogestrel drug substance stability study design, proposed drug product specifications, proposed etonogestrel drug substance specifications, and proposed in-process specifications and methods used to monitor routine drug product manufacturing.

Proposal dated October 14, 1999, confirmed by FDA November 3, 1999

- For the non-clinical section, line listings of the animal data will not be provided as SAS transport files, since most of the reports will be scanned and provided as PDF files.
- The chemistry, manufacturing and controls and non-clinical sections will not contain bookmarks as these contain old reports and documents which will be scanned, however, the overall index will be hyperlinked to the beginning of each subsection or report.
- Several clinical reports which provide data on prototype vaginal rings (rings which differ from the NuvaRing® design with respect to their composition, however, with the same declared release rate for both ENG and EE) will be cross-referenced to IND No. [redacted] This NDA will contain clinical reports of the NuvaRing® (EVA, 1 compartment ring) design and the two dose finding studies performed with silastic rings.

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Meeting with FDA December 12, 1999
The preclinical package, which includes the 2 year rat carcinogenicity study discussed in 1991 and 1995, and the two genotoxicity studies requested in 1998, is now considered complete.

In accordance with 21 CFR 314.70(a), an identical field copy of the Chemistry, Manufacturing and Controls section of this NDA has been prepared for simultaneous submission to the District Office of the FDA in North Brunswick, New Jersey.

Please note that Organon Inc. considers this application and all correspondence related thereto as confidential proprietary and trade secret information and hereby claims protection from disclosure under the applicable sections of 18 U.S.C. and Title 21 of the Code of Federal Regulations.

We believe that the enclosed NDA is complete and well-organized to facilitate your review. Should you have any questions or comments regarding this submission, please do not hesitate to contact Edwina Muir at 973-325-4540.

Sincerely,

Albert P. Mayo
Executive Director
Regulatory Affairs

ELM

HAND DELIVERED
Enclosures
Form FDA 356h

Review Copies:
Chemistry Review Copy, Volumes 1.1 to 1.16
Pharmacology Review Copy, Volumes 1.1, 1.3, 1.17 to 1.54
Biopharmaceutics Review Copy, Volumes 1.1, 1.3, 1.55 to 1.73
Medical Review Copy, Volumes 1.1 to 1.3, 1.74 to 1.149
Biostatistics Review Copy, Volumes 1.1, 1.3, 1.74 to 1.148

Cover Letter to:
Ms. Jennifer Mercier, HFD-580

Copy to: District Office, Volumes 1.3 to 1.16
Food and Drug Administration
120 North Center Drive, Bldg. C
North Brunswick, NJ 08902

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-187

Organon, Inc.
Attention: Edwina Muir
Director, Regulatory Affairs
375 Mt. Pleasant Avenue
West Orange, NJ 07052

Dear Ms. Muir:

We acknowledge receipt on August 3, 2001 of your August 2, 2001 resubmission to your new drug application (NDA) for NuvaRing® (etongestrel/ethinyl estradiol vaginal ring).

This resubmission contains a revised label submitted in response to our April 27, 2001 action letter.

We consider this a complete class 1 response to our action letter. Therefore, the primary user fee goal date is October 3, 2001 and the secondary user fee goal date is December 3, 2001.

If you have any questions, call me at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Jennifer Mercier, B.S.
Regulatory Project Manager
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville MD 20857

NDA 21-187

INFORMATION REQUEST LETTER

Organon, Inc.
Attention: Edward Nellis
Assistant Manager, Regulatory Affairs
375 Mt. Pleasant Avenue
West Orange, NJ 07052

Dear Mr. Nellis:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for NuvaRing® (etonogestrel/ethinyl estradiol vaginal ring) .

We also refer to your submission dated February 28, 2001, which constituted a complete response to our approvable letter dated December 22, 2000.

The Office of Drug Evaluation III and the Division of Reproductive and Urologic Drug Products have reviewed the proposed labeling for your application and have the following comments and information requests. This letter will serve as our response to your formal meeting request noted in your February 28, 2001 letter. We need your prompt written response to continue our evaluation of your NDA.

1. Please see the enclosed label for specific comments identified by double underline for additions and ~~strikethrough~~ for deletions. Additional requests are noted in [brackets].

2. The carton label should have the following information added:

   "The patient should avoid storing NuvaRing® in direct sunlight or at temperatures above 86°F (30°C)."

3. Please provide information regarding the number of women who used a diaphragm as an additional method of contraception during the Phase 3 clinical trials and the results from concomitant use of NuvaRing® with the diaphragm.

If you have any questions, call Jennifer Mercier, B.S., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}
Terri Rumble
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-187

DISCIPLINE REVIEW LETTER

Organon, Inc.
Attention: Edwina Muir
Director, Regualtory Affairs
375 Mt. Pleasant Avenue
West Orange, NJ 07052

Dear Ms. Muir:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for NuvaRing (etonogestrel/ethinyl estradiol ring).

We also refer to your submissions dated April 21, August 11, October 6, and November 14, 2000 and February 28, 2001.

Our review of the Clinical Pharmacology and Biopharmaceutics section of your submissions is complete, and we have identified the following deficiencies:

1. Please conduct an *in vivo* and *in vitro* drug interaction studies for etonogestrel (ENG) and ethinyl estradiol (EE) with systemic cytochrome P450 3A4 isoenzyme inducers and inhibitors as well as to determine the induction and inhibition potential of etonogestrel and ethinyl estradiol to cytochrome P450 3A4 isoenzyme and conjugation enzymes for better characterization of NuvaRing s drug interaction potential.

2. The proposed etonogestrel and ethinyl estradiol *in vitro/in vivo* correlations (IVIVC) are not acceptable at this time. Please address the following comments:

   Please provide either internal or external validation for the ENG and EE IVIVC. See "Guidance for Industry SUPAC-MR: Modified Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; *In vitro* Dissolution Testing and *In Vivo* Bioequivalence Documentation, USHHS, FDA, CDER, September 1997, CMC 8" for reference; though for oral MR products, principles may apply to NuvaRing You indicated your intention to use Studies 34255 (interaction) and 34226 (pharmacodynamic) to validate your IVIVC during the proposed postapproval changes meeting on November 16, 2000.

   Please describe the details of deconvoluting the serum ENG or EE concentrations via intravaginal administration with the corresponding serum ENG or EE concentrations via intravenous administration to estimate the *in vivo* ENG or EE absorption rate from combination contraceptive vaginal ring (CCVR). Only a reference

[redacted] in page 077 of volume 55 of 149 volumes was cited. Thus, the validity of the ENG or EE *in vivo* absorption rate cannot be assessed.

Please provide data to demonstrate that the *in vitro* release method is independent of conditions such as release media and agitation during development. For the 1-point linear IVIVC, serum ENG concentrations for the Silastic prototype ring had to be multiplied with 1.47 in order to fit those with NuvaRing. You justified this multiplication factor as variability difference for the assay used between the Silastic prototypes and CCVR. However, substantiation should be provided for the difference (1.47 factor) in etonogestrel bioanalytical assays for the prototype and NuvaRing.

Please provide the *ex vivo* analyses data for the amounts of ENG and EE remaining in the combined contraceptive vaginal rings used in Study 34225, which were missing from Appendix B of Study report 34225.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Jennifer Mercier, B.S., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

Terri Rumble
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-187

Organon, Inc.
Attention: Edwina Muir
Director, Regulatory Affairs
375 Mt. Pleasant Avenue
West Orange, NJ 07052

Dear Ms. Muir:

We acknowledge receipt on March 1, 2001 of your February 28, 2001 resubmission to your new drug application (NDA) for NuvaRing® (etonorgestrel/ethinyl estradiol ring).

This resubmission contains additional labeling information submitted in response to our December 22, 2000 action letter.

We consider this a complete class 1 response to our action letter. Therefore, the primary user fee goal date is May 1, 2001.

If you have any questions, call Jennifer Mercier, B.S., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Terri Rumble
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

NDA 21-187

DISCIPLINE REVIEW LETTER

Organon, Inc.
Attention: Edwina Muir
Director, Regulatory Affairs
375 Mt. Pleasant Avenue
West Orange, NJ 07052

Dear Ms. Muir:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for NuvaRing® (etonogestrel/ethinyl estradiol).

Our review of the Clinical Pharmacology and Biopharmaceutics section of your submission is complete, and we have identified the following deficiencies:

1. The proposed etonogestrel and ethinyl estradiol *in vitro/in vivo* correlations (IVIVC) are not acceptable at this time. For the IVIVC, please provide the following:

    a. internal or external validation
    b. details of deconvolution to obtain the *in vivo* etonogestrel and ethinyl estradiol absorption rates
    c. substantiation of the difference [redacted] in etonogestrel bioanalytical assays for the prototype and NuvaRing®
    d. data to demonstrate that the *in vitro* release method is independent of conditions such as release media and agitation during development
    e. the *ex vivo* analyses data for the amounts of etonogestrel and ethinyl estradiol remaining in the combined contraceptive vaginal rings used in Study 34225, which were missing from Appendix B of Study report 34225

2. You are strongly encouraged to conduct *in vivo* and *in vitro* drug interaction studies for NuvaRing® coadministered with systemic cytochrome P450 3A4 isoenzyme inducers and inhibitors, as well as to determine the induction and inhibition potential of etonogestrel and ethinyl estradiol to cytochrome P450 3A4 isoenzymes and conjugation enzymes, for better characterization of NuvaRing®'s drug interaction potential.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug

user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Jennifer Mercier, B.S., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

Terri Rumble
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Mercier

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-187

Organon
Attention: Edward Nellis
375 Mt. Pleasant Avenue
West Orange, NJ 07052

SEP 27 2000

Dear Mr. Nellis:

We acknowledge receipt on September 21, 2000, of your September 20, 2000, correspondence requesting a meeting to discuss CMC issues pertaining to your drug NuvaRing (estagestrel/ethinly estradiol ring). FDA categorizes meetings into three types:

Type A: A meeting that is necessary for an otherwise stalled drug development program to proceed.
Type B: A meeting described under drug regulations (e.g., Pre-IND, End of Phase 1 (for Subpart E or Subpart H or similar products), End of Phase 2/Pre-Phase 3, Pre NDA).
Type C: All meetings other than those that qualify for Type A or B.

Your correspondence did not indicate the type of meeting. However, based on the statement of purpose, objectives, and proposed agenda, we consider the meeting to be a Type C. This meeting has been scheduled for:

Date:	November 16, 2000
Time:	10:00 am
Location:	Parklawn Building, Conference Center, Room "C"
CDER participants:	Drs. Allen, Shames, Davis, Rhee, Lin, Parekh, Lau, Gibbs, Koepke, Ms. Mercier and Rumble

The background information for this meeting should be received by the Agency at least one month prior to the meeting. If we do not receive it by October 16, 2000, rescheduling of the meeting may be necessary.

If you have any questions, contact Jennifer Mercier, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

/S/ 9/26/00

Terri Rumble, B.S.N.
Chief, Project Management Staff
Division of Reproductive and
Urologic Drug Products (HFD-580)
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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NDA 21-187

INFORMATION REQUEST LETTER

Organon Inc.
Attention: Ed Nellis, Regulatory Affairs
375 Mt. Pleasant Avenue
West Orange
New Jersey 07052

SEP 2 0 2000

Dear Mr. Nellis:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for NuvaRing (etonogestrel/ethinyl estradiol ring) 0.120 mg/0.015mg per day over a 3-week period.

We are reviewing the Clinical, Chemistry and Clinical Pharmacology and Biopharmaceutics sections of your submission and have the following comments and information requests. We need your prompt written response to continue our evaluation of your NDA.

Clinical Pharmacology and Biopharmaceutics:

Please provide individual values for the *in vitro* release test results on the combination contraceptive vaginal rings that were used in the clinical safety and efficacy studies; in addition, please submit the corresponding lot and clinical study numbers.

Clinical:

1. Please provide the dosage of administration of the nonoxynol-9 spermicide used in the study to determine the effect of N-9 on serum hormonal levels with NuvaRing.

2. Please complete the information in the attached tables regarding:
   a. bleeding patterns,
   b. vaginal ring acceptability, and
   c. cycle control acceptability.

Chemistry:

Drug Substance:

1. DMF's [redacted] are inadequate to support this NDA. Deficiencies in these DMF's were conveyed to the DMF holder.

2. The drug related impurity specification and residual solvents specification listed on pages 61 and 182 in volume 1.5 are not consistent with each other. Please clarify which specifications are to be used for acceptance release of ethinyl estradiol.

Drug Product:

1. Please clarify whether reprocessing operations are conducted during the manufacturing of the drug product rings.

2. Please provide the requirements necessary in order for the *in-vitro* release values to conform to the specifications.

3. The Release and End of Shelf Life specification for Content of Degradation Products Related to Etonogestrel should be revised as follows: Org 32084 from ≤ 1% to ≤ 0.5%; Total Degradation Products from ≤ 3% to ≤ 1.5%. In addition, since no unidentified degradation products were observed, this specification should be revised from ≤ 1% to ≤ 0.1%. The Org 31977 specification is acceptable.

4. The Release and End of Shelf Life specification for Content of Degradation Products Related to Ethinyl Estradiol should be revised as follows: Org 31891 from ≤ 1% to ≤ 0.5%.

5. Based on the batch analysis data and the results in the Development Pharmaceutics section of the NDA (page 83 in Volume 1.7) which showed that rings passed the specification of ≥ 3 N/m^2, but failed at the weld joints, the tensile strength specification should be revised to ≥ 5 N/mm^2, with the following acceptance criteria: the mean of the six rings is greater than or equal to 5 N/mm^2, and each individual ring must be no less than 4.25 N/mm^2 (85% of the specification).

6. It is clear that 12 rings are tested when performing the *in-vitro* release test. However, please clarify the requirements for the release values to conform to the specifications.

[redacted]

[redacted]

9. In order to maintain consistency and to conform to the requirements for USP 24, Uniformity of Dosage Units <905>, the number of samples tested for content uniformity in the stability program should be revised to 10 samples.

10. Please revise the first sentence in stability commitment #1 to the following: "We will conduct stability studies on the first three (3) post-approval commercial batches." In addition, please add the following statement to the commitment: "Extend the expiration dating based upon full shelf-life data obtained from the first three commercial marketed batches covering the entire extended shelf-life and tested according to the approved stability protocol."

11. Your proposal for a shelf-life of 24 months at 2-8°C, followed by 7 months at a temperature up to 30°C is currently under review and the Division's recommendation will be conveyed at a later time.

12. We recommend that the proposed alternative post marketing stability surveillance program not be implemented.

13. In the Description section of the Physician Insert please use one of the following etonogestrel chemical names, as published in the USP Dictionary of USAN and International Drug Names: 1) 18,19-dinor-17α-pregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-11-methylene-, or 2) 13-ethyl-17-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one. In addition, the molecular weight of ethinyl estradiol should be revised to 296.40.

14. In the How Supplied section of the Physician Insert please include the manufacturer's name as provided for in 21 CFR 201.1(h)(5).

If you have any questions, call Jennifer Mercier, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

/S/

Susan Allen, MD, MPH
Division Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Attachment: Table #1 Bleeding Patterns
Table XX Vaginal Ring Acceptability
Table YY Cycle Control Acceptability

Table #1: Studies 68003 and 34219 Bleeding Patterns

	Study 68003[1]	Study 34219[1]	LNG/EE data[2]
Median Duration of Withdrawal Bleeding	X.X days	Y.Y days	Z.Z days
Onset of Withdrawal Bleeding: median day (interquartile range)	xx days after ring insertion (x-y days)		
% with at least one Withdrawal Bleeding lasting 10 days or more	Approx. xx%		
% with at least 1 episode of "early" withdrawal bleeding			
% with at least 1 episode of "late" withdrawal bleeding			
% with 10-11 episodes of intended bleeding pattern	x.y %		N.A.
% with Breakthrough Bleeding and/or spotting for at least 1 cycle	x.y %		
% with at least one time of amenorrhea lasting > 60 days during treatment	x.y%		

[1]During the second through twelfth cycles of treatment
[2]During the second through sixth cycles of treatment

Table XX Vaginal Ring Acceptability: Questions Relating to Ring Usage and Acceptance per Questions # 5 and # 14 at Last Visit for Completers and Discontinuers - Adequate and Well-Controlled Studies Combined (Intent-to-Treat Group)

Question Number	Last assessment	N	Frequency and percentage of answers											
			Not Applicable		Bleeding/ Spotting		Intercourse Interference		Falling out of the Ring		Uncomfortable		Other (specify)	
			n	%	n	%	n	%	n	%	n	%	n	%
# 5: Reason for Ring Removal During Day 1-21	Completers													
	Discontinuers													
	Combined													
# 14: Top Three Reasons for Disliking Ring	Completers													
	Discontinuers													
	Combined													

N = Number of subjects ; n = Number of subjects with a particular answer

Table YY Cycle Control Acceptability: Questions Relating to Ring Usage per Questions # 11 and # 12 at Last Visit for Completers and Discontinuers - Adequate and Well-Controlled Studies Combined (Intent-to-Treat Group)

Question Number	Last assessment	N	Frequency and percentage of answers									
			Much Shorter or Less		Shorter or Less		Same		Longer or More		Much Longer or More	
			n	%	n	%	n	%	n	%	n	%
# 11: Change in Duration of Period from pre-study	Completers											
	Discontinuers											
	Combined											
# 12: Change in Menstrual Pain from pre-study	Completers											
	Discontinuers											
	Combined											
# ?: Change in Volume of Flow from pre-study	Completers											
	Discontinuers											
	Combined											

N = Number of subjects ; n = Number of subjects with a particular answer

*the third ? above comes from baseline data obtained on page 8 of the Case Report Form, Menstrual characteristics

2. Usual volume of flow:

- ☐ scanty (1-2 pads per day)
- ☐ moderate (3-4 pads per day)
- ☐ heavy (> 4 pads per day)

APPEARS THIS WAY
ON ORIGINAL

Merck

NDA 21-187

Organon, Inc.
Attention: Edward Nellis
Assistant Manager, Regulatory Affairs
375 Mt. Pleasant Ave.
West Orange, NJ 07052

JUL 21 2000

Dear Mr. Nellis:

Please refer to your December 28, 1999 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for NuvaRing (etonogestrel/ethinyl estradiol ring).

We are reviewing the Pharmacology/Toxicology section of your submission and have the following comments and information requests. We need your prompt written response to continue our evaluation of your NDA.

1. Please inform the Division whether the 2-year carcinogenocity data has been submitted to the Division of Biometrics for review. If it has not been submitted, please contact Dr. Karl Lin at 301-827-3093 for instructions on the submission of datasets.
2. Please submit the pharmacokinetic data for 3-keto desogestrel from the rat carcinogenicity study conducted with Desogestrel that was requested in the Agency's letter dated July 27, 1998.
3. Please provide compilation of all neoplastic histopathological alterations for Table (Neoplasm Classification Summary) on page 0184, Volume 45 of the NDA. Please indicate its location in the NDA if it has already been submitted.
4. Please provide organ weight data requested in the Agency's letter dated July 27, 1998.

If you have any questions, please contact Eufrecina DeGuia, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

/S/

Susan Allen, M.D., M.P.H.
Director
Division of Reproductive and Urologic Drug Products;
DRUDP (HFD-580)
Office of Drug Evaluation III
Center for Drug Evaluation and Research

7/21/00

D 1F

NDA 21-187

Organon, Inc.
Attention: Albert Mayo
Executive Director, Regulatory Affairs
375 Mt. Pleasant Avenue
West Orange, NJ 07052

Dear Mr. Mayo:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

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

Therapeutic Classification: Standard (S)

Date of Application: December 28, 1999

Date of Receipt: December 28, 1999

Our Reference Number: NDA 21-187

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 28, 2000 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be October 28, 2000 and the secondary user fee goal date will be December 28, 2000.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within 120 days of receipt of your pediatric drug development plan, we will notify you of the pediatric studies that are required under section 21 CFR 314.55.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from

the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will proceed with the pediatric drug development plan that you submit and notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Jennifer Mercier, Project Manager, at (301) 827-4260.

Sincerely,

/S/

Terri Rumble
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research