If a bleeding pattern superiority claim is sought by a sponsor, the criteria for approval should be very strict (the NuvaRing® label contains a graph that clearly suggests superiority over the LNG/EE comparator in the first cycle of use).

Vaginal factors

Clinical concerns unique to a vaginal ring compared to an oral contraceptive include the following:

- Tolerability for the subject and her partner in regard to the presence of a vaginal device
- Expulsion rates
- Effect on vaginitis (this will be discussed in the safety section of this review)

The sponsor reported that 80% of women had no problems with insertion, 85% had no problem with removal, and 82% never or rarely felt NuvaRing® during intercourse. Of the subjects' partners, 91% never or rarely minded that their partner was using NuvaRing®.

The data from six clinical trials (68003, 34219, 34220, 34221, 34222, and 68004) indicated a 1.6% expulsion rate and a 0.6% partial expulsion rate. Though subjects with uterine prolapse, cystocele, and rectocele were excluded, this rate is in the acceptable range. The sponsor appropriately addresses the expulsion issue for the patient in the patient package insert.

Safety

The safety database includes the large clinical studies mentioned above (68003, 34219) in addition to the metabolic studies (34220, 34221, 34222) and the local tolerability study (68004). A total of 1,870 woman years of exposure to NuvaRing® for safety data was collected by the sponsor for this NDA.

The safety concerns focus on adverse events associated with combination hormonal contraceptives and local effects of the ring and hormones in regard to the cervix and vagina. Additionally there is a specific focus on "third generation" hormonal contraception in regard to thromboembolic disease, since etonogestrel is the active metabolite of desogestrel.

There was one reported case of venous thrombosis in the NuvaRing® safety database. As mentioned in the primary medical officer's review this study subject (#0088 in study 34220) developed the problem in her first cycle of NuvaRing®. Occasional smoking was the only risk factor for this 26-year-old woman. A number of coagulatory parameter were within normal limits and there was no evidence of hereditary coagulation factor V gene defect. The subject's sister was reported to have a Factor XIII deficiency but the study subject herself was found to be normal for Factor XIII.

Because venous thromboembolism (VTE) is rare with present day hormonal contraceptives, a large number of individuals will be required to assess the true incidence of VTE with NuvaRing® to see if it is similar to that reported with oral administration of desogestrel and gestodene. Though there are no significant signals from this present study in regard to VTE, the labeling for this product should contain the same information on VTE that is required for the approved desogestrel products.

The single death reported from the safety data base was do to a motor vehicle accident and unrelated to NuvaRing®. The serious adverse events that were considered possibly or definitely related to NuvaRing® included the one reported VTE, 3 cases of gallbladder disease, one case of severe vomiting, one case of abdominal pain, and 3 cases with psychiatric symptoms.

As mentioned in the primary medical officer's review a total of 8 subjects with a normal Pap smear at screening went on to develop a high grade dysplastic Pap smear at last assessment. This represents 0.3% of 2,322 women in combined trials and is not significantly greater than what is discovered in the general population. The peak prevalence (age 25-29) for severe dysplasia is 0.5%. The peak prevalence for mild to moderate dysplasia is 2.6%

There was no evidence from the larger clinical trials or the local effects study (68004) utilizing colposcopy that NuvaRing® induces significant vaginal irritation (i.e., ulcerations, ecchymoses, petechiae) Vaginitis was reported in 14.1% of 2,501 women using NuvaRing®. Leukorrhea was reported in 5.8%. The causal relationship to NuvaRing® is difficult to determine since both of these conditions can result secondarily to a host of local and systemic factors (intercourse, tampon use, cosmetics, antibiotics). The discontinuation rate for vaginitis and leukorrhea reported at 2.2% may be a truer indication of the relationship of the device to these conditions. This device is less rigid and less bulky than diaphragms and pessaries and would not be expected from those criteria to be as irritating.

Chemistry/ Manufacturing

NuvaRing® is combined contraceptive vaginal ring (CCVR) with an outer diameter of 54 mm and a cross-sectional diameter of 4mm. 120micrograms of etonogestrel and 15micrograms of ethinyl estradiol are released daily. The ring is made from an ethylene vinylacetate copolymer (Evatane®). The core contains a higher percentage of vinylacetate than the skin. [redacted] supplies Evatane® materials. NuvaRing® is manufactured by N.V. Organon, Oss, The Netherlands. The proposed commercial batch is [redacted] rings. The rings will be packaged in reclosable aluminum laminate sachets.

Release and stability testing is critical for device releasing hormonal contraceptives. Compared to [redacted] NuvaRing® is a single

device. Thus, individual ring specifications will be stressed in addition to maintenance of mean release rates.

Prolonged storage of NuvaRing® at higher temperatures such as 25C[redacted] and 30C/[redacted] results in a "burst" release of etonogestrel as reflected in the day 1 release rate. The clinical implications of this effect are unknown.

The primary outstanding issues in regard to CMC include DMF deficiencies, site inspection, and establishment of release and stability criteria.

Product Name

OPDRA has no objections to the use of the proprietary name "NuvaRing®"

Pre-clinical Pharmacology and Toxicology

The following is a summary of key findings from the pre-clinical pharmacology and toxicology review.

Since etonogestrel (3-keto-desogestrel) is the active metabolite of desogestrel, the safety of 3-keto-desogestrel is also supported by the toxicity studies conducted for oral desogestrel. Many of the nonclinical toxicity studies were performed in the 1970s prior to current GLP and ICH guidances.

Local toxicity of placebo vaginal rings was determined in a 6-month Rhesus monkey study with no histopathological evidence of vaginal or cervical mucosal reaction.

Etonogestrel showed no evidence of genotoxicity (Ames, in-vivo mouse micronucleus, or in-vitro chromosomal aberration assay in Chinese hamster ovary cells). There was no evidence of carcinogenicity for etonogestrel in a 2 year study in rats with subcutaneous implants. There was no concern regarding return to fertility after withdrawal of treatment.

One issue still undergoing review concerns the finding of bronchioalveolar adenomas and carcinomas in rodents. This finding was not identified in the desogestrel studies.

Biopharmaceutics

No approvability issues have been raised to date by biopharmaceutics. Key points from the clinical pharmacology and biopharmaceutics review includes the following.

An interaction study with NuvaRing® showed an increased serum etonogestrel and serum ethinyl estradiol AUC associated with miconazole nitrate (17% and 16% respectively) An interaction study with nonoxynol-9 did not affect the serum etonogestrel and serum ethinyl estradiol.

[redacted]

In support.of the primary medical reviewer, this reviewer also concurs in recommending a phase 4 clinical study that addresses the impact of tampons on drug absorption. This should assess not only blood levels and ovulatory inhibition, but also tampon levels of hormonal drug product.

Since etonogestrel and ethinyl estradiol are primarily metabolized via cytochrome P450 3A4, OCPB/DPEII is strongly encouraging the sponsor to perform additional drug interaction studies.

OCPB/DPEII found that the proposed etonogestrel and ethinyl estradiol in vitro-in vivo correlations are not acceptable due to different release rates for the Silastic® prototypes compared to the ethylene vinylacetate copolymer in NuvaRing®. Additional information was requested on in-vitro release testing.

Division of Scientific Investigations- Clinical Inspection Summary

No violations were observed that would affect the reliability or integrity of the data submitted in support of this NDA.

Three selected sites [redacted] were found acceptable.

Labeling

Key aspects of NuvaRing® labeling are listed below:

Similarities and differences of a vaginal hormone releasing device compared to oral contraceptives are required. Class labeling for oral contraceptives can provide a template upon which the appropriate information for NuvaRing® is added. Additional information on vaginal devices relates to insertional and removal techniques, use during intercourse, expulsion, and specific adverse events such as vaginitis.

This label requires the same warning information contained in desogestrel labels in regard to VTE.

Bleeding pattern information specific to NuvaRing® (both short and long term) should be provided in the label. Comparative bleeding pattern information from the smaller metabolic studies should not be included in the label.

The specifics of the efficacy results from both the U.S. and European studies should be included in addition to the combined results.

/S/ 10/6/00

Gerald Willett, M.D.
Acting Reproductive Medical Team Leader
HFD-580

cc:
Division File NDA 21-187
Susan Allen, MD
Daniel Shames, MD
Dan Davis, MD
Jennifer Mercier

Group Leader Memorandum
NDA 21-187

DEC 22 2000

Drug	**NuvaRing®**
Generic Drug Name	**etonogestrel/ethinyl estradiol vaginal ring**
Dose	**ethylene vinylacetate (EVA) vaginal ring containing 11.7 mg etonogestrel and 2.7 mg ethinyl estradiol released at a rate of 0.120 mg/day etonogestrel and 0.015 mg/day ethinyl estradiol**
Indication	**prevention of pregnancy**
Applicant	**Organon, Inc.**
Date of Submission	**12/29/99**
Date of Memorandum	**12/22/00**
Reviewer	**Dena R. Hixon, M.D., FACOG** **Team Leader, DRUDP**

Summary

NuvaRing® is a combined hormonal contraceptive in the form of a flexible transparent vaginal ring with an outer diameter of 54 mm and a cross-sectional diameter of 4 mm. It contains 2.7 mg of the estrogen ethinyl estradiol (EE) which is released into the vagina at the rate of 0.015 mg/day and 11.7 mg of the new progestin etonogestrel (ENG) which is released into the vagina at a rate of 0.120 mg/day. Each ring is intended to be inserted into the vagina and left in place for 21 days and then removed for a 7-day ring free interval, similar to a typical oral contraceptive dosing regimen of pill-taking for 21 days followed by a 7-day pill free interval.

As noted in the primary and secondary reviews dated 10/6/00, the data presented are adequate to support safety and efficacy of NuvaRing® for marketing in the U.S.

Background

Ethinyl estradiol is a well-characterized estrogen, widely used in oral contraceptive products. Etonogestrel is a new progestin which is the active metabolite of desogestrel, a third generation progestin contained in Desogen® and Mircette™ (oral contraceptives marketed by Organon) and Ortho-Cept® (marketed by Ortho Pharmaceutical

Corporation). Desogestrel-containing oral contraceptives have been marketed in the U.S. since 1993 and in Europe since 1981. Epidemiology studies have suggested a two-fold increase in the risk of venous thrombo-embolism (VTE) with desogestrel use compared with use of certain second generation progestins. NuvaRing® has never been marketed, and it is unknown whether the increased risk of VTE applies to the vaginal administration of etonogestrel.

The combined contraceptive vaginal ring (CCVR) provides similar efficacy and similar menstrual bleeding patterns to those seen with oral contraceptives and without the need for daily pill taking.

Efficacy

Reports of two large phase III clinical studies, 68003 in the U.S. and Canada, and 34219 in Europe and Israel support the efficacy of NuvaRing®. These two nearly identical studies were open label uncontrolled clinical trials in healthy women ages 18 to 41 using NuvaRing® for contraception for up to 13 cycles with pregnancy testing at discontinuation or at the end of the study and as needed at study visits.

In both studies combined, 2262 women were treated for a total of 23,297 cycles. A total of 22 pregnancies were conceived during treatment, giving an overall Pearl Index (PI) of 1.23 pregnancies per 100 women-years of treatment (1.86 in 68003 and 0.64 in 34219). Twelve of these pregnancies occurred with treatment according to the recommended treatment regimen. The PI for per protocol ("perfect" use) pregnancies was 1.45 for Study 68003, 0.53 for Study 34219, and 0.92 for the combined studies.

When only women under age 35 are considered, the PI for all subjects treated in Study 68003 is 2.02 and in the combined studies 1.30. The per protocol PI was 1.04 for the combined studies.

A total of 27 pregnancies were conceived after discontinuation of NuvaRing®. One of these occurred 4 days after ring removal, and is considered to be a per protocol method failure. The other 26 pregnancies had estimated dates of conception from 7 to 98 days after ring removal. Review of these cases did not suggest contraceptive failure.

Reviewer's Comments

1. *The pregnancy rates reported with NuvaRing® use are similar to those found with use of various combined oral contraceptives.*
2. *Pregnancies occurring during treatment per protocol were randomly distributed throughout 13 cycles of use with no apparent change in the pregnancy rate with increasing duration of NuvaRing® use.*
3. *The 26 pregnancies that were conceived between 7 and 98 days after ring removal suggest prompt return of fertility after discontinuation of treatment.*
4. *The numbers given above are slightly different than those presented by the sponsor and reflect the primary reviewer's analysis of the data for each of the reported pregnancies.*

5. *The pregnancy rates in the European/Israeli study 34219 were lower than in the U.S. study 68003. This may in part be explained by the following:*
   - *A higher proportion of subjects using OCs as their last method of contraception prior to enrollment, 67% in 34219 vs. 47% in 68003*
   - *Better compliance, 91% in 34219 vs. 79% in 68003*
   - *Lower discontinuation rate, 30% in 34219 vs. 41% in 68003*
6. *In the combined studies, 17% of subjects were 35 years of age or older. Therefore, the PI was calculated separately for women under age 35. Although the PI was higher in these younger subjects, it was still acceptable.*
7. *Most of the subjects in both studies were Caucasian (89% in 68003 and 99% in 34219). Studies have not been conducted in different ethnic groups, but efficacy is not expected to be different for other ethnic groups based on experience with OCs.*

Bleeding patterns

The sponsor reported the following bleeding patterns in the combined phase III trials:
- The median day of onset of withdrawal bleeding was cycle day 24 ± 1 day.
- The median duration of withdrawal bleeding was 5 days.
- At least one episode of prolonged bleeding (longer than 10 days) occurred for 11.3 % of subjects.
- The intended bleeding pattern (withdrawal bleeding during the 7 ring-free days and no bleeding or spotting on any other day of the cycle) occurred in 60 to 69% of evaluable cycles.
  More subjects reported only the intended bleeding pattern throughout cycles 10-12 (67%) than throughout cycles 1-3 (62%)
- At least one episode of breakthrough bleeding or spotting (bleeding or spotting episodes occurring only while the ring was in place) occurred for 46% of subjects. Overall, breakthrough bleeding or spotting was reported in 5.1 to 7.9% of evaluable cycles. This was more common in cycles not treated according to the prescribed regimen.
- Absence of withdrawal bleeding occurred in 1.5 to 2.9% of evaluable cycles.
- Withdrawal bleeding started prior to ring removal (usually spotting only) in 6 to 9 % of evaluable cycles.
- Withdrawal bleeding continued beyond the 7 ring-free days in 20 to 25% of evaluable cycles.

Only 19 (0.8%) subjects (10 in 68003 and 9 in 34219) discontinued the study because of bleeding irregularities.

Reviewer's comment
- *These reported bleeding patterns are similar to those previously described with combined oral contraceptive use.*
- *The incidence of breakthrough bleeding and spotting was higher in Study 68003 than in Study 34219. This may be due in part to the higher number of previous OC users in 34219.*

- *The primary clinical reviewer suggested that bleeding evaluation over 90-day reference periods would be more useful than the sponsor's analysis of individual cycles. This reviewer believes that the cycle by cycle analysis is more useful for a method such as NuvaRing® that is administered in 28-day cycles.*

Safety and Tolerance

Altogether in the phase III efficacy trials and the supporting trials, 24,391 cycles of NuvaRing® exposure were evaluated. The supporting trials included three smaller metabolic studies in Europe with a total of 121 women treated for a total of 634 cycles, and a local effects study in the U.S. with 58 women treated for a total of 460 cycles.

The only death reported in the combined studies was the result of a motor vehicle accident.

The following serious adverse events (SAEs) may have been related to NuvaRing® use: one case each of deep venous thrombosis (DVT), anxiety, vomiting, abdominal pain, psychosis, depression, and cholecystitis, and two cases of cholelithiasis.

> The one case of DVT was reported as a SAE in a 26 year old woman with one previous pregnancy interruption. Her symptoms developed after only 8 days of NuvaRing® use. The diagnosis was confirmed by venography after hospitalization. NuvaRing® use was discontinued and anticoagulant therapy initiated. The woman had previously used a desogestrel-containing OC. An intensive work-up revealed no risk factors for venous thrombosis.
>
> Two additional subjects discontinued from the phase III trials due to thrombophlebitis. A 32 year old woman experienced superficial thrombosis 2 months after initial ring insertion. The ring was removed and the complaint resolved. Another 37 year old woman had a diagnosis of thrombophlebitis by a non-study physician in the 2nd cycle of NuvaRing® use. Both women discontinued from the study and were subsequently lost to follow up.

In the phase III studies, 15% of subjects discontinued NuvaRing® treatment due to AEs, mostly drug-related. Device-related problems resulted in discontinuation for 2.4% of subjects. The problems included expulsion, coital problems, foreign body sensation, vaginal discomfort, vaginitis and leukorrhea. Headache resulted in discontinuation for 1.2% of subjects and emotional lability for 1.1%.

Overall, the most frequently reported AEs were vaginitis (14.1%), headache (9.8%), upper respiratory tract infection (8.0%) and leukorrhea (5.8%). Weight gain was an AE for 5% of subjects.

Reviewer's comments

- *The reported case of DVT supports the need to include the warning regarding a possible increased risk of VTE with 3rd generation progestins in the label for this product.*

Laboratory values

Clinically significant abnormal values occurred for the following parameters in the phase III studies: high ALAT, ASAT, total bilirubin, gamma-GT, potassium, and sodium. These abnormal values occurred in $\leq$ 0.3% of subjects. Upward shifts in ALAT occurred in 4.8% of subjects, ASAT in 3.0%, and downward shifts in total bilirubin in 5.1% of subjects. All of the significant abnormal values returned to normal. Only one (an elevated ASAT) was reported as an AE, and no subject discontinued the study prematurely because of abnormal laboratory values. There were no clinically relevant mean changes from baseline for any of the blood chemistry parameters in any of the studies.

Lipids

In a comparative study of 44 NuvaRing® users and 45 OC users, the NuvaRing® group was reported to show an increase in HDL-cholesterol and a decrease in LDL-cholesterol compared to the OC group. However, the primary reviewer found that the LDL was actually increased in the OC group and unchanged in the NuvaRing® group.

Reviewer's comment

I agree with the primary reviewer that the sponsor's conclusions about the effect of NuvaRing® on lipid parameters are of uncertain clinical significance and should not be included in the label for this product.

Blood pressure

Clinically significant increases in blood pressure were seen in 1.9% and 1.6% of subjects, respectively. Clinically significant decreases in these parameters were seen in 2.1% and 0.8% of subjects.

Weight

Clinically significant changes in body weight ($\geq$ 7% change from baseline weight) were seen as follows: decreases in 9.3% of subjects and increases in 14.1%. In the combined clinical trials, weight gain was reported as an AE in 5% of subjects, and 1% of subjects discontinued the trials because of weight gain.

Reviewer's comment

These changes in blood pressure and weight are similar to those seen in trials of other hormonal contraceptives.

Cervical cytology

Cervical Pap smears changed from a baseline result of I, IIa, or IIb to a result at last assessment of IIIa for 33 (1.3%) subjects and IIIb-IV for 7 (0.3%) subjects. Three subjects (0.2%) had a result of IIIa at both screening and last visit, and 3 additional subjects had IIIb-IV at both screening and last visit.

Reviewer's comment
I agree with the primary reviewer that this low percentage of subjects with Pap smears changing from normal to class IIIb-IV is not unusual for a population of sexually active women.

Vaginal flora
Interim results of a local effects study revealed no significant changes in microbiology findings to suggest either a favorable or unfavorable effect on vaginal microflora.

Pregnancy outcomes
Of the 22 pregnancies conceived during treatment in the clinical studies, 3 live births of healthy infants were reported. There have been no reports of congenital anomalies, stillbirths or major neonatal problems. Nine pregnancies were ongoing at the end of the studies, and outcomes for those pregnancies are unknown. There were 8 abortions. Outcomes of the other 2 pregnancies are unknown.

Reviewer's comment
Given the lack of pregnancy outcome data, no conclusions can be made regarding the effect of NuvaRing® on exposed fetuses. The sponsor agreed in a teleconference on 12/11/00 (and confirmed in writing on 12/13/00 and 12/20/00) to a phase IV commitment to follow-up all spontaneous reports of pregnancy to obtain information on the duration of fetal exposure of each pregnancy to NuvaRing® and on pregnancy outcome including spontaneous abortion, premature delivery, stillbirth, or live birth, and congenital anomalies.

Safety update
A safety update was received on November 1, 2000 covering the time period up to 10/1/00. There were no AEs, SAEs, or deaths, and no new safety concerns. NuvaRing® has not been marketed anywhere in the world, and there is no safety information on use of the product for more than 13 cycles.

Acceptability of NuvaRing®

Most women had no problem with insertion (80%) or removal (85%) of NuvaRing® at any time during the studies, and 86% reported that they never or rarely removed the ring temporarily. Eighty-two percent of the women and 69% of their sexual partners reported that they rarely or never felt the ring during intercourse.

In the combined phase III studies, 35% of all subjects treated discontinued the study before completing 13 cycles of use. In 90% of all treated cycles, the women complied with the prescribed dosing schedule.

Reviewer's Comment
The rate of discontinuation is similar to that seen in other contraceptive trials. The compliance with prescribed dosing is better than that usually seen with oral contraceptive trials.

Clinical Assessment and Recommendations

The primary reviewer previously recommended that the difference in pregnancy rates between US and European studies (PI of 1.86 vs. 0.64, PP 1.45 vs. 0.52) be included in the label. After further discussion with the Office of Drug Evaluation III it was decided that detailed efficacy results from clinical contraceptive trials not be included in the label because of numerous variations in trial design that could affect the efficacy results reported. A Clinical Studies section is not needed for this product as there are no important new safety concerns specific to this product.

I agree with the primary medical reviewer's recommendation that this application is approvable, pending the sponsor's acceptance of recommended labeling, with the following phase IV commitments:

1. Conduct a clinical study assessing serum ENG and EE concentrations and ovulation inhibition in women receiving multiple treatments of oil-based vaginal miconazole nitrate preparations. Use of the oil-based vehicle as a control arm is suggested. The sponsor agreed to submit a draft protocol within 6 months of approval.
2. Conduct a clinical study to address the impact of tampon use on drug absorption, including serum ENG and EE concentrations.
   - The previous Group Leader review recommended that the sponsor also assess tampon levels of the hormones. This reviewer finds the above study to assess serum ENG and EE concentrations adequate to address the impact of tampon use on NuvaRing® efficacy. However, it was suggested that assessment of hormone absorption by tampons could also be evaluated at the sponsor's discretion. The sponsor agreed to submit a draft protocol within 6 months of approval.
3. Follow-up all spontaneous reports of pregnancies with NuvaRing® use to obtain information regarding duration of exposure of each pregnancy to NuvaRing® and pregnancy outcomes, including live births, stillbirths, premature births, spontaneous abortions, and congenital anomalies.

Non-Clinical Assessments

Pharmacotoxicology

As noted in the previous Group Leader Review, etonogestrel (ENG) is the active metabolite of desogestrel, and the safety of ENG is also supported by the clinical experience with desogestrel. The toxicity studies previously conducted for oral desogestrel also support the safety of ENG, although many of the nonclinical toxicity studies were performed in the 1970s, prior to the current GLP and ICH guidelines.

Bronchioalveolar adenomas and carcinomas were noted in a rodent study with statistical significance compared to a placebo group. However, the incidence was not different than the baseline rate for the laboratory where the studies were conducted. The Executive CAC ruled this finding to be of no significance to humans. However, a brief descriptive statement of these findings is included in the Carcinogenesis section of the label for completeness.

The primary pharmacotoxicology reviewer noted that the serum concentrations of ENG achieved with NuvaRing® are 13 times the minimum concentrations shown to inhibit ovulation in humans (90 pg/ml). However, the sponsor has conducted 3 dose-finding studies and selected the dosage based on both ovulation inhibition and menstrual cycle control. The serum concentrations of ENG achieved with NuvaRing® are similar to the minimum concentrations seen at steady state with the marketed desogestrel-containing OC Desogen®, and roughly 22% of the maximum concentrations at steady state with Desogen®.

I agree with the final recommendation that this application is approvable, pending the sponsor's acceptance of the recommended labeling.

Chemistry, CDRH, and Microbiology

Following prolonged storage at 25 and 30^{0}C, NuvaRing® was found to produce an erratic "burst" of ENG release, with day 1 release rates roughly twice those seen at any time after day 1. Such an effect was not observed with storage for 24 months under refrigeration at 5^{0}C. This "burst" effect is not expected to be clinically significant, as the serum ENG concentrations produced are expected to be no higher than maximum serum concentrations seen at steady state with administration of Desogen® OCs. Therefore, the label for this product recommends storage under refrigeration prior to sale, and then at room temperature by the consumer for up to 7 months. Patient labeling recommends avoiding exposure to direct sunlight or prolonged storage at temperatures above 86^0.

Initial release rate specifications recommended by the primary chemistry reviewer give an upper bound of EE release on day 1 of 30 µg/day based on data presented by the sponsor. However, the sponsor originally requested an upper limit of 45ug/day for EE release, and in subsequent communication with the Division, requested an upper limit of 35ug/day for EE release. The sponsor based their request upon release rates with some of their developmental batches which were manufactured on a different scale. The projected Cmax with the 35ug/day EE release rate is 53 pg/ml, which is less than half the Cmax produced with use of the marketed product Desogen.

Although the sponsor's requested initial release rate specification of $\leq$35 ug/day for EE presents no apparent safety or efficacy concern, this is a quality control issue, and the 35 µg/day limit is not acceptable. The sponsor agreed to the recommended limit of 30 µg/day in a teleconference on 12/11/00.

The primary and secondary chemistry reviewers requested a **phase IV commitment** of the sponsor to provide a validated alternative to their automated dissolution method within 12 months after approval. The sponsor agreed to this in a teleconference on 12/11/00 and confirmed in writing on 12/13/00.

I agree with the recommendation of the primary and secondary chemistry reviewers that this application is approvable, pending the sponsor's acceptance of the recommended labeling, with the above phase IV commitment.

Clinical Pharmacology

As previously noted, a drug interaction study showed a 17% increase in serum ENG and a 16% increase in serum EE AUC was seen when single doses of intravaginal miconazole nitrate were administered to NuvaRing® users. Administration of nonoxynol-9 did not affect the serum ENG or EE. The primary clinical pharmacology reviewer recommended a phase IV commitment for an in vitro dissolution test in the presence and absence of the oil-based 1200mg miconazole nitrate capsule.

This reviewer finds that the clinical phase IV study discussed above is adequate to address the concern about drug interactions with oil-based vaginal miconazole nitrate. I agree with the primary clinical pharmacology reviewer's recommendation that this application is approvable pending the sponsor's acceptance of the recommended labeling.

DSI

Inspections are completed and are satisfactory.

Tradename

As of 10/11/00 OPDRA and the Division concur that the proposed tradename is acceptable.

Facilities Inspection

All sites have been inspected and found to be satisfactory.

Labeling

OPDRA made several recommendations regarding container labeling and the Patient Package Insert (PPI). The sponsor agreed to some of the recommendations from OPDRA and provided rationale for not making other recommended revisions. The one unresolved issue is the recommendation from OPDRA to include the word "vaginal" in the established name of the product, etonogestrel/ethinyl estradiol vaginal ring. The sponsor declines to make this revision, as they believe that the route of administration is not commonly incorporated into the established name, and "vaginal ring" is not approved as a labeling term in the EU. The chemistry reviewers agree with OPDRA that the term should be included in the established name, as with the other approved vaginal ring product.

Final labeling was sent to the sponsor on 12/22/00 incorporating all of the recommended changes from all disciplines, but they were not willing to accept the proposed labeling from the Division. Therefore, an Approvable action was taken.

Conclusions and Recommendations

I agree with the recommendations of the primary and secondary reviewers of all disciplines that this application for NuvaRing® is approvable, pending the sponsor's acceptance of the recommended labeling and resolution of any other outstanding

issues, with the following phase IV commitments as agreed to by the sponsor on 12/13/00 and 12/20/00:

1. **Conduct a clinical study assessing serum ENG and EE concentrations and ovulation inhibition in women receiving multiple treatments of oil-based vaginal miconazole nitrate preparations. Use of the oil-based vehicle as a control arm is suggested. The sponsor agreed to submit a draft protocol within 6 months of approval.**
2. **Conduct a clinical study to address the impact of tampon use on drug absorption, including serum ENG and EE concentrations.**
   - **The previous Group Leader review recommended that the sponsor also assess tampon levels of the hormones. This reviewer finds the above study to assess serum ENG and EE concentrations adequate to address the impact of tampon use on NuvaRing® efficacy. However, it was suggested that assessment of hormone absorption by tampons could be evaluated at the sponsor's discretion. The sponsor agreed to submit a draft protocol within 6 months of approval.**
3. **Follow-up all spontaneous reports of pregnancies with NuvaRing® use to obtain information regarding duration of fetal exposure of each pregnancy to NuvaRing® and pregnancy outcomes, including live births, stillbirths, premature births, spontaneous abortions, and congenital anomalies.**
4. **Provide an alternative to the in vitro dissolution method currently used within 12 months post approval.**

/S/ 12/22/00

Dena R. Hixon, M.D., FACOG
Team Leader/DRUDP

I Concur.

/S/ 12/22/00

Susan S. Allen, M.D., MPH
Director, DRUDP

cc: HFD-580 / S. Allen /D. Shames/D. Hixon/D. Davis

Group Leader Memorandum
NDA 21-187
Complete Response to Approvable Letter

Drug	**NuvaRing®**
Generic Drug Name	**etonogestrel/ethinyl estradiol vaginal ring**
Dose	**ethylene vinylacetate (EVA) vaginal ring containing 11.7 mg etonogestrel and 2.7 mg ethinyl estradiol released at a rate of 0.120 mg/day etonogestrel and 0.015 mg/day ethinyl estradiol**
Indication	**prevention of pregnancy**
Applicant	**Organon, Inc.**
Date of Submission	**8/02/01**
Date of Memorandum	**10/02/01**
Reviewer	**Dena R. Hixon, M.D., FACOG** **Team Leader, DRUDP**

Summary
This submission is a Complete Response to an Approvable Letter issued by the Agency on April 27, 2001. It contains a safety update and annotated labeling. The information presented is sufficient to support marketing of NuvaRing® with the labeling revisions recommended to the sponsor on September 21, 2001.

Background
NuvaRing® is a combination hormonal contraceptive containing ethinyl estradiol (EE) and the new progestin etonogestrel (ENG) delivered continuously from a flexible transparent vaginal ring. It is intended to be inserted into the vagina and left in place for 21 days and then removed for a 7-day ring free interval, similar to a typical oral contraceptive dosing regimen of pill-taking for 21 days followed by a 7-day pill free interval.

Etonogestrel is a new progestin that is the active metabolite of the third generation progestin desogestrel, contained in several marketed oral contraceptives. Epidemiology studies have suggested a two-fold increase in the risk of venous thrombo-embolism (VTE) with desogestrel use compared with use of certain second generation progestins. NuvaRing® has never been marketed, and it is unknown whether the increased risk of VTE applies to the vaginal administration of etonogestrel.

NuvaRing® is a hormonal contraceptive product with a different route of administration than any approved hormonal contraceptive product. Failure rates and bleeding patterns with NuvaRing® use are similar to those seen with combined oral contraceptive use and without the need for daily pill taking.

Regulatory History

NDA 21-187 was first submitted on December 28, 1999 and received an Approvable action on December 22, 2000. A Complete Response to the Approvable Letter was submitted on February 28, 2001 and received an Approvable action on April 27, 2001. As noted in the 10/6/00, 12/12/00, 12/22/00, and 4/27/01 primary and secondary reviews, these submissions were found adequate to support safety and efficacy of NuvaRing® for marketing in the U.S. However, the sponsor was unable to reach agreement with the Agency regarding appropriate labeling for the product.

The sponsor has agreed to the following phase IV commitments on 12/13/00 and 12/20/00 and on 4/27/01:

1. Conduct a clinical study assessing serum ENG and EE concentrations and ovulation inhibition in women using NuvaRing® and receiving multiple treatments of oil-based vaginal miconazole nitrate preparations. Use of the oil-based vehicle as a control arm is suggested. The sponsor agreed to submit a draft protocol within 6 months of approval.
2. Conduct a clinical study to address the impact of tampon use on drug absorption, including serum ENG and EE concentrations. The sponsor agreed to submit a draft protocol within 6 months of approval.
3. Follow-up all spontaneous reports of pregnancies with NuvaRing® use to obtain information regarding duration of fetal exposure of each pregnancy to NuvaRing® and pregnancy outcomes, including live births, stillbirths, premature births, spontaneous abortions, and congenital anomalies.
4. Provide an alternative to the in vitro dissolution method currently used within 12 months post approval.

Reviewer's comment

On June 21, 2001, the sponsor submitted a phase IV protocol (#34232) for a 2-arm randomized crossover, pharmacokinetic study assessing serum ENG and EE concentrations and ovulation inhibition in women receiving the following vaginal products:

- *In Arm A, 6 women will receive 200 mg oil-based vaginal miconazole nitrate suppositories and 6 controls will receive the oil based vehicle. The study drug will be administered on cycle days 8-10 of a 21-day NuvaRing cycle, followed by a 7-day ring-free interval. Each group will receive the opposite treatment in the following cycle.*
- *In Arm B, 6 women will use tampons on cycle days 8-10, and 6 control subjects will use no vaginal products. Each group will receive the opposite "treatment" in the following cycle.*

In response to agency comments, the sponsor committed to several modifications to the protocol in a letter dated July 19, 2001. The changes included redesigning Arm A to include treatment with water-based 4% vaginal miconazole nitrate cream in one group and treatment with the oil based miconazole nitrate vaginal suppository in the other group.

In a teleconference on September 26, 2001 and in a subsequent fax letter dated September 27, 2001, the sponsor committed to initiate study 34232 within 6 months after approval and to submit results within 6 months of completion. The sponsor also agreed again to the other phase IV commitments, with the following revision to #3:

- *Submit a plan for follow-up of all spontaneous reports of pregnancy with NuvaRing® use to obtain information regarding duration of fetal exposure to NuvaRing® for each pregnancy and pregnancy outcomes, including live births, stillbirths, premature births, spontaneous abortions, and congenital anomalies. The plan, including 6 month intervals for submitting data and a 5 year time span (following approval) for follow-up, should be submitted within 6 months after approval.*

The current submission is the sponsor's complete response to the April 27, 2001 Approvable Letter. It includes the sponsor's annotated proposed labeling revisions and a safety update.

Safety update

The current safety update revealed no new safety concerns for this product. Information was presented from the one ongoing 26 cycle clinical trial in Europe and Chile. At the time of the safety update, NuvaRing® had not yet been marketed in any country although N.V. Organon received Marketing Authorization from the Dutch Medicines Evaluation Board on February 14, 2001 and is proceeding with the Mutual Recognition Procedure within the European Union.

Labeling update

The primary reviewer has recommended revisions to the sponsor's proposed labeling regarding bleeding patterns, weight gain, non-contraceptive benefits, and use of a diaphragm as a back-up method of contraception.

Reviewer's comments:

- *I agree with the primary reviewer that it is not appropriate to pool bleeding pattern data from the 2 studies. If the sponsor wishes to include data from the European trials regarding bleeding patterns, it must be presented separately from the US trial data. It is acceptable to include data from cycles 1-13, since the data in cycles 1 and 13 is similar to that in cycles 2-12.*
- *I agree that weight gain should be listed with the adverse events occurring in $\geq$ 5% of women or a statement about the actual recorded weight changes should be included.*
- *I agree that the risks associated with COCs must be included for safety reasons. However, it is not appropriate to include benefits that have not been substantiated for the proposed product. The non-contraceptive benefits of COCs are specific to oral contraceptives and have not been included in the labeling of hormonal contraceptives with other routes of administration.*
- *I agree that a diaphragm is not appropriate when back-up contraception is needed with NuvaRing®, and a statement that NuvaRing® could interfere with correct placement and position of a diaphragm should remain once in both the PI and PPI.*

Clinical Assessment and Recommendations

I agree with the primary reviewer's recommendations for revisions to the sponsor's proposed labeling as noted above.

Non-Clinical Assessments

Pharmacotoxicology

I agree with the pharmacotoxicology reviewer's recommendation that adequate data has been presented to the agency to justify removing any mention of lung broncho/alveolar adenomas from the labeling. I also agree that any comparison of animal vs. human exposure in the label should be based upon the actual serum concentrations of etonogestrel instead of the dose per kg of body weight administered.

Chemistry, CDRH, and Microbiology

No new chemistry or manufacturing information was presented for review. In preparation for a prior approval supplement to be submitted after approval for a scale-up in manufacturing process, the sponsor proposed to submit a CBE after approval for a 4-month room temperature storage limit after distribution to the user. Whereas the previously accepted storage limit was 7 months,

the agency recommended changing the labeling prior to action on this submission to include a 4-month room temperature storage limit. The sponsor agreed to make this labeling change in a teleconference on September 26, 2001.

Clinical Pharmacology
No new pharmacokinetic or pharmacodynamic data was presented for review.

DSI
All inspections were completed and satisfactory in the initial review cycle. Additional inspections were not required.

Tradename
The proposed tradename was approved in the initial review cycle and is still acceptable to OPDRA.

Facilities Inspection
All sites were satisfactory in the initial review cycle and remain satisfactory.

Labeling
Multiple edits to the proposed label were recommended to the sponsor on September 21, 2001. Final agreement on labeling was reached in teleconferences on September 28, 2001 and October 1, 2001, and is reflected in the final label submitted by the sponsor on October 1, 2001 and October 2, 2001.

Conclusions and Recommendations
This application may be approved with the labeling submitted on October 1, 2001 with the revisions submitted October 2, 2001 and the Phase IV commitments as noted above.

Dena R. Hixon, M.D., FACOG
Team Leader/DRUDP

Daniel Shames, M.D., FCS
Acting Director/DRUDP

cc: HFD-580 / S. Allen /D. Shames/D. Hixon/D. Davis

Mercier

Meeting Minutes

Date: August 14, 2000 **Time:** 1:00-2:00 PM **Location:** Parklawn; 17B-43

NDA 21-187 **Drug:** NuvaRing™ (etonogestrel/ethinyl estradiol ring)

Indication: Contraception

Sponsor: Organon, Inc.

Type of Meeting: Status Meeting

Meeting Chair: Dr. Susan Allen

Meeting Recorder: Jeanine Best for Jennifer Mercier

FDA Attendees:
Susan Allen, M.D., M.P.H., Director, Division of Reproductive and Urologic Drug Products, (DRUDP; HFD-580)
Jerry Willett, M.D., Acting Team Leader, DRUDP (HFD-580)
Dan Davis, M.D., Medical Officer, DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D., Chemistry Team Leader, Division Of New Drug Chemistry II (DNDC II) @ DRUDP, (HFD-580)
David Lin, Ph.D., Chemist, DNDC II @ DRUDP (HFD-580)
Ameeta Parekh, Ph.D., Phamacokintic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Johnny Lau, R.Ph., Ph.D, Pharmakokinetic Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP, (HFD-580)
Krishan Raheja, D.V.M., Ph.D., Pharmacologist, DRUDP (HFD-580)
Moh Jee Ng, Ph.D., Statistician, Division of Biometrics II (DB II; HFD-715)
Jeanine Best, M.S.N., R.N., Regulatory Project Manager, DRUDP (HFD-580)

Meeting Objective: To discuss the status of the reviews and approvability of this NDA.

Background: NuvaRing™ is a progestin/estrogen combination contraceptive vaginal ring (CCVR) product that was submitted for review on December 28, 1999; 10-month PDUFA date is October 29, 2000 and the application requires Office concurrence and sign-off. NuvoRing™ is a cyclical hormonal drug product and each ring is used for three weeks duration with one week of ring-free use. Each ring releases 0.120 mg/day of etonogestrel (a metabolite of desogestrel; a third generation progestin), and 0.015 mg/day of ethinyl estradiol over a three-week period.

Discussion:
Chemistry

- review nearing conclusion; no major approvability issues identified at this time; awaiting DMF deficiency response for the drug substance etonogestrel
- stability issue involving dissolution specifications; sponsor is providing a generous range; Division would like to see the specifications tightened

- Division prefers one set of specifications for stability and release rate

Biopharmaceutics:

- draft review is complete
- Day 1 is the crucial day for release rate; etongestrel demonstrates a burst on Day 1; sponsor has not performed extensive time-point sampling on Day one *in vitro* dissolution or on serum blood levels, necessary to characterize the peak; this is not a clinical concern, but instead a quality issue
- the sponsor used water for the dissolution testing; media with different pH's have not been utilized for dissolution testing
- the clinical formulation is identical to the to-be-marketed formulation
- NuvaRing inhibits activity at CYP3A4 pathway; no induction studies performed and no drug:drug interaction studies performed
- Division does not accept the IV/IVC correlation data (based on a three compartment prototype with different release rates that the to-be-marketed product); there is no internal or external validation available; this is not an approvability issue, but would need to be addressed before future manufacturing changes could take place

Pharmacology/Toxicology:

- review nearing completion; labeling issues to be addressed via electronic label revisions
- awaiting submission of some carcinogenicity studies data to submit to the CAC committee for review and approval
- reprotoxicity studies performed in 1975-1976; unsure if studies were performed with the same lots; studies may not meet the current criteria; doses used are below human levels; some reprotoxicity studies may need to be repeated as part of a Phase 4 commitment unless supported on the basis of desogestrel approval

Clinical:

- review underway; several issues will need to be addressed in the labeling
  - bleeding control statement in label; sponsor presented data from three small studies and compared with the oral contraceptive [redacted] sponsor has not established a superiority claim and will not be allowed to use their statement in the label
  - Sponsor has added a line to the Trussell Table with regard to efficacy of their product; the [redacted] cannot be altered without the permission of the author; the Sponsor needs to present a complete **Clinical Trials** section in their label showing the differences between the U.S and the European trials
  - the Pearl Index for the European trial was lower than in the U.S. trial, .6 versus 1.7 for the ITT, and .3 versus .9 for perfect use; the combined Pearl Index was 1.18
  - there was one case of VTE and one case of superficial thrombophlebitis in the clinical trials; see the May 22, 2000 Mircette Supplement Request Letter for appropriate label language regarding this occurrence with third generation progestins
  - Sponsor proposes to alter the standard language with regard to cigarette use in combination estrogen/progestin users; the Sponsor is presenting old data from 1981; sponsor will need to revise to the current accepted data
- the CCVR demonstrated minor vaginal irritation, low expulsion and an increase in vaginitis (14% of users), of which the sponsor attributes 50% to use of the product

- the Sponsor recommends immediate use of the product after a 1st trimester abortion and a four week wait after a delivery or a 2nd trimester abortion
- Sponsor performed a re-analysis of the efficacy data and the changes are small number difference; D. Davis to re-analyze the data

Biometrics

- review is underway
- awaiting the Medical Officer's re-analysis of the efficacy data to finalize the Pearl rates; also need the sponsor to provide the efficacy data for females less than 35 years based on the re-analysis of the pregnancy data

Decisions made:

- reviewers to begin label edits on the [redacted] Physician and Patient 30 November and Medical Officer to also edit [redacted] Patient Package Insert 30 Nov 1999

Action Items:

- reviewers to complete initial label edits on the "N" Drive by COB August 31, 2000

/S/
Minutes Preparer

/S/

/S/
Concurrence, Chair

8/25/00

Meeting Minutes

Date: August 22, 2001 **Time:** 9:30 – 10:30 AM **Location:** Parklawn; 17B-43

NDA 21-187 **Drug:** NuvaRing® (etonogestrel/ethinyl estradiol vaginal ring)

Indication: Contraception

Type Of Meeting: Labeling

Meeting Chair: Dena Hixon, M.D.

Meeting Recorder: Jennifer Mercier

FDA Attendees:
Dena Hixon, M.D. – Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Krishan Raheja, Ph.D., D.V.M. – Pharmacologist, DRUDP (HFD-580)
S.W. Johnny Lau, R.Ph., Ph.D. – Biopharmaceutics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Jennifer Mercier, B.S. – Regulatory Project Manager, DRUDP (HFD-580)

Background:
NDA 21-187 was originally submitted on December 28, 1999, then approvable on December 22, 2000. The sponsor resubmitted on February 28, 2001 and found approvable again on April 27, 2001. The sponsor has again resubmitted on August 2, 2001 with a goal date of October 3, 2001.

Purpose of the Meeting:
To discuss the review status of the information submitted on August 2, 2001.

Decisions Made:
- All reviews are complete and are awaiting final sign-off.
- Label
  - All labeling changes should be made to the N drive in preparation to send the label to the sponsor.
  - The sponsor has proposed to keep the European data in the label for the bleeding patterns; upon further review, FDA would consider using both the European and US data for the bleeding patterns, but would not allow pooling of the data from the two studies. The data would have to be presented separately.
  - The sponsor also would like to use cycles 1-13 in the label instead of the FDA proposed 2-12.
  - The sponsor also would like to delete all the references to the proper placement and position of the diaphragm in the label; they would like to limit the amount of

times this statement is used in the label. The Division will recommend keeping one statement about this in the PI and one in the PPI.

Action Items:

- Action package must be to the office on Friday, September 21, 2001.
- Send the label to the sponsor.

Minutes Preparer

Minutes Concurrence

Cc:
Drafted: September 20, 2001
Initialed: Lau9.20.01/Hixon9.20.01
Final: September 24, 2001

Teleconference Minutes

Date: November 8, 2000 **Time:** 9:30 – 10:30 AM **Location:** Parklawn; 17B-45

NDA 21-187 **Drug:** NuvaRing® (etonogestrel/ethinyl estradiol)

Indication: vaginal contraceptive ring

Sponsor: Organon, Inc.

Type of Meeting: Chemistry Guidance

FDA Chair: David Lin, Ph.D.

FDA Attendees:
David Lin, Ph.D. – Chemist, Division of New Drug Chemistry II (DNDCII) @ Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
S.W. Johnny Lau, R.Ph., Ph.D. – Pharmacokinetic Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Jennifer Mercier, B.S. – Regulatory Project Manager, DRUDP (HFD-580)

External Attendees:
Thomas Pituk, Ph.D. - Group Director (Regulatory Affairs / CMC)
Edwina Muir - Director (Regulatory Affairs)
Edward Nellis - Assistant Manager (Regulatory Affairs)
Tom Sam, Ph.D. - Team Leader (Regulatory Affairs)
Ruud Groenewegen, MSc. - Section Head (Product Development)
Marjan van der Werf-Pieters, Ph.D. - Int'l Project Manager (Reproductive Medicine)

Meeting Objective: To provide comments to the sponsor's response to the Information Request letter dated September 20, 2000.

Decisions made:

- the Division would prefer that the regulatory and shelf-life specifications for the *in-vitro* release rate be the same for this product

- Drug Product Specifications for Degradation Products
  - the information in the NDA states that there are less than 0.1% of unidentified degradation products; the sponsor needs to submit data to support the specification of less than 1%
  - the sponsor proposes not to tighten the specifications for the other degradation products
  - a final decision will be made following review of this additional data

- The recommended NuvaRing® *in vitro* release specifications are as follows:

	ENG (etonogetrel) (µg/day/ring)	EE (ethinyl estradiol) (µg/day/ring)
Day 1	≤ 360	≤ 30
Day 2 - 21	120 (mean) (96 - 144)	15 mean (10 - 20)
Day 21	≥ 80	≥ 10

- In vitro release acceptance criteria is as follows:

  Day 1: The individual daily amounts of ENG or EE released for each of the 12 rings tested has to be less than or equal to the stated limit (sponsor's proposal).

  Days 2 through 21:

  Stage I: the mean should be within the specification range (96-144 µg ENG/day/ring and 10-20 µg EE/day/ring); not less than 11 samples should be within ± 10% of the specification mean (120 µg ENG/day/ring and 15 µg EE/day/ring) for the specification range that is 84-156 µg ENG/day/ring and 8.5-21.5 µg EE/day/ring; and no 1 sample will be outside ± 15% of the specification mean for the specification range that is 78-162 µg ENG/day/ring and 7.7-22.3 µg EE/day/ring.

  Stage II: If more than 1 sample is outside the ±10%, but within ±15%, the test must be repeated with another 12 rings, which must meet Stage I requirements.

  Day 21: The individual daily ENG and EE amounts released for each of the 12 rings has to be greater than or equal to the stated limit.

- the sponsor needs to clarify the tensile strength test in the NDA
- the sponsor is reminded that the stability commitment is on the first three commercial batches post approval; if the sponsor is planning to use the pre-approval batches for their stability commitment information is needed that to ensure that the pre-approval batches are the same as the to-be-marketed batches presented in the NDA
- the proposed expiration date seems reasonable; but the reviewer will make a final decision after receiving the additional data
- the West Orange, New Jersey site is listed as a withhold approval because of the problems with it's last inspection; the chemist reviewed the application and the sponsor can opt to remove this site from the NDA
- the sponsor needs to propose a manual dissolution method; the process in the NDA is automated and cannot be validated by the FDA laboratories; this may could be a Phase 4 commitment

/S/ 11/20/00

Minutes Preparer

/S/

Concurrence

Note: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

Teleconference Meeting Minutes

Date: December 6, 2000 **Time:** 10:30 – 11:00 AM **Location:** Parklawn; 17B-45

NDA 21-187 **Drug:** NuvaRing® (etonogestrel/ethinyl estradiol)

Indication: vaginal contraceptive ring

Sponsor: Organon, Inc.

Type of Meeting: Chemistry Guidance

FDA Chair: David Lin, Ph.D.

FDA Attendees:
David Lin, Ph.D. – Chemist, Division of New Drug Chemistry II DNDCII @ Division of Reproductive Drug Products (DRUDP; HFD-580)
S.W. Johnny Lau, R.Ph., Ph.D. - Pharmacokinetic Reviewer, OCPB @ DRUDP (HFD-580)
Jennifer Mercier, B.S. – Regulatory Project Manager, DRUDP (HFD-580)

Meeting Objective: To discuss outstanding issues for this application.

Decisions made:
- the sponsor needs to provide a manual method for the in vitro drug release rate method; currently the method is automated, but a manual method is needed so that it can be validated by FDA lab; if the sponsor is unable to complete this task by the goal date, then this will have to be a Phase 4 commitment
- the Division has reviewed the sponsor's response in the November 14, 2000 chemistry amendment; the sponsor's proposal for the ethinyl estradiol release specification for Day 1 ≤35 µg per day per ring, the Division has reviewed all the information submitted by the sponsor and stands by it's original recommendation of ≤30µg per day per ring

Action Items:
- the sponsor should submit the manual method for the dissolution method
- the sponsor should submit either acceptance of the recommended release specification or provide additional information to support their proposal
- fax meeting minutes to sponsor within 30 days

/S/ /S/ 12/12/00

Minutes Prepared Concurrence

Note: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

Teleconference Meeting Minutes

Date: December 11, 2000 **Time:** 1:30 – 2:30 PM **Location:** Parklawn: 14B-45

NDA 21-187 **Drug:** NuvaRing® (etonogestrel/ethinyl estradiol)

Indication: vaginal contraceptive ring

Sponsor: Organon, Inc.

Type of Meeting: Chemistry/Clinical

FDA Chair: Dena Hixon, M.D.

FDA Attendees:
Dena Hixon, M.D. – Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP: HFD-580)
Daniel Davis, M.D. – Medical Officer, DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D. – Team Leader, Division of New Drug Chemistry II (DNDCII) @ Division of Reproductive and Urologic Drug Products (DRUDP: HFD-580)
David Lin, Ph.D. – Chemist, DNDCII @ DRUDP (HFD-580)
S.W. Johnny Lau, R.Ph., Ph.D. – Pharmacokinetic Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Jennifer Mercier, B.S. – Regulatory Project Manager, DRUDP (HFD-580)

External Attendees:
Edwina Muir - Director, Regulatory Affairs, Organon, Inc.
Thomas Pituk, Ph.D. - CMC Group Director, Regulatory Affairs, Organon, Inc.
Ed Nellis - Assistant Manager, Regulatory Affairs, Organon, Inc.
Tom Sam, Ph.D. - Team Leader, Regulatory Affairs, Organon, Inc.
Marjan van der Werf-Pieters, Ph.D. - Int'l. Project Manager, Reproductive Medicine, Oragnon, Inc.
Titia Mulders, Ph.D. - Int'l. Project Manager, Reproductive Medicine, Organon, Inc.

Meeting Objective: To discuss final chemistry issues and some Phase 4 commitments.

Decisions made:
Chemistry

- the sponsor agrees that the Day 1 ethinyl estradiol dissolution specification is [redacted] per day per ring; the sponsor can propose changes in a supplement to the NDA if they have any problems meeting this specification post approval
- the sponsor will revise the submission dated November 14, 2000: the sponsor will add the word "mean" after the % signs
- the sponsor has committed to provide an alternative method for the *in vitro* release method within 12 months of approval: a manual dissolution method is suggested by the Division

Clinical

- the sponsor has committed to conducting a study on the effect of oil-based vaginal products used for perhaps 4-7 days on the serum levels of etonogestrel and ethinyl estradiol: the sponsor has committed in sending in a draft protocol within 6 months of approval for this NDA
- the sponsor has committed to conducting a study on the use of tampons with the drug product: the sponsor has committed in sending in a draft protocol within 6 months of approval for this study
- the sponsor has also committed to attempting to follow-up on spontaneous reporting of pregnancy on this product

Action Items:

- the sponsor should submit to the NDA the Phase 4 commitments with the timeframe for submission of these studies by Wednesday, December 13, 2000
- the sponsor should submit the revised labeling by Tuesday, December 12, 2000
- the sponsor will revise amendment dated November 14, 2000 and resubmit to NDA
- meeting minutes will be faxed to the sponsor within 30 days

/S/
Minutes Preparer

/S/
Concurrence

Note: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

Memorandum

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

From: David Lin, Ph.D. /S/ 9/6/01

Date: September 6, 2001

Re: T-con with Ed Nellis to clarify 11/16/00 Chemistry Meeting

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During the November 16, 2000 meeting with the sponsor to discuss post-approval manufacturing changes for this product, it was recommended that at time of supplement submission 6 months of stability data be provided, with an additional 3 months during the review cycle. However, the sponsor does not have adequate time to generate these data before submission of the supplement. The sponsor will only be able to provide a total of 6 months of accelerated stability data. It was reiterated that based on the data provided to the NDA, the reviewer has concerns about the "burst effect" of the product after extended storage at room temperature. With the current labeling of 7 months of room temperature storage after removal from refrigerated conditions, the 6 months of room temperature might not be adequate to address the burst effect. The sponsor has therefore proposed to reduce the expiry to 4 months of room temperature storage following refrigerated storage by submitting a CBE supplement following approval of the NDA. Then a Prior Approval Supplement will be submitted for drug product manufacturing changes with 3 months of accelerated stability data [redacted] followed by three additional months, two months after filing of the supplement. The reviewer finds the sponsor's revised proposal to be acceptable.

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

Teleconference Meeting Minutes

Date: September 26, 2001 **Time:** 2:00 – 2:45 PM **Location:** Parklawn; 17B-43

NDA 21-187 **Drug:** NuvaRing® (etonogestrel/ethinyl estradiol vaginal ring)

Indication: Contraception

Type Of Meeting: Guidance

Meeting Chair: Dena Hixon, M.D.

Meeting Recorder: Jennifer Mercier

FDA Attendees:
Susan Allen, M.D., M.P.H. – Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Dena Hixon, M.D. – Team Leader, (DRUDP; HFD-580)
Moo-Jhong Rhee, Ph.D. – Team Leader, Division of New Drug Chemistry II (DNDCII) @ DRUDP (HFD-580)
Jennifer Mercier, B.S. – Regulatory Project Manager, DRUDP (HFD-580)

External Attendees:
Edwina Muir – Regulatory Affairs, Organon, Inc.
Ed Nellis – Regulatory Affairs, Organon, Inc.
Chinu Murphy – CMC, Organon, Inc.
Ed Sulfus – CMC, Organon, Inc.

Background:
NDA 21-187 was originally submitted on December 28, 1999, an approvable action was taken on December 22, 2000. The sponsor resubmitted on February 28, 2001 and a second approvable action was taken on April 27, 2001. The sponsor has again resubmitted on August 2, 2001 with a goal date of October 3, 2001.

Purpose of the Meeting:
To wrap up issues regarding the appovability of this drug product.

Decisions Made:

Phase 4 commitment

- The sponsor must commit to initiate study 34232 within 6 months after approval and submit the results of that study within 6 months of completion.
- The sponsor must commit to submit a plan for follow-up of all spontaneous reports of pregnancy with NuvaRing® use to obtain information regarding duration of fetal exposure to NuvaRing® for each pregnancy and pregnancy outcomes, including live births, stillbirths, premature births, spontaneous abortions, and congenital anomalies.

The plan, including 6 month intervals for submitting data and a 5 year time span (after approval) for follow-up, should be submitted within 6 months after approval.

- The sponsor must commit to provide an alternative to the *in vitro* dissolution method currently used within 12 months post approval.

Label

- The sponsor has stated that they will get a list of issues that they would like to discuss at the meeting on Friday, September 28, 2001, to the Division by Thursday morning.

Pharmacology

- The sponsor has submitted the two page report from the re-read of the rat lung slides in the resubmission to the NDA on August 2, 2001.

Chemistry

- The NDA supports approval of the storage expiry of 7 months, but the sponsor plans to submit a CBE supplement shortly after approval to reduce this expiry to 4 months.
- The Division has concern regarding the reduction of the storage expiry and education of patients and physicians regarding this change post-approval.
- The Division recommends amending the NDA to reflect the 4 months storage expiry and submit the proper labeling prior to the action date.
- The sponsor is concerned about the timeframe that they have to get those amendments into the NDA prior to the action date; the sponsor will commit to amending the labels as needed by Friday, September 28, 2001.

Action Items:

- The sponsor will submit the revised Phase 4 commitments communicated during this t-con prior to the action date.
- The sponsor will submit revised labeling in an amendment to the NDA by Friday, September 28, 2001.
- The sponsor will submit to the Division all labeling issues by Thursday, September 27, 2001 for the meeting on Friday, September 28, 2001.

_____ _____

Minutes Preparer Minutes Concurrence

Teleconference Meeting Minutes

Date: September 28, 2001 **Time:** 9:30 – 10:00 AM **Location:** Parklawn; 17B-43

NDA 21-187 **Drug:** NuvaRing® (etonogestrel/ethinyl estradiol vaginal ring)

Indication: Contraception

Type Of Meeting: Labeling Discussions

Meeting Chair: Dena Hixon, M.D.

Meeting Recorder: Jennifer Mercier

FDA Attendees:
Dena Hixon, M.D. – Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Jennifer Mercier, B.S. – Regulatory Project Manager, DRUDP (HFD-580)

External Attendees:
Edwina Muir - Regulatory Affairs, Organon Inc.
Ed Nellis - Regulatory Affairs, Organon Inc.
Nancy Alexander - Medical Services, Organon Inc.
Janske Aarts - Clinical Development, Organon Inc.
Titia Mulders - Project Management, NV Organon
Willem de Boer - Regulatory Affairs, NV Organon

Background:
NDA 21-187 was originally submitted on December 28, 1999, then approvable on December 22, 2000. The sponsor resubmitted on February 28, 2001 and found approvable again on April 27, 2001. The sponsor has again resubmitted on August 2, 2001 with a goal date of October 3, 2001.

Purpose of the Meeting:
To finalize the sponsor's proposed label.

Decisions Made:
- See attached label.

Action Items:
- The sponsor will fax copies of the carton labels September 28, 2001.
- The sponsor will submit an amendment to the NDA regarding the revised label.

Minutes Preparer

Minutes Concurrence

Teleconference Meeting Minutes

Date: October 1, 2001 **Time:** 4:15 – 4:30 PM **Location:** Parklawn; 17B-43

NDA 21-187 **Drug:** NuvaRing® (etonogestrel/ethinyl estradiol vaginal ring)

Indication: Contraception

Type Of Meeting: Labeling Discussions

Meeting Chair: Dena Hixon, M.D.

Meeting Recorder: Jennifer Mercier

FDA Attendees:
Dena Hixon, M.D. – Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Jennifer Mercier, B.S. – Regulatory Project Manager, DRUDP (HFD-580)

External Attendees:
Edwina Muir - Regulatory Affairs, Organon Inc.
Ed Nellis - Regulatory Affairs, Organon Inc.

Background:
NDA 21-187 was originally submitted on December 28, 1999, then approvable on December 22, 2000. The sponsor resubmitted on February 28, 2001 and found approvable again on April 27, 2001. The sponsor has again resubmitted on August 2, 2001 with a goal date of October 3, 2001.

Purpose of the Meeting:
To finalize the sponsor's proposed label.

Decisions Made:
- See attached label.

Action Items:

_____ _____

Minutes Preparer Minutes Concurrence

Attachment:

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY
APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Organon Inc.	December 20, 2000
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE (FAX) Number** *(Include Area Code)*
(973) 325-4904 (E. Nellis)	(973) 325-4769
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* **IF APPLICABLE**
375 Mt. Pleasant Avenue West Orange, New Jersey 07052	Organon Inc. 375 Mt. Pleasant Avenue West Orange, New Jersey 07052 (973) 325-4904 (E. Nellis) / (973) 325-4769 (Fax)

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-187

ESTABLISHED NAME (*e.g., Proper name, USP/USAN name*)	PROPRIETARY NAME (*trade name*) IF ANY
etonogestrel/ethinyl estradiol ring	NuvaRing®

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (*If any*)	CODE NAME (*If any*)
etonogestrel 13-Ethyl-17-hydroxy-11-methylene-18,19-dinor-17 -pregn-4-en-20-yn-3-one. ethinyl estradiol (19-nor-17 -pregna-1,3,5(10)-trien-20-yne-3,17-diol	Org 37681

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Ring	0.120 mg etonogestrel per day / 0.015 mg ethinyl estradiol per day	Vaginal

(PROPOSED) INDICATION(S) FOR USE:
Prevention of pregnancy while providing excellent menstrual cycle control in women who elect contraceptives as a method of contraception.

APPLICATION INFORMATION

APPLICATION TYPE (check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY, MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER OF DATE OF AGREEMENT TO PARTIAL SUBMISSION:

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
General Correspondence: Phase 4 Commitments (Revised)

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at this site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See original NDA.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

See original NDA.

This application contains the following items: *(Check all that apply)*	
	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
	8. Clinical data section (e.g., 314.50(d)(5); 21 CFR 601.2)
	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
	12. Case reports forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k)(3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Edwina Nellis (for)	Edwina L. Muir Director, Regulatory Affairs	12/20/2000

ADDRESS (*Street, City, State, and ZIP Code*)	Telephone Number
375 Mt Pleasant Avenue West Orange, New Jersey 07052	(973) 325-4904 (E. Nellis)

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

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