4.8.5 Method Failure (Perfect Use) Evaluation

Reviewer's comment:
Although the data presented in the preceding sections by the sponsor for the "per protocol" population clearly is much better than the "ITT" population, it is the Pearl Index of the Intent-to-Treat Group or the All-Subjects-Treated Group that is traditionally used by the FDA because it is considered to be more clinically meaningful. Furthermore, according to the MO analysis there were three more NuvaRing subjects (# 4321, 1934 and 4820) added to the 68003 study "per protocol" population, and one more NuvaRing subject (# 0524) added to the 34219 study "per protocol" population which lessens the difference between the PP and non-PP Pearl Indices. Because of the definite difference in all the Pearl Indices between the two large pivotal studies, this reviewer favors noting that difference in the Final Printed Label. Since the study protocols are virtually identical, the reason(s) for the difference in Pearl Indices is unclear. It could be due to differences in demographics, drug compliance, study completion rates, data recording in the two study populations, or differences in overall investigators' strictness in carrying out the two studies (NuvaRing® use instructions, data collection and recording, interpretation of data, etc).

4.8.6 Secondary Efficacy Parameter: Cycle Control (Bleeding patterns)

REVIEWER NOTE: on September 20, 2000 our Division requested additional information from the sponsor concerning cycle control (bleeding patterns) and other matters. A response was not received by October 5, 2000, so Tables # 22 and 23 are incomplete and further analysis and comments about cycle control will follow as an addendum at a later date.

From the sponsor's ISE: Cycles were defined by consecutive start-dates recorded on diary cards in Study 34219 or via interactive voice response system (IVRS) in Study 68003. These cycles were subdivided in ring-periods and ring-free periods, where a ring period was defined from start-date of a new ring until the last day of that cycle with any ring use, ie, the last day with a positive number of ring-use hours (>0 hours and ≤ 24 hours). Ring and ring-free periods were calculated in precise hours. However, since bleeding patterns were recorded on a daily basis only, rather than on an hourly basis, bleeding pattern recorded on the first and/or last day of the period of ring-use (on which the ring was used for only a limited number of hours and ideally 24 hours) was assigned to either the ring or ring-free period using conventions as specified in the individual clinical study reports.

Because of the possible influence of missing data or unclear data for the bleeding parameters, specific data handling conventions were used during the analysis of bleeding events. These conventions can be found in the individual clinical study reports for the two large studies. For the cycle control analyses, irrespective of what was recorded via IVRS or on the diary cards, "no bleeding" was imputed for the first 7 days of Cycle 1 because many women started their initial treatment during a bleeding period.

The statistical analysis of the cycles focused on the following parameters:

- occurrence of breakthrough bleeding/spotting (BrB/S)
- absence of withdrawal bleeding/spotting (AWB)
- occurrence of breakthrough bleeding (BrB)
- occurrence of breakthrough spotting [spotting only] (BrS)
- occurrence of early withdrawal bleeding (EWB)
- occurrence of continued withdrawal bleeding (CWB)

- number of breakthrough bleeding/spotting days
- number of withdrawal bleeding days
- occurrence of early withdrawal bleeding with only spotting days in the ring period
- occurrence of continued withdrawal bleeding with spotting days only
- occurrence of intended bleeding pattern

The most important events related to cycle control are considered breakthrough bleeding/spotting (BrB/S) and absence of withdrawal bleeding/spotting (AWB). In view of the vaginal route of administration, early and continued bleeding are considered relevant because of insertion and removal during a bleeding/spotting event. Intended bleeding is representative of the "ideal" bleeding pattern in which bleeding/spotting occurs only during the ring-free period. The remainder of the bleeding events listed above are considered less important events related to cycle control and are not discussed here. Information on these events can be found in the individual clinical study reports.

Reviewer's comment:
The sponsor has focused on BrB/S and AWB as the two most important events related to cycle control. The NDA does not present clear data concerning the average length of the subjects' menses [the median # days of intended bleeding], the onset of intended bleeding [when to expect menstruation relative to ring removal], amount of bleeding [compared to the subject's usual menses], and prolonged bleeding. Elizabeth Belsey[13], WHO expert on menstrual bleeding patterns, has established criteria for "bleeding patterns that are clinically undesirable" using the following definitions:

- **Amenorrhea: no bleeding or spotting throughout a 90-day reference period**
- **Prolonged bleeding: at least 1 bleeding/spotting episode lasting more than 9 days**
- **Frequent bleeding: more than 4 bleeding/spotting episodes within the same 90-day reference**
- **Infrequent bleeding: less than 2 bleeding/spotting episodes in the same reference period**
- **Combinations of the above categories: prolonged and infrequent, prolonged and frequent, prolonged and irregular**

Because traditional hormonal contraception [namely OC pills] have usually been associated with "regular, shorter, lighter menses" with a very predictable onset relative to a 28-day cycle, data of this type would be very useful for the prescribing healthcare provider and the consumer. It is unclear if the sponsor analyzed the extensive data on bleeding patterns in this fashion, but similar data has been requested of the sponsor.

For the sponsor's analysis, a cycle was considered non-evaluable if there were 3 or more consecutive days with missing information on bleeding and/or if the cycle was shorter than 22 days or exceeded 35 days. The cycle analysis for the ITT group was restricted to evaluable cycles. The PP cycle analysis is not restricted because non-evaluable cycles are, by definition, not PP cycles. Figures representing relative frequencies of bleeding variables of all ITT cycles are presented in the ISE.

Bleeding data were collected in the local effects study (068004) but will not be discussed here because only interim data [data as of April 1999; projected study completion date was November 1999] are available for study 068004 and also cycle control was not the primary objective of this study.

Relative frequencies of bleeding/spotting and bleeding days showed a consistent pattern throughout all 13 cycles for the two large studies. The majority of subjects experienced bleeding/spotting in the second half of the ring-free period. The relative frequencies of bleeding/spotting days are very low during the second half of the first week and

[13] Belsey EM, Pinol APY, Menstrual Patterns in Untreated Women, *Contraception* 1997; 55:57-65.

the second week of each ring period. The relative frequencies of bleeding days are very low during almost all ring period days [days 1-21].

Reviewer's comment:
Bleeding was defined as any bloody discharge requiring more than one sanitary napkin or tampon per day. Spotting was defined as any bloody discharge that did not require more than one napkin or tampon per day. The definitions used in the analysis of bleeding parameters were identical for the two studies. Bleeding patterns were evaluated by cycle control analysis: the first 7 days of Cycle # 1 were excluded and the incidence of bleeding events such as intermenstrual bleeding (IMB), breakthrough bleeding and breakthrough spotting (BrB/S), early withdrawal bleeding (EWB), continued withdrawal bleeding/spotting (CWB) and absence of withdrawal bleeding (AWB) were tabulated per cycle rather than per individual subject over time.

Per Sponsor's ISE, incidences of breakthrough bleeding/spotting episodes over Cycles 1-13 for the two large studies combined ranged from 5.1% - 7.9% of ITT evaluable cycles of (ranges of 7.2% - 11.7% for Study 068003 and 2.6% - 6.4% for Study 34219). The incidences were higher for ITT cycles than for PP cycles for Study 068003 and both studies combined.

Reviewer comment: the incidence of BrB/S noted above is per cycle- in other words, 5 to 8% of all the subjects combined had BrB/S each cycle. The cumulative chance of each subject having BrB/S over 13 cycles is not given, and the percentage of subjects who had no BrB/S for the duration of their treatment is not given. This would be helpful data. It is also interesting to note that the highest (worst) incidence of BrB/S throughout the European study was still less than the lowest (best) incidence in the US study.

The incidence of absence of withdrawal bleeding (AWB) over Cycles 1-13 ranged from 1.5% - 2.9% of ITT evaluable cycles of both studies combined (ranges of 2.3% - 3.8% for Study 068003 and 0.6% - 2.1% for Study 34219). The incidences were higher for ITT cycles than for PP cycles for Study 068003 and both studies combined.

Reviewer comment: the incidence of AWB noted above is per cycle- in other words, 1.5 to 2.9% of all the combined subjects experienced no withdrawal bleeding each cycle. The cumulative chance of each subject having AWB over 13 cycles is not given, and the percentage of subjects who had AWB for the duration of a 60- or 90-day reference period is not given. This would be helpful data.

The incidence of intended bleeding pattern (IBP) over Cycles 1-12 ranged from 59.9% - 68.5% of ITT evaluable cycles of the two adequate and well-controlled studies combined (ranges of 58.5% - 67.4% for Study 068003 and 61.2% - 69.3% for Study 34219). The incidences of intended bleeding pattern were generally slightly lower for ITT cycles than for PP cycles for Study 068003 and both studies combined.

Reviewer comment:
The exact sponsor definition for IBP is "cycles without breakthrough bleeding/spotting, absence of withdrawal bleeding, early withdrawal bleeding, or a continued withdrawal bleeding." In simple terms, an IBP was a withdrawal menstrual period between Days 22-28 that did not continue into Day 1 of the next cycle. This is a fairly strict definition and eliminates those women who experienced some bleeding/spotting into the next ring cycle. From the sponsor's data then, during a year's use of NuvaRing, for each cycle there is on average a 64% (~ 2/3) chance of having an "intended" menstrual period as defined by the sponsor. Comparing data from cycles 1-3 with cycles 10-12 in both studies, on average 4.5% more subjects had an IBP [62.2% for cycles 1-3 and 66.7% for cycles 10-12]. Thus the trend is toward better cycle control over one year of NuvaRing® use. The cumulative chance of each subject having an "intended bleeding pattern" over a longer reference period is not given; this information is requested from the sponsor.

The incidence of early withdrawal bleeding (EWB) over Cycles 1-12 ranged from 5.6% - 8.8% of ITT evaluable cycles of the two adequate and well-controlled studies combined (ranges of 5.5% - 9.9% for Study 068003 and 5.4% - 7.7% for Study 34219). For most subjects, EWB was restricted to spotting only. The incidences were comparable for ITT and PP cycles. The incidence of continued withdrawal bleeding (CWB) over Cycles 1-12 was relatively constant ranging from 19.5% to 25.2% of ITT evaluable cycles of the two studies combined, with similar incidences for both studies. As with the early withdrawal, continued withdrawal bleeding consisted mostly of spotting days only.

Reviewer comment:
The exact sponsor definition for CWB is "that portion of the withdrawal bleeding that continued into the ring period of the next cycle." The data shows that 19 to 25% of the subjects each cycle had bleeding/spotting that persisted at least into Day 1 of the next ring insertion. At first this does not seem desirable, but it may be entirely acceptable if the onset of withdrawal bleeding occurs later in the ring free period and the overall length and amount of withdrawal bleeding is in the "normal" range. Median duration of withdrawal bleeding and onset of withdrawal bleeding [median day: interquartile range] are included in the additional information requested from the sponsor.

Table # 21 (from MO). Overall Bleeding Patterns in Studies 68003 and 34219

Bleeding Pattern Range per cycle over 13 cycles	Study 68003 ITT evaluable cycles	Study 34219 ITT evaluable cycles	Combined ITT evaluable cycles
Breakthrough Bleeding /Spotting (BrB/S)	7.2 – 11.7%	2.6 – 6.4%	5.1 – 7.9%
Absence Withdrawal Bleeding (AWB)	2.3 – 3.8%	0.6 – 2.1%	1.5 – 2.9%
Intended Bleeding Pattern (IBP)	58.5 – 67.4%	61.2 – 69.3%	59.9 – 68.5%
Early Withdrawal Bleeding (EWB)	5.5 – 9.9%	5.4 –7.7%	5.6 – 8.8%
Continued Withdrawal Bleeding (CWB)			19.5 – 25.2%

Reviewer comment:
As noted in the previous comments, the above table shows the range (low and high) of a given bleeding pattern for each cycle (per cycle) over the 13-cycle study. For example [not shown here, but shown in Table 31 of the ISE, pg. 82], in study 68003 the lowest incidence of BrB/S of 7.2% occurred in cycle 13 and the highest incidence of 11.7% occurred in cycle 3; in study 34219 the lowest incidence of 2.6% occurred in cycle 11 and the highest incidence of 6.4% occurred in cycle 7. There is no overall trend in the above bleeding patterns during the 13 cycles. The European data from study 34219 did show a better pattern overall (less BrB/S, less AWB, less EWB, and more IBP) compared to the US study 68003. As noted in previous reviewer comments, several of the worst European results are still better than the best of the US results.
The sponsor did not perform any reference period analyses for the bleeding patterns in the two large studies although this information would be useful.

Discontinuations due to bleeding irregularities

Ten subjects in study 68003 and 9 in study 34219 discontinued early because of bleeding irregularities. This represented only 0.8% (19/2322) of the combined AST group.

Reviewer's comments:
It is difficult to ascertain what is included in this category, but the percentage here is very low. Other menstrual problems including abnormal uterine bleeding (menorrhagia, intermenstrual bleeding, prolonged vaginal bleeding, or amenorrhea), premenstrual tension, and dysmenorrhea were not specifically included on the CRF. The CRF did have individual check boxes for AE/SAE, Non-acceptance of the CCVR concept, Pregnancy, and Other Reason, please specify. It is important to note that 23.4% of subjects in study 68003 and 13.4% of subjects in study 34219 discontinued for "Other Reasons" which includes "unspecified reasons" and "non-acceptance of the CCVR concept."

4.8.7 Ring acceptability

Acceptability of the NuvaRing® was evaluated in the two large studies on the basis of answers to questions completed by each subject at different timepoints during the studies (after Cycles 3, 6, and 13 or last assessment). The frequency of answers as given at Cycles 3 and 6 were, in general, similar to that of answers given at the last assessment. The majority of women did not have any problems with insertion (80%) or removal (85%) of NuvaRing® at any time during the studies. Temporary removal of the ring occurred with low frequency as 86% of subjects in the combined studies reported "never" or "rarely" to have temporarily removed the ring. Eighty-two percent of the women did not feel (never/rarely) NuvaRing® during intercourse; 69% of the partners did not feel (never/rarely) NuvaRing® during intercourse. 91% of the partners never or rarely minded that the subject was using NuvaRing®.

At last assessment, 85% of the Combined group were satisfied (combination of "agree" and "strongly agree") with the use of NuvaRing®, and 90% of subjects in this group would recommend this method to others. The opinion of women who completed the study was obviously different from women who discontinued the study: 96% of Completers versus 60% of Discontinuers were satisfied with NuvaRing®, and 97% of Completers versus 75% of Discontinuers would recommend this method to others.

REVIEWER NOTE: on September 20, 2000 our Division requested additional information and completion of the following two tables from the sponsor. A response was not received by October 5, 2000, so Tables # 22 and 23, which follow, are incomplete. Further analysis and comments about cycle control acceptability and NuvaRing® acceptability will follow as an addendum at a later date.

Table # 22. Cycle Control Acceptability: Questions Relating to Ring Usage per Questions # 11 and # 12 at Last Visit for Completers and Discontinuers – Two Large 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

Note: The data in this table were obtained from Appendix B, Table 9.A.1.

*the third question 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)

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Table #23. Vaginal Ring Acceptability: Questions Relating to Ring Usage and Acceptance per Questions # 5 and # 14 at Last Visit for Completers and Discontinuers – Two Large 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

4.9 Safety analyses

Safety evaluation was based on the incidence of adverse experiences (AEs), discontinuations due to AEs, changes from screening to last assessment in vital signs, physical examination findings (including blood pressure, weight, breast and pelvic exam, cervical Pap smear, and thromboembolism), laboratory results and pregnancy outcome. Adverse experiences and serious adverse experiences (SAEs) were categorized by the study period in which they occurred: pre-treatment, in-treatment, or post-treatment. Serious adverse experiences were defined as an event that was one of the following: fatal or life-threatening, was permanently disabling, required an inpatient hospitalization, was a congenital anomaly, was cancer, or was caused by an overdose (whether or not it was related to the study drug). Relationship of AE to study drug was defined as:

- None- no relationship to study drug
- Unlikely- a relationship is not likely, but not impossible
- Possible- a relationship is not likely, but may exist
- Probable- a relationship has not been clearly demonstrated but is likely
- Definite- a reaction which follows a reasonable temporal sequence from administration of study drug and which is confirmed by improvement on stopping the drug and reappearance of the reaction on repeated exposure

Reviewer's comment:
This is the standard definition for the relationship of study drug to AE; it is entirely dependent on the investigator's opinion, although the sponsor may disagree and state so in the NDA submission.

From the sponsor's Integrated Summary of Safety (ISS) follows the brief summary of Adverse Events (AEs).

Deaths
One death was reported, Subject 1411 in Study 34219, who died in a car accident after the in-treatment period. The death was not related to study drug in the opinion of the investigator and Organon.

Serious Adverse Events
For the Two large clinical, Metabolic and Local Effects studies combined, a total of 48 subjects had SAEs during the in-treatment period (extended by 30 days after the last day of ring use), 47 in the NuvaRing® group and one in the LNG/EE oral contraceptive group. All subjects recovered from their SAEs with or without sequelae with the exception of two subjects whose SAEs were still present at the end of the study. The most frequent system-organ class in which SAEs occurred was gastro-intestinal system disorders. Four subjects had SAEs that were considered by the investigator to be possibly, probably, or definitely drug-related: Subject 4832 (anxiety) in Study 068003, Subjects 1126 (vomiting) and 1347 (cholelithiasis) in Study 34219, and Subject 0088 (thrombophlebitis deep) in Study 34220 [lipid metabolism]. Additionally, SAEs for 5 subjects in the NuvaRing® group and one subject in the LNG/EE OC group (1202 [abdominal pain], 2454 [cholelithiasis], 3403 [psychosis], and 4820 [depression] in Study 068003, 0441 [cholecystitis] in Study 34219, 0023 [depression, LNG/EE OC group] in Study 34220) were considered to be possibly drug-related by Organon even though the investigators thought they were unlikely or not related. Two subjects (4832 in Study 068003 and 0088 in Study 34220) discontinued study drug because of an SAE.

4.9.1Discontinuations Due to AEs

In the two large clinical studies, 15.1% (351/2322) of the treated subjects discontinued due to AEs; most were drug-related AEs. The incidence of discontinuations due to AEs was the same in both studies (15.1%), and there were hardly any differences between the two studies in the incidence of discontinuation due to AEs by system-organ class. The most common system-organ class for which AEs resulting in discontinuation were reported was reproductive disorders, female, (6.1%). Within this system-organ class the most common AEs leading to discontinuation were device related problems (such as WHO defined terms: expulsion, coital problems, foreign body feeling), vaginal discomfort, vaginitis and leukorrhea, most of which were considered to be drug-related by the investigators. Other system-organ classes for which [redacted] (from sponsor): psychiatric disorders (2.6%), central and peripheral nervous system disorders (1.9%), gastro-intestinal system disorders (1.3%), and metabolic and nutritional disorders (1.1%). Over all system-organ classes, the most frequent AEs for which subjects discontinued were female device related problems (2.5%), headache (1.3%), emotional lability (1.2%), and weight increase (1.0%). Other clinically relevant AEs causing discontinuation included five subjects in the Neoplasm system-organ class (breast fibroadenosis, uterine fibroid, ovarian cyst, cervical smear test positive), two subjects due to vascular (extracardiac) disorders, (thrombophlebitis superficial, thrombophlebitis;), six subjects due to cervical dysplasia, three subjects due to bleeding irregularities, and six subjects due to reproductive disorders, male (device related problems such as male discomfort and ring felt by partner).

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Table # 24: Number (%) of Subjects who Discontinued Due to Adverse Events by WHO System-Organ Class and Relationship to Study Drug — Study 68003 (All-Subjects-Treated Group) and Combined Studies

WHO system-organ class (class 1)	USA 068003 (N=1177)								Combined Studies (N=2322)							
	Related		Not related		Unknown		Total		Related		Not related		Unknown		Total	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Skin and appendages disorders	10	0.8	2	0.2	0	0.0	12	1.0	14	0.6	3	0.1	0	0.0	17	0.7
[redacted]	[redacted]															
[redacted]	[redacted]															
[redacted]	[redacted]															
Endocrine disorders	2	0.2	0	0.0	0	0.0	2	0.2	2	0.1	0	0.0	0	0.0	2	0.1
Cardiovascular disorders, general	4	0.3	1	0.1	0	0.0	5	0.4	6	0.3	1	0.0	0	0.0	7	0.3
Heart rate and rhythm disorders	1	0.1	0	0.0	0	0.0	1	0.1	1	0.0	0	0.0	0	0.0	1	0.0
Vascular (extracardiac) disorders	1	0.1	0	0.0	0	0.0	1	0.1	2	0.1	0	0.0	0	0.0	2	0.1
Respiratory system disorders	0	0.0	1	0.1	0	0.0	1	0.1	0	0.0	1	0.0	0	0.0	1	0.0
Urinary system disorders	1	0.1	1	0.1	0	0.0	2	0.2	3	0.1	1	0.0	0	0.0	4	0.2
Reproductive disorders, male	0	0.0	0	0.0	3	0.3	3	0.3	3	0.1	0	0.0	3	0.1	6	0.3
[redacted]	[redacted]															
Neoplasm	1	0.1	3	0.3	0	0.0	4	0.3	2	0.1	3	0.1	0	0.0	5	0.2
Body as a whole - general disorders	6	0.5	2	0.2	0	0.0	8	0.7	15	0.6	3	0.1	0	0.0	18	0.8
Secondary terms	0	0.0	1	0.1	0	0.0	1	0.1	0	0.0	2	0.1	0	0.0	2	0.1
TOTALS	**149**	**12.6**	**26**	**2.5**	**4**	**0.4**	**179**	**15.3**	**312**	**13.8**	**39**	**1.5**	**7**	**0.3**	**367**	**15.6**

Notes: Relationship to study drug according to the judgement of the investigator: related = definitely, probably, possibly; not related = unlikely, not related; unknown = not specified by the investigator

Reviewer comment:
As noted above, a total of 351 of the 2322 subjects (15.6%) discontinued from the two large studies due to adverse events. The most common system-organ class for which AEs caused discontinuations was female reproductive disorders. This category included 15 sub-categories: the total number of discontinuations was N=145, and the four most common sub-categories were device related problems [such as expulsion, coital problems, foreign body feeling] (N=58), vaginal discomfort (N=22), vaginitis (N= 16), and leukorrhea (N=13). These 4 sub-categories accounted for 75% (109/145) of the subjects.

In the Metabolic studies, a higher incidence of discontinuation due to AEs was seen in the NuvaRing® group (12/121 [9.9%]) than in the LNG/EE OC group (4/126 [3.2%]). This difference was mainly due to the higher incidence of discontinuation due to AEs in the psychiatric disorders and reproductive disorders, female system-organ classes. All but one subject in the NuvaRing® group discontinued due to a drug-related AE. Subjects were most commonly discontinued for AEs in the psychiatric disorders and reproductive disorders, female system-organ classes in the NuvaRing® group and for AEs in the skin and appendages disorders system-organ classes in the LNG/EE OC group. In the NuvaRing® group, the most common AEs for which subjects discontinued were libido decreased

(4.1%) in the psychiatric disorders system-organ class and vaginal discomfort (1.7%) in the reproductive disorders, female system-organ class. In the LNG/EE OC group, the AEs in the skin and appendages disorders system-organ classes that led to discontinuation were acne (0.8%) and eczema (0.8%). All of these events were considered related to study drug by the investigator.

In Local Effects Study 68004, 8 of 58 subjects (13.8%) discontinued due to an AE, 6 of which were drug-related. Subjects were most commonly discontinued for AEs in the reproductive disorders, female system-organ class (6.9%), mainly due to breast pain female and device-related problems (all drug-related).

In the two large clinical, Metabolic, and Local Effects studies combined, 371/2501 (14.8%) NuvaRing® treated subjects discontinued due to AEs, the majority of which were considered to be drug-related by the investigator. Most commonly, subjects discontinued due to AEs in the reproductive disorders, female system-organ class. More than half the subjects who discontinued due to an AE in this system-organ class discontinued due to device related problems and vaginal discomfort, most of which were considered to be drug-related. Other system-organ classes for which >1% of NuvaRing® treated subjects reported an AE leading to discontinuation were psychiatric disorders (2.7%), central and peripheral nervous system disorders (1.8%), and gastro-intestinal system disorders (1.3%). Within these system-organ classes, subjects most commonly discontinued due to emotional lability, headache, and nausea, respectively. Most of these events were considered to be drug-related. Over all system-organ classes, the most frequent AEs for which subjects discontinued were device-related problems (2.4%), headache (1.2%), emotional lability (1.1%).

4.9.2 Overall Incidence of Adverse Events

In the two large clinical studies 1522/2322 (65.5%) treated subjects had at least one AE and 870 (37.5%) had a drug-related AE. For most system-organ classes the incidence of AEs was comparable between the two studies. The highest incidence of AEs was in the reproductive disorders, female, system-organ class (33.2%), as was the highest incidence of drug-related AEs (20.9%). The most common AEs in this system-organ class were vaginitis, leukorrhea, and device related problems (14.3%, 6.1%, and 4.8%, respectively). Most of the cases of leukorrhea and device related problems (such as WHO included terms expulsion, coital problems, and foreign body feeling) were considered to be drug related, while most of the vaginitis cases were not related. Over all system-organ classes, the most frequent AEs reported were vaginitis (14.3%), headache (10.1%), upper respiratory tract infection (8.2%), and leukorrhea (6.1%). The most frequent drug-related AEs reported were headache (5.8%), vaginitis (5.6%), leukorrhea (4.8%), and device related problems (4.4%). Weight increase was reported as an AE for 5.0% of subjects. Device related problems (reproductive disorders, male) were reported for 2.0% of subjects, most of which were for male discomfort (ring felt by partner).

In the 3 metabolic studies the incidence of AEs was similar for the NuvaRing® and LNG/EE OC groups (57.9% and 54.0%, respectively). The incidence of drug related AEs was higher in the NuvaRing® group than in the LNG/EE OC group (33.9% and 24.6%, respectively), partly due to the AEs device related problems and vaginal discomfort, which were only reported in the NuvaRing® group. For the NuvaRing® group the system-organ class with the highest incidence of AEs was the Reproductive Disorders, Female, (21.5%). Within this system-organ class, the most common AE reported was vaginitis (8.3%). A lower percentage of subjects in the LNG/EE OC group (12.7%) had an AE in this system-organ class, the most common of which were vaginitis (4.0%) and breast pain female (4.0%). Drug related AEs were reported most often in the reproductive disorders, female and psychiatric disorders system-organ classes for both treatment groups. The incidence of drug related AEs in these system-organ classes was somewhat higher in the NuvaRing® group than in the LNG/EE OC group. This finding was not surprising for reproductive disorders due to the device related problems and vaginal discomfort, which do not occur for LNG/EE OC users. Over all system-organ classes the most common AEs reported were libido decreased, vaginitis, and influenza-like symptoms (each at an incidence of 8.3%) for the NuvaRing® group. The incidence of libido decreased and vaginitis was greater in the NuvaRing® group than in the LNG/EE OC group. The most common AEs in the LNG/EE OC

group were upper respiratory tract infection and influenza-like symptoms (each 7.9%). The most common drug-related AEs reported were libido decreased (8.3%) for the NuvaRing® group and depression (4.8%) for the LNG/EE OC group. No subjects in the NuvaRing® group reported depression and no subjects in the LNG/EE OC group reported libido decreased.

In Local Effects study 068004, 69% of subjects reported an AE and 34.5% reported a drug-related AE. Adverse events were most commonly reported in the reproductive disorders, female system-organ class, with 37.9% of subjects having at least one AE and 22.4% having at least one drug-related AE in this system-organ class. The most common AEs in this system-organ class were vaginitis (19.0%), vaginal discomfort (8.6%), and breast pain (6.9%).

In the two large clinical, Metabolic and Local Effects studies combined, 65.3% (1632/2501), of the NuvaRing® treated subjects had at least one AE, and 931 (37.2%) had a drug-related AE. For the NuvaRing® group, the highest incidence of AEs was in the reproductive disorders, female system-organ class (32.7%) as was the highest incidence of drug-related AEs (20.7%). The most common AEs in this system-organ class were vaginitis (14.1%), leukorrhea (5.8%), and device related problems (4.7%). Most of the cases of leukorrhea and device related problems were considered to be drug-related while most of the vaginitis cases were not related. Over all system-organ classes, the most frequent AEs in the NuvaRing® group were vaginitis (14.1%), headache (9.8%), upper respiratory tract infection (8.0%), and leukorrhea (5.8%). The most frequent drug-related AEs reported were headache (5.7%), vaginitis (5.5%), leukorrhea (4.6%), and device related problems (4.3%). Weight increase was reported for 4.9% of subjects in the NuvaRing® group. Common AEs (≥5% in the NuvaRing® group using pooled data of the two large clinical, Metabolic and Local Effects Studies) are vaginitis, headache, upper respiratory tract infection, leukorrhea, sinusitis, and nausea.

4.9.3 Serious Adverse Events

From the sponsor's ISE: in the two large efficacy trials, during the in-treatment period (extended by 30 days after the last day of ring use), 45 subjects had SAEs, 19 in Study 068003 and 26 in Study 34219. All subjects recovered from their SAEs with or without sequelae with the exception of two subjects in Study 34219 (0560 [patella fracture], 0961 [bulimia]), whose SAEs were still present at the end of the study. The most frequent system-organ class in which SAEs occurred was gastro-intestinal system disorders, with 14 subjects having an SAE in this system-organ class. Three subjects had SAEs that were considered by the investigator to be possibly or definitely drug-related, Subject 4832 (anxiety) in Study 068003, and Subjects 1126 (vomiting) and 1347 (cholelithiasis) in Study 34219. For Subject 4832, the SAE was originally diagnosed as transient ischemic attack, which was recorded by the investigator on the CRF as possibly drug-related. However, further assessment of the subjects' condition led to a final diagnosis of anxiety attack, which according to a letter from the investigator was considered to be unlikely related to study medication. Additionally, SAEs for five subjects (1202 [abdominal pain], 2454 [cholelithiasis], 3403 [psychosis], and 4820 [depression] in Study 068003, and 0441 [cholecystitis] in Study 34219) were considered to be possibly drug-related by Organon even though the investigators thought they were unlikely or not related. Only one subject (4832, Study 068003) discontinued study drug because of an SAE.

Three subjects in Study 34219 had SAEs after the in-treatment period (extended by 30 days after the last day of ring use), 1082 [dyspnea, cardiomyopathy, drug abuse], 1208 [abscess], and 1411 [died in a car accident]. Subject 1208 also had an SAE (abscess) during the in-treatment period.

In the Metabolic and Local Effects studies (All-Subjects-Treated group), three SAEs were reported all in Study 34220 (see Table 30). Two of these were in the NuvaRing® group (Subjects 0087 [strabismus] and 0088 [thrombophlebitis deep]) and one in the LNG/EE OC group (Subject 0023 [depression]). In the opinion of the investigator, the SAEs for Subjects 0087 and 0023 were considered not related to study drug, while the SAE for Subject 0088 was considered probably related. In the opinion of the Organon safety physician, the SAEs for Subjects 0023 and 0088 were possibly related to study drug. All three subjects recovered from their events.

Subject 0088, 26 years old, one pregnancy interruption in the past, had been using the NuvaRing® for only 8 days when she developed symptoms of a deep venous thrombosis in the left leg. The diagnosis was confirmed after hospitalization. Use of the ring was immediately discontinued and anticoagulant treatment was started. She was discharged one week later and treated with anticoagulant therapy for more than three months. She made a full recovery. Prior to the NuvaRing® the woman had been using an intrauterine device, but in the past she had used OCs including a desogestrel-containing one. After discontinuation of the anticoagulants an intensive work-up related to risk factors for venous thrombosis was done. Except for occasional smoking, no abnormalities were found.

Reviewer comment:
Subject 0088's narrative was reviewed. Venography performed in the hospital (Kuopio study site 039) revealed DVT in the left lower leg. The subject was treated with [redacted] and warfarin from 12/18/98 until 3/31/99. Special lab tests performed after discontinuation of anticoagulant therapy were negative: these tests included AT-III, SPA, Protein C and S activity, F-XIII, and hereditary coagulation factor V gene defect (FV R506Q) causing APC resistance. According to the investigator the event was probably related to the NuvaRing.

Two additional subjects discontinued from the two large trials due to thrombophlebitis: Subject 3010 in study 68003 and subject 0871 is study 34219. Due to lack of follow-up it is difficult to draw meaningful conclusions from these two subjects. A brief summary follows.

Subject 3010, 32 years old, experienced superficial thrombosis on 2/23/98, 2 months after initial ring insertion. The ring was removed on 3/3/98 and the complaint resolved on 3/30/98. The subject was subsequently lost to follow-up so no further information is available.

Subject 0871, 37 years old, had her initial ring insertion on 2/25/98. On 4/14/98, a physician other than the investigator made a diagnosis of thrombophlebitis. This led to discontinuation from the study and the subject was lost to follow-up. The treatment is unknown. According to the investigator the event was possibly related to the NuvaRing.

4.9.4 Frequent Adverse Events by Age Category

The sponsor evaluated the incidence of common AEs (i.e., those AEs that occurred with an incidence of ≥5% of the NuvaRing® treated subjects based on the WHO preferred term) in the population of subjects from the Two large clinical, Metabolic, and Local Effects Studies combined to determine if they occurred at differential incidences for the baseline demographic characteristics of age, body mass index, race, and starter/switcher status (i.e., whether or not a subject had switched from another hormonal contraceptive immediately prior to entering one of the studies). The incidence of subjects reporting the common AEs was examined in the following subgroups:

- Age: ≤30 years, >30 years
- Body mass index: <25 kg/m^2, ≥25 kg/m^2
- Race: Caucasian, non-Caucasian
- Status: starter, switcher, not specified

Table # 25 below presents the incidence of common AEs by preferred term, treatment group and subgroup for age at screening for the two large clinical, Metabolic and Local Effects Studies combined (All-Subjects-Treated Group). There were no clinically meaningful differences in the incidence of common adverse events that could be attributed to differences in any of the 4 demographic characteristics listed above.

Table # 25. Incidence of Common Adverse Events by Preferred Term, Treatment Group and Age at Screening — Adequate and Well Controlled, Metabolic and Local Effects Studies Combined (All-Subjects-Treated Group)

Adverse event (WHO preferred term)	NuvaRing				NuvaRing	
	Age <=30 years		Age >30 years		All Ages Combined	
	(N=1625)		(N=876)		(N=2501)	
	n	%	n	%	N	%
Vaginitis	230	14.2	123	14.0	353	14.1
Headache	143	8.8	103	11.8	246	9.8
Upper resp tract infection	141	8.7	60	6.8	201	8.0
Leukorrhoea	102	6.3	44	5.0	146	5.8
Sinusitis	86	5.3	57	6.5	143	5.7
Nausea	92	5.7	39	4.5	131	5.2

N = number of subjects in subgroup

n = number of subjects in subgroup with the common AE

Note: Common AEs are AEs (preferred terms) with incidence of at least 5% in the Nuvaring® -treated subjects

4.9.5 Changes in lab values

Hematology

From the sponsor's ISE, in the two large trials few subjects had clinically significant abnormal values for leukocyte and platelet counts, hemoglobin and hematocrit. For the combined studies the most common clinically significant abnormal hematology values were increased mature neutrophils (1.7%; all cases from Study 34219, since this parameter was not measured in Study 068003), and decreased lymphocytes (1.5%). The most common notable downward shifts were for neutrophils [mature neutrophils (7.3%) in Study 34219 and total neutrophils (5.1%) in Study 068003]. Notable downward shifts were also commonly observed for leukocyte count (4.3%). Notable upward shifts occurred most commonly for leukocyte count (2.1%).

In the 3 metabolic studies few subjects in either group had clinically significant abnormal values for leukocyte and platelet counts, hemoglobin, and hematocrit. Most of the clinically significant abnormal values reported were for changes in leukocyte differential count parameters, but these changes were not considered to be clinically relevant. For the NuvaRing® group, notable downward shifts were most commonly observed for hematocrit (8.3%) and hemoglobin (7.1%). The most common notable upward shift was basophils (8.5%).

In the two large clinical and 3 metabolic studies combined, clinically significant abnormal values occurred in ≤0.5% of the NuvaRing®-treated subjects for leukocyte and platelet counts, hemoglobin and hematocrit.
There were no clinically relevant mean changes from baseline for any of the hematology parameters in the NuvaRing® or LNG/EE OC groups.

Reviewer comment: the reviewer concurs.

Blood Chemistry

In the two large trials, clinically significant abnormal values occurred for only six parameters (high ALAT, ASAT, total bilirubin, gamma-GT, potassium, and sodium), and for these parameters the incidence of these values was very low (≤0.3%). The most frequently occurring notable shifts were upward shifts in ALAT (4.8%) and ASAT (3.0%), and downward shifts in total bilirubin (5.1%). These shifts were reported at higher incidences in Study 068003 than in Study 34219. For all other parameters the incidence of notable shifts in the combined studies was ≤1.4%. In the Metabolic studies no subjects in either the NuvaRing® or LNG/EE OC group had potentially clinically significant blood chemistry values. There were no clinically relevant mean changes from baseline for any of the blood chemistry parameters in the NuvaRing® or LNG/EE OC groups in any of the studies.

Lipid Metabolism

Parameters of lipid metabolism were assessed during and after 6 cycles of NuvaRing® use and compared to those during and after 6 cycles of 150/30 LNG/EE administration (Study 34220). The measured parameters included total cholesterol, HDL-cholesterol, HDL_2-cholesterol HDL_3-cholesterol LDL-cholesterol, total tryglycerides, apolipoprotein A-I, apolipoprotein A-II, apolipoprotein B, and lipoprotein (a).

Compared to LNG/EE OC treatment, NuvaRing® treatment resulted in higher HDL-cholesterol levels and lower LDL-cholesterol levels. The total cholesterol levels were not different between the two groups. Higher apolipoprotein A-I levels were observed in NuvaRing® group. Changes seen in lipid metabolism with NuvaRing® are in line with changes that are normally observed for DSG-containing combined oral contraceptives. Compared to the LNG/EE OC, NuvaRing® had a favorable effect on the lipid metabolism.

Reviewer comment:
Study 34220 was an open-label group-comparative evaluation of 44 NuvaRing and 45 OC users over 6 cycles. Data on baseline values in both groups is ignored. The above statement that NuvaRing treatment resulted in "lower" LDL-cholesterol levels is, in fact, due to an actual increase in the LDL-C levels in the OC group and no change or decrease in the NuvaRing group. Thus the impression left by the sponsor in the ISE and their proposed label is somewhat misleading. This study was not blinded (a double-dummy design could have been easily used), was not designed to show superiority, and had only one OC comparative arm when additional arms may have shown very different results. The statistical and clinical significance of the results can also be questioned. It is this reviewer's opinion that the sponsor's conclusions are of limited value, of uncertain clinical significance, and should not be included in the Final Printed Label.

4.9.5 Changes in vital signs, weight, physical and gynecological exams

In the two large studies blood pressure (sitting) and body weight were measured at screening, in the first week following Cycles 3, 6 and 9, and at the last assessment (either after Cycle 13 or at premature discontinuation). Height was measured at screening only. Data were recorded on the Physical Examination or Vital Signs Forms. In both studies combined, clinically significant increases in systolic blood pressure were observed in 39 (1.9%) subjects, while increases in diastolic blood pressure were observed in 34 (1.6%) subjects. Clinically significant decreases in systolic and diastolic blood pressure occurred in 45 (2.1%) and 16 (0.8%) subjects, respectively. The two studies, 068003 and 34219, were similar with respect to the low incidence of clinically significant blood pressure abnormalities.

In both studies combined, clinically significant decreases in body weight were observed in 195 (9.3%) subjects, while increases in body weight were observed in 295 (14.1%) subjects. The incidence of clinically significant increases in body weight was higher in Study 068003 compared with Study 34219 (18.1% vs. 10.2%), while the incidence of decreases in body weight was comparable between the two studies (10.3% and 8.4%). An increase or decrease ≥ 7% from the baseline weight was considered to be clinically significant.

Reviewer comment:
The reviewer agrees with the sponsor's above conclusions concerning systolic and diastolic blood pressure changes and weight change findings. None of these parameters was a common AE or reason for discontinuing from the study. It is interesting to note that either a clinically significant increase or decrease was observed in a total of 490 or 21% of the combined large study populations. With other combination hormonal contraception products weight gain can be a troublesome side effect; with NuvaRing the percentage of women who had a "clinically significant" increase is acceptable and not a safety concern.

For the two large studies, complete physical examination and breast examinations were performed at screening and at the last assessment (either after Cycle 13 or at premature discontinuation). Data were recorded on the Physical Examination and Breast Examination Forms. A pelvic examination, including a cervical smear, was performed at screening, in the first week following Cycle 6, and at the last assessment (either after Cycle 13 or at premature discontinuation)

Pelvic examination findings were recorded on the Gynecological Examination Form. Cervical smear reports from the central laboratory were added to the subject's case file.

Shift tables were used to categorize the changes from baseline in physical, gynecological, and breast examination categories. The number of subjects who had changes from normal at baseline (screening) to abnormal at last measurement was tabulated. Shift tables were also used to categorize the changes in cervical smear categories from baseline to last measurement.

Reviewer comment:
There were no findings from the sponsor's analysis of changes in the physical, breast, or pelvic examinations that were alarming or of clinical concern. Vaginitis was the most frequent change; this is discussed in the previous sections concerning most frequent AEs and discontinuations due to AEs.

The cervical Pap smear result was Pap I at screening and last assessment for the majority of subjects (84.1%). A total of 33 subjects (1.3%) changed from normal Pap smear result of I, IIa or IIb at screening to a Pap result of IIIa at last assessment. Three subjects (0.2%) had Pap IIIa (low grade SIL) at both screening and at last visit, and 3 subjects (0.2%) had Pap IIIb-IV (high grade SIL) at both screening and at last visit. Two subjects with a Pap IIIb-IV (high grade SIL) at screening are missing from this shift analysis since no-post-baseline assessment was available.

Clinically relevant shifts of particular note are the subjects with a "normal" Pap result at screening (Pap I, IIa or IIb) and a Pap result of IIIb-IV at last assessment. Seven subjects with a normal Pap result at screening and a Pap result of IIIb-IV at last assessment were noted. Four of the subjects participated in Study 068003: Subject 3310 had a normal Pap at screening and Cycle 6, and a Pap IIIb-IV at Cycle 13. Subjects 1625 and 5502 had a normal Pap at screening, a Pap IIb at Cycle 6, and Pap IIIb-IV at Cycle 13. Subject 2722 had Pap IIIb-IV at Cycle 6 and was discontinued due to dysplasia. The subject had cryosurgery for removal of the cervical lesion. Three of the subjects participated in Study 34219: Subject 1304 had Pap I at screening and Pap IIIb/IV at Cycle 13. Subject 0175 had a normal Pap I at screening and discontinued because of a Pap IIIb/IV result at Cycle 6. Subject 0290 had a Pap IIb at screening and Cycle 6 and a Pap IIIb/IV at Cycle 13.

There were two other subjects (0936 and 0766) with clinically relevant Pap findings. Subject 0936 discontinued the study because of a Pap IIIb/IV result at Cycle 6. Her cervical cytology sample at screening was normal (Pap IIb). After discontinuation, a conization was performed. The pathology report showed severe dysplasia. The cervical cytology sample which was collected one month after conization was diagnosed as Pap I. Subject 0766 discontinued the study because of the adverse event "adenocarcinoma; cervical smear test positive". Her first screening Pap was

Reviewer comment:
At first impression it is of concern that 8 of the above subjects changed from normal Pap smears to a class IIIb-IV. This represents, however, only 0.30% of the 2,322 women in the combined clinical trials. This low percentage is acceptable for this population of women, namely, age 18-40 and sexually active.

Table # 26 (sponsor's) from the Local Effects Study 68004 (N= 47) presents the microbiology results from screening to Cycle 6 and last assessment. Forty-three subjects had a microbiology assessment at screening and Cycle 6, and 47 subjects had both a screening and last assessment. The overall incidence of normal observations (Grade I) was approximately 50% at screening, and 70% at Cycle 6 and last assessment. The microbiology results reveal patterns of both worsening and improvement at Cycle 6 and last assessment, relative to screening. A total of 8 (18.6%) subjects showed a worsening at Cycle 6, with three (7.0%) changing from I to II and five (11.6%) from II to III. No subject showed a Grade I to III shift at Cycle 6. A total of 12 (27.9%) subjects showed an improvement, with five (11.6%) changing from II to I and seven (16.3%) from III to II or I. Cycle 6 and last assessment results showed a similar pattern of results.

Table # 26: Summary of Microbiology Findings for the Vaginal Gram Stain Lab Definitions according to the Nugent Score – Screening vs. Cycle 6 and Last Assessment (All Subjects-Treated Group) in Study 68004

	Cycle 6				Last assessment			
	Grade I	Grade II	Grade III	Total	Grade I	Grade II	Grade III	Total
Screening	n %	n %	n %	n %	n %	n %	n %	n %
Grade I	18 (41.9)	3 (7.0)	0 (0.0)	21 (48.8)	21 (44.7)	3 (6.4)	0 (0.0)	24 (51.1)
Grade II	5 (11.6)	3 (7.0)	5 (11.6)	13 (30.2)	5 (10.6)	3 (6.4)	5 (10.6)	13 (27.7)
Grade III	6 (14.0)	1 (2.3)	2 (4.7)	9 (20.9)	7 (14.9)	2 (4.3)	1 (2.1)	10 (21.3)
Total	29 (67.4)	7 (16.3)	7 (16.3)	43 (100.0)	33 (70.2)	8 (17.0)	6 (12.8)	47 (100.0)

Note: Grade I (Normal) - Lactobacillus morphotypes dominate with few other morphotypes identifiable.
Grade II (Intermediate) - Lactobacillus morphotypes reduced with other morphotypes increased.
Grade III (Bacterial vaginosis) - absent Lactobacillus morphotypes with great increase in other morphotypes.

Reviewer comment:
The above table demonstrates the expected vaginal flora changes over time in a group of sexually active women. There is no evidence that the ring is clearly associated with a pattern of improvement or unacceptable worsening in the microflora.

4.9.6 Pregnancy outcomes

The pregnancy outcome for the 22 during-treatment pregnancies in the two large studies had three live births, nine pregnancies continued (no stated results), eight abortions, and two unknown outcomes. No congenital anomalies, stillbirths, or major newborn problems were reported in the three delivered pregnancies.

Reviewer's comment:
This data for pregnancy outcome is too incomplete to draw any meaningful conclusions. I t is somewhat surprising that a specific outcome (8 abortions and 3 deliveries) was known for only 11 of the 22 pregnancies.

5.0 REVIEWER'S OVERVIEW OF EFFICACY

A total of 2,322 enrolled women in the two large clinical trials used the NuvaRing for at least one day. Of these, 35.4% (821) discontinued from the combined studies before completing 13 cycles. The study included women up to age 41; 402 women (17.3% of the 2,322 enrollment) were age 35-41. There were a total of 23,297 cycles of exposure in the combined studies, thus the target of a total of 10,000 cycles was far exceeded.

The sponsor reported twenty-one during-treatment pregnancies. The reviewer added one more pregnancy (Subject 4321) to the during-treatment calculations. Subset analyses were done for the individual studies, and for the per protocol (PP) subjects and by age categories of 18-34 and ≥ 35 years. The results from the European study were consistently better than the US study (6 vs. 16 pregnancies, 30% vs. 41% discontinuation, 91.6% vs. 82% PP use), although the reasons for this finding are unclear.

In the AST (all subjects treated) 1,920 women age 18-34 who used NuvaRing, there were 19 reviewer and 18 sponsor determined pregnancies. The reviewer Pearl Index for this age group is 1.30 per 100 woman-years. In the AST 402 women age 35-41 who used NuvaRing, there were 3 pregnancies. The cumulative exposure was 326 woman-years. The Pearl Index for this age group is 0.92 per 100 woman-years. The reviewer Pearl Index for the combined studies for the AST group (all ages) is 1.23, which is an acceptable rate.

In the PP (per protocol) analysis, the reviewer had 12 pregnancies and the sponsor had 8, thus resulting in different Pearl Indices. 86.8% of the subjects were considered as per protocol. Combining the two studies for the PP group (all ages), the sponsor's PP Pearl Index is 0.617 and the reviewer's PP Pearl Index is 0.915.

A secondary efficacy parameter was cycle control (bleeding patterns). The European findings were consistently better than the US findings. Combining data from the two studies, bleeding patterns showed the following findings per individual cycle:

- Breakthrough bleeding/spotting: 5.1-7.9% of subjects
- Absence of withdrawal bleeding: 1.5-2.9%
- Early withdrawal bleeding: 5.6-8.8%
- Continued withdrawal bleeding: 19.5-25%
- Normal withdrawal bleeding: 60-68.5%

Although the sponsor did 3 small comparative studies that evaluated cycle control, these studies were not approved *a priori* as superiority trials, and the choice of only one comparative OC was arbitrary on the sponsor's behalf. No marketing claims should be made implying superiority, such as "better" or "excellent" cycle control with NuvaRing.

In summary, NuvaRing formulation shows adequate efficacy with an overall Pearl Index [combined studies, AST, all ages] of 1.23 per 100 woman-years and 13-cycle Life Table cumulative pregnancy rate of 1.18%] and acceptable cycle control for approval for pregnancy prevention.

6.0 REVIEWER'S OVERVIEW OF SAFETY

The sponsor's latest safety updates (January 07 and April 27, 2000) were reviewed. There were no reported AE's and no subjects have taken NuvaRing since the trials were completed.

In the overall All Treated Subjects group for NuvaRing, there were 2,501 women who completed over 24,350 cycles of use. Although this represents a large safety database, conclusions concerning safety relate to a population of

women, predominantly Caucasian (93%), who used NuvaRing for 13 months and who were current OC users (52%) or condom/foam users (34%). In general, analyses of serious AEs, frequent AEs, discontinuations due to AEs, changes in lab values, changes in physical and pelvic findings show very similar results for the large US trial and the large European trial.

Of NuvaRing®-treated subjects, approximately 15% discontinued due to an AE, primarily due to ring specific-AEs related to device problems and vaginal discomfort. The most frequent system-organ class AEs (reported by ≥ 1% of subjects) leading to discontinuation included specifically: device related problems (2.5%), vaginal symptoms [discomfort, vaginitis, leukorrhea] (2.2%), headache (1.3%), emotional lability (1.2%), and weight increase (1.0%). The most commonly reported AEs in the AST group (≥5% in the trials, N= 2,501) were vaginitis (14.1%), headache (9.8%), upper respiratory tract infection (8.0%), leukorrhea (5.8%), sinusitis (5.7%), and nausea (5.2%). There did not appear to be an increased incidence of these common AEs with long-term NuvaRing use, and there were no clinically meaningful differences in the incidence of these AEs that could be attributed to differences in demographic characteristics, age, body mass index, race, and starter/switcher status.

The most controversial safety issue is the increased risk of venous thromboembolism (VTE) in desogestrel/ etonogestrel containing combination hormonal contraceptives. The combined studies with 2,501 subjects using NuvaRing reported one subject, # 0088 in the lipid metabolism Study 34220, with a deep venous thromboembolism (DVT):

> **The DVT occurred in a 26 year old non-smoker who used NuvaRing only 8 days during Cycle # 1. The diagnosis was confirmed by venography and she was treated with anticoagulants for 3 ½ months. Special coagulation lab tests were performed after discontinuation of anticoagulants and were negative.**

The non-fatal VTE risk reported in the 1995 retrospective case-control WHO study [21 centers in 17 countries] was 16/100,000 in levonorgestrel containing OC users and 28-29/100,000 for desogestrel and gestodene OC users. There was one non-fatal VTEs in the 1,870 woman-years of exposure to NuvaRing®. This translates to an occurrence of non-fatal VTE of 53.5/100,000 woman-years, which is higher than the WHO predicted occurrence in desogestrel containing OCs. This may not be a valid comparison because the WHO study was based on a retrospective analysis. It should also be noted that compared to OCs previously reviewed by the FDA, this VTE occurrence is not statistically significant.

In studies of this size one is not likely to see a difference in safety parameters such as DVT, stroke, or MI which have continued to be a subject of concern with regard to the progestin desogestrel [etonogestrel is the active metabolite]. In 1995, four studies found a higher risk for VTE for third generation OCs as discussed on pages 12-15 of this review. At the end of 1998, three major studies without sponsoring from the pharmaceutical industry also found a higher risk of VTE for third generation OCs, unlike three sponsored studies.[14] According to epidemiology professor JP Vandenbroucke,[15] in his February 5, 2000 letter to the BMJ editor:

> "to date, of nine studies without sponsoring, one study found no difference and the other eight found relative risks between 0.8 and 4.0 (summary relative risk 2.4); four sponsored studies found relative risks between 0.8 and 1.5 (summary relative risk 1.1)."

[14] Vanderbroucke JP. Medical journals and the shaping of medical knowledge. *Lancet* 1998; 352: p. 2001-06.
[15] Vanderbroucke JP. Competing interests and controversy about third generation OCs. *British Journal of Medicine*; 2000; 320: p. 381.

Reviews of the increased risk of VTE with desogestrel by RMC Herings (*Lancet* '99)[16], AM Walker (*Contraception* '98)[17], the World Health Organization, the Transnational study, and the Boston Collaborative study have all **concluded that there is an increased risk (summary relative risk of 2.0 or greater) of DVT with desogestrel containing OCs. This is especially an issue with young women who were exposed to desogestrel as their initial (first-time-ever) OC use.** Furthermore, in women who are classified as thrombophilic (deficiencies of protein C, protein S, or antithrombin; or mutations in Factor V Leiden or prothrombin 20210 A), the risk of developing DVT during the first year of use, compared with longer use, was increased 11-fold (95% CI 2.1-57.3).[18] Another alarming report came from a national case-control study of fatal pulmonary embolism in New Zealand woman of childbearing age; for current users of combined oral contraceptives, the relative risk was 5.1 for levonorgestrel OCs, and 14.9 for desogestrel or gestodene OCs. (*Lancet*, 6/2000).[19] The authors write "the high mortality in New Zealand may partly reflect the extensive use of third-generation oral contraceptives, which seem to carry a higher risk of VTE than older contraceptives."

In summary, review of the literature continues to show a safety concern of an increased risk of VTE, specifically deep vein thrombosis (DVT), in desogestrel-containing oral contraceptives compared to second generation OCs. The one case of VTE in these two trials is not statistically different from the other third generation desogestrel-containing OCs approved for marketing in the U.S. However, in this reviewer's opinion, there remains considerable concern in the literature over an increased risk of VTE events with desogestrel-containing oral contraceptives. With approval of this product, the label should clearly reflect the safety concern about an increased risk of VTE in desogestrel/etonogestrel-containing combination hormonal contraceptives, including NuvaRing®.

7.0 REVIEWER'S COMMENTS ON PROPOSED LABELING

The proposed labeling is a combination of the June 1999 *draft* guidance for OC class labeling, the August 1996 label for Desogen, the recently revised (2000) label for Mircette®, and new information. Class labeling for OCs is being revised and should generally apply to this OC. The sponsor was recently given notice from our Division that certain changes were needed in the Mircette label concerning the increased risk of VTEs and other vascular problems in OC products containing the progestin desogestrel. **The VTE risk changes were made in the Mircette® and should be incorporated into the NuvaRing label. This could be effectively accomplished by adding the third generation oral contraceptive VTE statement found under 1. a. Thromboembolic Disorders and Other Vascular Problems in the WARNINGS section.**

The biopharmacology reviewer has made recommendations for changes in the label that would reflect several possible Drug-Drug interactions with the CYP 3A4 metabolic pathway for desogestrel. These changes will be incorporated into the final label.

The instructions on how to use the ring are detailed and somewhat complicated. They cover the following topics:

- NuvaRing® insertion and removal
- WHEN to start the FIRST ring
- Day 1 start vs. later start
- What to do during the month

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[16] Herings RMC, Urquhart J, Leufkens HGM. Venous thromboembolism among new users of different oral contraceptives. *Lancet* 1999; 354: p. 127-28.
[17] Walker AM. Newer oral contraceptives and the risk of venous thromboembolism. *Contraception* 1998;57:169-81.
[18] Bloemenkamp KWM, et. al., Correspondence: Venous thromboembolism and OCs. *Lancet* 10/23/99; 354: p. 1469.
[19] Parkin L, Skegg DCG, etonogestrel. al., Oral contraceptives and fatal pulmonary embolism. *Lancet* 6/17/2000; 355: p. 2133-4.

- What to do if the ring is inadvertently expelled or removed
- What to do if the ring is used for > 21 days
- When to use a "back-up" method of contraception
- Disposal of a used NuvaRing®

Backup methods of contraception listed in the physician and patient labels could include "such as condoms, foam, gels, or inserts" or "such as condoms and spermicides." The label is not specific and simply uses the term "additional barrier method of birth control" or "alternative contraceptive method."

The sponsor's proposed label contained no data from the large clinical trials about the design of the two identical studies, number of women enrolled, number of cycles completed, or product efficacy (Pearl Index or Life Table pregnancy rate). Furthermore, the proposed label does not contain any specific safety data about NuvaRing®: most common AEs; AEs causing discontinuation; serious AEs, etc. Final labeling negotiations will take these facts into consideration. It is this reviewer's opinion that such data should be included in the label in addition to the information from the guidance for class labeling for all OC products.

The final NuvaRing label should include the following clinical statement placed after Table II, (adapted from Hatcher et al.):

> **In a large 13-cycle USA trial, 1,177 women completed 11,188 cycles with NuvaRing and 16 pregnancies occurred during treatment; the pregnancy rate was 1.86 per 100 women-years. In a large 13-cycle European trial, 1,145 women completed 12,109 cycles with NuvaRing and 6 pregnancies occurred during treatment; the pregnancy rate was 0.64 per 100 women-years. Combining this data, 2,322 women (ages 18-41) completed 23,298 cycles with NuvaRing and a total of 22 pregnancies occurred during treatment. This represents an overall pregnancy rate of 1.23 per 100 women-years. In 1,920 women ages 18-34, the overall pregnancy rate was 1.30 per 100 women-years. These rates include women who did not use NuvaRing as prescribed (per protocol).**

8.0 REVIEWER'S RECOMMENDATIONS FOR REGULATORY ACTION

Approval of NuvaRing® (etonogestrel/ethinyl estradiol vaginal ring) as a vaginal combination hormonal contraceptive is recommended for prevention of pregnancy. The Final Printed Label (FPL) should reflect the increased risk of venous thromboembolism (VTE) associated with combination hormonal contraceptives containing a so-called third-generation progestin such as desogestrel. Etonogestrel, the active progestin released from the ring, is the active metabolite of desogestrel. It is this reviewer's opinion that in addition to the class labeling for oral contraceptives, the FPL should also include some of the factual efficacy and safety data from the two large clinical trials, such as demographic information, number of subjects, cycles of exposure, pregnancies, common AEs and discontinuations due to AEs. Specific information about bleeding patterns with initial use and extended (up to 13 cycles) use would also be very valuable. This will help to better inform both healthcare providers and consumers about this new delivery system for combination hormonal contraception. The instructions to patients about how and when to use the ring are somewhat complicated, but are well-illustrated and acceptable. The FPL also addresses issues that are unique to this new delivery system, such as expulsion of the ring, prolonged use of the ring, and accidental removal.

Concerns about decreased efficacy due to interactions between the contraceptive steroids (progestin and estrogen) released by NuvaRing® and other drugs have been addressed. Other drug-drug interactions are also noted in the label. Chemistry stability of the ring in its foil sachet at room temperature has been established, but the actual serum levels of the steroids are noted to be highest (burst effect) in the first 24 hours after ring insertion, after which the serum levels remain relatively constant for the next 20 days of normal ring use. It is uncertain if the burst effect may be altered by improper storage of the ring by a consumer after purchase from a pharmacy (where NuvaRing® is stored under refrigeration).

Phase 4 Studies

The vaginal administration of a single dose of 1200 mg of an oil-based miconazole nitrate increased the serum concentrations of etonogestrel and ethinyl estradiol by approximately 17% and 16%, respectively. It is unknown if this change will impact the safety and efficacy of NuvaRing. Furthermore, the sponsor has no data on longer use (multiple doses) of miconazole nitrate (or any other oil-based products). Use of tampons could also impact the efficacy of NuvaRing by absorbing the contraceptive steroids released by the ring. Phase 4 commitments should be required for approval of NuvaRing: the sponsor should commit to completing further studies on the effect of commonly used oil-based vaginal drugs/products [such as miconazoles, Vaseline™, etc.] and different tampons on the PK/PD, efficacy and safety of NuvaRing.

/S/ 10/6/00
10/6/2000

Daniel Davis, M.D.
Medical Officer, HFD-580
DRUDP

/S/ 10/6/00

Gerald Willett, M.D.
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NDA 21-187
Division file
DFS: to be electronically submitted by the medical officer

DEC 18 2000

HFD-580: DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS

Addendum to Original Medical Officer's Review

NDA: 21-187 NuvaRing

Original Dates:
Date submitted: 12/28/99
CDER stamp: 12/29/99
PDUFA date: 10/29/00, extended to 12/29/00
MOR Original: 10/06/00
Addendum: 12/12/00

Key words: contraception, NuvaRing, etonogestrel, ethinyl estradiol, contraceptive vaginal ring, combination hormonal contraception

Sponsor: Organon Inc.
375 Mt. Pleasant Avenue
West Orange, NJ 07052

Drug names:
Generic: etonogestrel and ethinyl estradiol
Trade: NuvaRing® (etonogestrel/ethinyl estradiol vaginal ring)
Chemical: etonogestrel chemical name:
(17α)-13-ethyl-17-hydroxy-11-methylene-18,19-dinorpregn-4-en-20-yn-3-one,
ethinyl estradiol chemical name:
19-nor-17α-pregna-1,3,5(10)-trien-20-yne-3, 17-diol

Drug class: Progestin and estrogen (steroids)
Route of administration: Vaginal
Dosage form: Ring, one compartment, flexible
Strength: Ring contains 11.7 mg etonogestrel and 2.7 mg ethinyl estradiol
to release ~ 0.120 mg/day of etonogestrel + ~0.015 mg/day of ethinyl estradiol for 21 days

Proposed indication: Prevention of pregnancy (hormonal contraception)

Related NDAs:

NDA 20-071 CTR 04 - Desogen® (desogestrel and ethinyl estradiol) Tablets - marketed product - Organon Inc.

[redacted]

NDA 20-301 CTR 04 - Ortho-Cept 21 and 28 (desogestrel and ethinyl estradiol) Tablets - marketed product - R.W. Johnson Pharmaceutical Research Institute, Raritan, NJ

NDA 20-713 CTR 25 - Mircette™ (desogestrel/ethinyl estradiol and ethinyl estradiol) Tablets - marketed product - Organon Inc.

[redacted]

Safety Update:

The sponsor submitted a 120-day safety update on April 27, 2000 stating that there were no further adverse events to report and that the product has not yet been marketed anywhere in the world. An additional safety submission was received on November 1, 2000 covering the time period to 10/1/00 and there were no further AEs, SAEs, or deaths to report. Therefore, there are no additional safety concerns for NuvaRing®. The potential increased incidence of venous thromboembolism (VTEs) associated with third generation OCs, including those containing desogestrel [the active metabolite is etonogestrel, the progestin in NuvaRing®] remains the major safety concern. No safety data exists on long-term use (> 13 cycles) of NuvaRing®.

Local Effects Study 68004 Update: see page 6 and 56 of the original MOR

The sponsor submitted a complete report on April 27, 2000. A total of 58 women were enrolled at two US sites. The cycle 3, 6, and 9 assessments were attended by 48, 44, and 43 subjects, respectively. Forty-one subjects completed all 13 cycles and 17 subjects discontinued prematurely. Review of the April 27th submission showed no significant new findings and no safety concerns. No clinically significant abnormalities in cervical and vaginal tissue were seen with NuvaRing® use and it has little effect on normal vaginal flora as assessed by cytology (Pap smears), colposcopy, and microbiology [cultures were not obtained, but Gram stain interpretation using the widely accepted Nugent score was used].

Changes in Blood Chemistry Parameters and Liver Function: see page 5 and 54 of the original MOR

In the two large trials (N= 1,738), clinically significant abnormal values occurred for only six (high ALAT, ASAT, total bilirubin, gamma-GT, potassium, and sodium) of the 13 blood chemistry parameters that were routinely tested. For these six parameters the incidence of these values was very low (≤0.3%).

- ALAT/SGPT was ≥ 102 U/L [normal range 0-50] in 4 of 1,708 subjects
- ASAT/SGOT was ≥ 102 U/L [normal range 0-50] in 5 of 1,708 subjects
- Bilirubin (total) was ≥ 34 umol/L [normal range 0-20] in 1 of 1,708 subjects
- Gamma-GT was ≥ 147 U/L [normal range 0-70] in 4 of 1,738 subjects
- Potassium was ≥ 5.94 mmol/L [normal range 3.6-4.9] in 2 of 1,721 subjects
- Sodium was ≥ 161.7 mmol/L [normal range 136-146] in 2 of 1,737 subjects

The most frequently occurring "notable shifts" were upward shifts in ALAT (78/1,633 = 4.8%) and ASAT (49/1,633 = 3.0%), and downward shifts in total bilirubin (83/1,634 = 5.1%). Only one of these shifts (an increased ASAT) was reported as an AE in one subject. These shifts were reported at higher incidences in Study 68003 than in Study 34219. For all other parameters the incidence of notable shifts in the combined studies was ≤1.4%. In the Metabolic studies no subjects in either the NuvaRing® or LNG/EE OC group had clinically significant blood chemistry values. There were no clinically relevant mean changes from baseline for any of the 13 blood chemistry parameters in the NuvaRing® or LNG/EE OC groups in any of the studies.

> **Reviewer comment: the sample size here is very large and the number of subjects with clinically significant abnormal values or "notable shifts" was small. Furthermore, the abnormal value was reported as an AE for only one subject. No serious adverse events (SAEs) were reported. Return to baseline occurred in all subjects with the above noted abnormal results and no subjects were discontinued from the studies because of the abnormal lab values. These changes do not appear to be a safety concern for the use of NuvaRing® as seen in the submitted studies.**

Sponsor Response to 9/20/00 Division Information Request Letter:

Several comments were made in the original medical officer review concerning the NDA submission and either an absence of comments or specific information about vaginal bleeding patterns. The Division requested additional clinical information from the sponsor in an IR letter concerning the following:

- Exact N-9 dose used in Study 34225 (a drug interaction PK study)
- Completion of Table # 1 for Bleeding Patterns
- Completion of Table XX for Vaginal Ring Acceptability
- Completion of Table YY for Cycle Control Acceptability

The sponsor's response, dated 10/6/2000, clearly stated the N-9 dose as 100mg, which is a commonly used dose and acceptable to the reviewer.

The sponsor split Table # 1 into 2 separate tables: in Table 1A the bleeding data from the two large clinical trials (68003 and 34219) are compared for the entire exposure period tested (months 2-12); in Table 1B an overall comparison between the data from subjects using either LNG/EE or NuvaRing® was made for the exposure of 6 cycles, "since that was the study duration for the metabolic studies" that had the LNG/EE oral contraceptive comparator arm.

> **Reviewer's comment: the sponsor Table 1A shows an overall acceptable pattern of cycle control and demonstrates again the better overall cycle control in the European Study 34219 compared to the US Study 68003. European women had more intended bleeding patterns (35% vs. 27%), a lower breakthrough bleeding and/or spotting rate (24% vs. 46%), and less women with amenorrhea lasting > 60 days during treatment (0.9% vs. 1.4%). Table 1B was not requested in the Division IR letter and states comparative data [NuvaRing® vs. an OC] from 3 small metabolic studies that were not designed to show superiority and did not have cycle control as a primary endpoint. The information provided in Table 1B should not be used for labeling or for promotional purposes, but does show a cycle control pattern for NuvaRing® that is very similar to the LNG/EE comparator oral contraceptive over a 6-month time period.**

Concerning Table XX for ring acceptability: in Question # 5, subjects were asked for the primary reason for ring removal during Day 1-21, and in Question # 14, subjects were asked for their top 3 reasons for disliking the ring. According to the sponsor, the data on both questions could not be placed in one Table and had to be separated into Table XX.A for Question 5 and Table XX.B for Question 14. This was because in Question #5 subjects were required to choose one answer, whereas in Question # 14 subjects were to rank their top three reasons.

> **Reviewer's comments:**
> **The data presented in the two sponsor tables shows that 64% of the women in the two large studies did not remove the ring at any time. For the 36% who did remove the ring, the 4 most common reasons were: 14% for interference with intercourse, 7% for "other", 5% because the ring fell out, and 2% for discomfort. Only 0.8% of women removed the ring because of bleeding/spotting.**
>
> **Approximately 92% of subjects liked the NuvaRing®, and 90% of all subjects would recommend the method to others. Of those women who did not find it acceptable, three top reasons for disliking the ring were equally named: ring falling out, interference with intercourse, and ring discomfort. The bleeding/spotting pattern was listed by <1% of all subjects as a top three reason for disliking NuvaRing®.**
>
> **The reviewer's overall impression is that NuvaRing® acceptability was very good and that cycle control problems were not a major reason for ring removal, ring dislike, or discontinuation from the studies.**

Table YY for cycle control acceptability had three components: changes in menstrual duration, menstrual pain, and menstrual flow compared to each subject's pre-study self-evaluation. The questions were asked at the last visit for completers and discontinuers in both large clinical trials. The sponsor could not answer the last part (self-assessment of menstrual blood loss) because data on menstrual blood flow was collected only at baseline, and not throughout the study.

Reviewer's comments:
Concerning change in menstrual duration due to NuvaRing® compared to the subject's pre-study menstrual pattern, there was not a large difference between subjects who completed the study versus those who discontinued. In comparison to prior menstrual patterns, duration of menses with NuvaRing® use was much shorter in 10% of subjects, shorter in 36%, the same in 47%, longer in 7%, and much longer in 1% [all percentages are rounded to the nearest %]. Thus, 93% of the women in the two large clinical trials had menstrual periods that were generally the same or shorter than they experienced just prior to enrollment in the study. This finding does not take into account how many of these women were not on a combination hormonal method prior to starting NuvaRing® [in this case it might be anticipated that menstrual periods would be shorter].

Concerning change in menstrual pain due to NuvaRing® use compared to pre-study, there again was not a large difference between subjects who completed the study versus those who discontinued. Menstrual pain was much less in 11% of women, less in 23%, the same in 57%, more in 8%, and much more in 1%. Thus, 91% of the women in the two large clinical trials had the same or less menstrual pain by the end of the study compared to their pre-study self-assessed pain. This finding also does not take into account the confounding factor of prior hormonal contraceptive use versus no use on comparative menstrual pain change when using NuvaRing®.

Because follow up data was not collected concerning menstrual flow, no conclusions can be made about the effect of NuvaRing® on menstrual blood flow (loss). It is noted that anemia was not found to be a clinical problem in the two large trials.

The reviewer's overall impression from the original NDA review and review of the sponsor's 10/06 submission is that the cycle control due to NuvaRing® is acceptable and not clinically significantly different from that expected with most oral contraceptives. The bleeding pattern over one year of use of NuvaRing® was examined in the non-comparative US trial with 1,177 women for a total of 11,188 cycles. Bleeding patterns were analyzed for each of the 13 cycles. The bleeding related discontinuation rate was very low.

Reviewer comment: the following patterns in the large US trial* were observed from cycle 2 through 12: *similar European and combined data is found on page 44 of the original MOR

Average onset of withdrawal bleeding: Day 24 ± 1 day
Median duration of withdrawal bleeding: 5 days
Per cycle range: data not available
Heavy bleeding: data not available
Prolonged bleeding (at least 1 episode ≥ 10 days): 11.3%
Early withdrawal bleeding (≥ 1 episode): 28%
Per cycle range: [redacted]
Cumulative chance of ≥ 1 episode of amenorrhea: not given
Per cycle amenorrhea range: [redacted] **average 3.2%)**
Amenorrhea > 60 days: 1.4%
Breakthrough bleeding/spotting (≥ 1 episode): 46%
Per cycle range: [redacted]

Labeling Update:

In November 2000, the Division sent to the sponsor major revisions to the original PI and PPI label. The original label proposed in the NDA contained the basic information and format found in the guidance document for class labeling for all oral contraceptives. The sponsor proposes a label identical to their desogestrel-containing oral contraceptive Mircette®, substituting the name NuvaRing® for Mircette. Like Mircette, NuvaRing® is a combination hormonal [estrogen and progestin] contraceptive, but unlike Mircette, it is a vaginal delivery system with a constant release of hormones for 21 days, rather than an oral dose of hormones administered every 24 hours. Therefore, throughout the final label, appropriate changes are made when using terms such as "combination oral contraceptives," "hormonal contraceptives," etc. Another issue is the sponsor's use of the statement, "In the absence of data, it is unknown whether NuvaRing® is distinct from combination oral contraceptives with regard to ....". In many places, because the sponsor has data from over 2,600 women using NuvaRing® for up to 13 cycles, the statement is changed to simply read, "It is unknown whether NuvaRing® is distinct from combination oral contraceptives with regard to ....".

Etonogestrel, the progestin in NuvaRing®, is the active metabolite of desogestrel, the progestin in Mircette®. Therefore, the Division requires that the label include the text that is required for all desogestrel-containing OCs regarding an approximate 2-fold increased risk of VTE with third generation OCs compared with certain second generation OCs.

The Division does not recommend including in the final label specific efficacy data from the two, large, non-comparative 13-cycle clinical trials. The main reason is that contraceptive clinical trials included in various NDA submissions differ in several respects:

- Length of product use in the trial(s): 6-12 months
- Comparative vs. non-comparative trial design
  - Choice of the active comparator if one is used
- Age range of trial subjects: inclusion criteria cut off at 35, 38, 40, 45, 50 years of age
- Number of cumulative woman-months (or woman-years) of product use
- Accuracy of determining date of conception and calculating product failure rates
- Per protocol [perfect] use vs. Typical [actual] use
  - Different definitions for per protocol use patients populations

NuvaRing® has an acceptable Pearl Index (pregnancies per 100 women-years of use) and cycle control pattern, but such specific data in the FPL should not be included. This would avoid the issue of misleading or unsubstantiated comparative marketing claims. Likewise, the sponsor had included in the original NDA label a Clinical Studies section concerning bleeding patterns. Bleeding patterns were evaluated in three small 6-cycle comparative studies involving a total of 135 women using NuvaRing® and 129 women using a low-dose [LGN/EE] combination OC. The text and graph cannot be included in the final label for the following reasons:

- the trial was not designed to show such a difference
- primary and secondary endpoints were not chosen before the study began
- the sponsor selected only the data that was most favorable to their product

Similarly, in the Warnings section on carbohydrate and lipid metabolic effects, the text concerning ten different lipoprotein metabolic parameters cannot be included. The sponsor evaluated changes from baseline to Cycle 6 in 40 women compared to the changes seen in a similar group of women on a combination OC for 6 cycles. This text cannot be included in the final label because the trial had a small sample size, was not designed to show superiority, and was not blinded (a double-dummy design could have been easily used). Furthermore, the sponsor has added all the subjects together to show mean average changes by treatment group [NuvaRing® vs. OC comparator], rather than individual subject's or percentile changes, or a range of changes. Laboratory parameters were compared at baseline and 6 months, and did not include any interim values. The statistical and clinical significance of the results can also be questioned; the information as presented is of uncertain clinical significance. **[For further discussion, see page 54 of the original 10/06 MOR.]**

Division recommended changes in the original proposed label also reflect clinical pharmacology (PK and PD) information relative to liver function and drug/drug interactions with regard to 1) the contraceptive effectiveness of NuvaRing® and, 2) the serum levels of the active progestin and estrogen. Limited new information is to be added concerning anti-HIV protease inhibitors, St. John's wort (hypericum perforatum), and atorvastatin.

Chemistry stability of the ring in its foil sachet at room temperature has been established. The actual serum levels of the steroids, however, are noted to be highest (burst effect) in the first 24 hours after ring insertion, after which the serum levels remain relatively constant for the next 20 days of normal ring use. It is uncertain if the burst effect may be altered by improper storage of the ring by a consumer after purchase from a pharmacy (where NuvaRing® is stored under refrigeration). Appropriate language about storage and temperature ranges is addressed in the label. The PPI label states: "Avoid exposure to direct sunlight or storage for prolonged periods at temperatures above 86^0."

The Dosage and Administration section of the PI and the entire PPI have been extensively edited. This was done because NuvaRing® is a new delivery system and a new molecular entity, so both providers (prescribers) and users will initially be unfamiliar with the product and its correct use. The PPI has been extensively revised by DDMAC to make the text and instructions more easily read and understood.

Phase IV Commitments:

A teleconference with the sponsor was held on 12/11/00 to discuss chemistry and clinical Phase 4 commitments. The sponsor made commitments addressing three Division clinical concerns:

- miconazole nitrate use [single high dose] and the 16-17% increase in serum etonogestrel and ethinyl estradiol levels
- tampon use and its potential effect on efficacy due to changes in serum etonogestrel and ethinyl estradiol levels [due to tampon absorption of the hormones]
- very limited follow-up data on pregnancies conceived while using/continuing NuvaRing®

Reviewer's comments:
The sponsor agreed to submit within 6 months a protocol for a clinical study addressing the issue of increased serum levels of etonogestrel and ethinyl estradiol with the use of NuvaRing® and prolonged use [perhaps 4-7 days] of oil-based vaginal products such as miconazole nitrate. Serum hormone levels and ovulation inhibition will be the primary focal points. Safety information will also be collected.

The sponsor agreed to submit within 6 months a protocol for a clinical study addressing the issue of potential changes [probable decrease] in serum hormone levels with the use of NuvaRing® and prolonged use [perhaps 4-7 days] of vaginal tampons. Serum hormone levels and ovulation inhibition will be the primary focal points. Actual tampon absorption of etonogestrel and ethinyl estradiol may be measured if feasible. Safety information will also be collected.

The pregnancy outcome for the 22 during-treatment pregnancies in the two large studies had three live births, nine pregnancies continued (no stated results), eight abortions, and two unknown outcomes. No congenital anomalies, stillbirths, or major newborn problems were reported in the three delivered pregnancies. The sponsor agreed to a Phase 4 commitment to collect as much data as possible on pregnancy outcomes from conceptions occurring during NuvaRing® use. Etonogestrel is a NME and the delivery system continually releases etonogestrel and ethinyl estradiol as compared to the once daily oral dose with traditional combination hormonal contraception. Information on spontaneous miscarriages, preterm births, full term births, stillbirths, and congenital anomalies will be of particular interest.

Final Reviewer Comments:

Approval of NuvaRing® (etonogestrel/ethinyl estradiol vaginal ring) as a vaginal combination hormonal contraceptive is recommended for prevention of pregnancy. This product will be the first FDA approved product containing the progestin etonogestrel and the first vaginal delivery system for combination hormonal contraception. The Final Printed Label (FPL) should reflect the increased risk of venous thromboembolism (VTE) associated with combination hormonal contraceptives containing a "third-generation progestin" such as desogestrel. Etonogestrel, the active progestin released directly from NuvaRing®, is the active metabolite in oral contraceptives containing desogestrel.

The reviewer's overall impression from the original NDA review and review of the sponsor's 10/06 submission is that the cycle control due to NuvaRing® is acceptable and not clinically significantly different from that expected with most oral contraceptives. Detailed information about bleeding patterns (cycle control) with initial use and extended (up to 13 cycles) use will not be included in the label. This would avoid the issue of misleading or unsubstantiated comparative marketing claims. The instructions to patients about how and when to use the ring are somewhat complicated, but are well illustrated and acceptable. The FPL also addresses issues that are unique to this new delivery system, such as expulsion of the ring, prolonged use of the ring, and accidental removal. Statements are made, when appropriate, that "it is unknown whether NuvaRing® is distinct from combination oral contraceptives with regard to" several areas discussed in the standard OC labeling.

/S/ 12/18/00

Daniel Davis, M.D.
Medical Officer, HFD-580
DRUDP

Date

/S/ 12/18/00

Dena Hixon, M.D.
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Jennifer Mercier, B.S.
NDA 21-187
Division file
DFS: to be electronically submitted by the medical officer

FINAL MOR

HFD-580: DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS

Medical Officer's Review of Complete Response to 4/27/01 Approvable Letter

NDA 21-187: **NuvaRing**

Sponsor's Complete Response to 4/27/01 letter
Date submitted: 8/02/01
CDER stamp: 8/03/01
MOR completed: 9/17/01

Original NDA Dates:
Date submitted: 12/28/99
CDER stamp: 12/29/99
PDUFA date: **10/29/00, extended to 12/29/00**

Original MOR: completed 10/06/00
MOR Addendum #1: completed 12/12/00
MOR Review of Sponsor Response to 12/22/00 Approvable Letter: completed 4/27/01

Key words: contraception, NuvaRing, etonogestrel, ethinyl estradiol, contraceptive vaginal ring, combination hormonal contraception

Sponsor: Organon Inc.
375 Mt. Pleasant Avenue
West Orange, NJ 07052

Drug names:
Generic: etonogestrel and ethinyl estradiol
Trade: NuvaRing® (etonogestrel/ethinyl estradiol ring)
Chemical: etonogestrel chemical name:
13-ethyl-17-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one,
ethinyl estradiol chemical name:
19-nor-17α-pregna-1,3,5(10)-trien-20-yne-3, 17-diol

Drug class: Progestin and estrogen (steroids)
Route of administration: Vaginal
Dosage form: Ring, one compartment, flexible
Strength: Ring contains 11.7 mg etonogestrel and 2.7 mg ethinyl estradiol:
Release ~ 0.120 mg/day of etonogestrel + ~0.015 mg/day of ethinyl estradiol for 21 days

Proposed indication: Prevention of pregnancy (hormonal contraception)

Related NDAs: See previous medical officer reviews

Background Regulatory History:

The original NDA received an Approvable Action on 12/22/00 because the sponsor was unable to reach an agreement with the Division on acceptable labeling. The sponsor's Complete Response to the original 12/22/00 Approvable Letter was a major multidiscipline amendment [CDER stamp date 3/1/01]. The submission included proposed labeling and a safety update. On 4/26/01 the sponsor informed our division that they could not accept the FDA labeling sent to the sponsor on 4/17/01. The primary areas of disagreement were the Carcinogenesis section, the Bleeding Irregularity section under Warnings, and the Non-Contraceptive Health Benefits section. The current submission is the sponsor's complete response to the Division's NDA Approvable Letter for NuvaRing® dated 4/27/01.

Safety Update:

Background: The sponsor submitted their first 120-day safety update on April 27, 2000 stating that there were no further adverse events to report and that the product has not yet been marketed anywhere in the world. An additional safety submission was received on November 1, 2000, covering the time period to 10/1/00 and there were no further AEs, SAEs, or deaths to report. Another safety update covered the period of 10/1/00 to 1/1/01 and there were no further AEs, SAEs, or deaths to report.

The current safety update covers the period of 1/1/01 to 6/15/01. The only ongoing trial is a European trial (Protocol 34224) to evaluate the effects of NuvaRing® on endometrial histology and on bone mineral density. The current submission includes all safety data on 131 subjects [102 NuvaRing® and 29 IUD] from trial start in October 1999 until the cutoff date of June 15, 2001 for this document. Since Trial 34224 is ongoing [a 26-cycle trial], data validation and analysis is not yet completed. To date, there are no deaths or SAEs in the 100 subjects using NuvaRing®. A total of nine NuvaRing® subjects had 13 AEs that resulted in early discontinuation. No hyperplasia or neoplasms were reported for any screening [N=82] or post baseline endometrial biopsies [N=12]. The discontinuation rates and reasons, and the incidence of AEs are similar to those seen in the two large clinical trials with NuvaRing®.

There is no postmarketing safety information because NuvaRing® is not yet marketed in any country. On February 14, 2001, N. V. Organon (Oss, The Netherlands) received Marketing Authorization for NuvaRing® from the Dutch Medicines Evaluation Board and is proceeding with the Mutual Recognition Procedure within the European Union. According to the sponsor no new safety information has been requested by or reported to foreign health authorities. For this safety update, a new literature search was done in the MEDLINE and EMBASE databases covering the period of January 2001 to June 15, 2001. The search produced three articles; there were no significant new clinical findings based on these publications.

> **Reviewer comment: There are no additional safety concerns for NuvaRing®. The potential increased incidence of venous thromboembolism (VTEs) associated with desogestrel-containing hormonal contraceptives remains the major safety concern. Etonogestrel, the progestin in NuvaRing®, is the active metabolite of desogestrel. No safety data exists on long-term use (> 13 cycles) of NuvaRing®, and it is unknown whether the increased incidence of VTE will be found with NuvaRing® use.**

Labeling Update:

General:

In November 2000, the Division sent to the sponsor major revisions to the original PI and PPI label. The original label proposed in the NDA contained the basic information and format found in the guidance document for class labeling for all oral contraceptives. The sponsor proposes a label very similar to that for their desogestrel-containing oral contraceptive Mircette®, substituting the name NuvaRing® for Mircette. Like Mircette, NuvaRing® is a combination hormonal [estrogen and progestin] contraceptive, but unlike Mircette, it is a vaginal delivery system with a constant release of hormones for 21 days, rather than an oral dose of hormones administered every 24 hours. Therefore, throughout the final label, the Division recommends appropriate changes when using terms such as "combination oral contraceptives," "hormonal contraceptives," etc. Another issue is the sponsor's use of the statement, "In the absence of data, it is unknown whether NuvaRing® is distinct from combination oral contraceptives with regard to ....". In many places, because the sponsor has data from over 2,500 women using NuvaRing® for up to 13 cycles, the sponsor has accepted the Division's recommendation that the statement should simply read, "It is unknown whether NuvaRing® is distinct from combination oral contraceptives with regard to ....".

> **Reviewer comment: In general, throughout the label appropriate changes have been made reflecting the above concern.**

Bleeding patterns:

The reviewer's overall impression from the original NDA review and review of the sponsor's 10/06/00 submission is that the cycle control due to NuvaRing® is acceptable and not clinically different from that expected with most oral contraceptives. The bleeding pattern over one year of use of NuvaRing® was examined in the non-comparative US trial with 1,177 women for a total of 11,188 cycles. Bleeding patterns were originally analyzed for each of the 13 cycles and analyzed further, per our Division's 9/20/00 request, on a more cumulative basis for cycles 2-12.

The sponsor's argues that although "there are some minor differences between the two studies for NuvaRing®," it is appropriate to include in the label data from both studies since this approach is consistent with the rest of the package insert. The sponsor also wants to include data from cycles 1-13 in the label.

Reviewer comments: The cycle control differences between the two studies were not minor [see table below]. The bleeding patterns seen in the equally large European trial were significantly better than those seen in the US trial. The sponsor proposes to use the combined data to describe bleeding patterns in the label. This would make the overall bleeding pattern appear much better than was seen in the US trial alone. The label should contain the US data alone or state the individual study data because of the differences in the two large trials. Comments on the European and combined data are found on page 44 of the original MOR.

Bleeding Pattern Range per cycle over 13 cycles	USA/Canada Study N = 1,117	European Study N = 1,145	Combined ITT evaluable cycles
% Subjects per Cycle with Breakthrough Bleeding /Spotting *	7.2 – 11.7%	2.6 – 6.4%	5.1 – 7.9%
% Subjects per Cycle with Absence of Withdrawal Bleeding *	2.3 – 3.8%	0.6 – 2.1%	1.5 – 2.9%
Intended Bleeding Pattern (IBP)	58.5 – 67.4%	61.2 – 69.3%	59.9 – 68.5%
Early Withdrawal Bleeding (EWB)	5.5 – 9.9%	5.4 –7.7%	5.6 – 8.8%
Continued Withdrawal Bleeding (CWB)			19.5 – 25.2%

***There is NO overlap in the results from these two large clinical studies.**

The Division felt that data from Cycle 1 should be excluded since all subjects would be either new starts or switching from another hormonal contraceptive and, in all cases, adjusting to a new hormonal regimen. The Division felt that Cycle 13 should be excluded because data on continued withdrawal bleeding would be inaccurate. In using the data for cycle control it is not crucial that Cycles 1 and 13 be excluded unless excluding the data is misleading or inaccurate.

The following patterns in the large US study 68003 were observed from cycle 2 through 12. Data of this type might be useful in the label, as NuvaRing® is the first vaginal delivery system for hormonal contraception:

- **Average onset of withdrawal bleeding: Day 24 ± 1 day**
  Per cycle range not given
- **Median duration of withdrawal bleeding: 5 days**
  Per cycle range: data not available
- **Breakthrough bleeding/spotting (≥ 1 episode): 46%**
  Per cycle range: [redacted]
- **Cumulative chance of ≥ 1 episode of amenorrhea: not given**
  Per cycle amenorrhea range: [redacted]
  Amenorrhea > 60 days: 1.4%
- **Heavy bleeding [menorrhagia]: data not available**
- **Prolonged bleeding (at least 1 episode ≥ 10 days): 11.3%**
- **Early withdrawal bleeding (≥ 1 episode): 28%**

Per cycle range: [redacted]

Use of a diaphragm as a backup contraceptive method:

The Division agrees with the sponsor that the agency's proposed statement is somewhat repetitive and that combined use of NuvaRing® and a diaphragm would be infrequent. The statement that "NuvaRing® may interfere with the correct placement and position of a diaphragm," however, still remains true.

> **Reviewer comments: The statement that NuvaRing® may interfere with the position and placement of a diaphragm should remain at least once in both the PI and PPI since a diaphragm might be used as a backup contraceptive method despite the fact that it is not rcommended.**

Weight gain:

The sponsor wants to remove weight gain from the list of most common adverse events reported by women using NuvaRing® in clinical trials. They argue that the reported incidence does not meet the criteria of ≥ 5%.

> **Reviewer comments: According to the sponsor's ISS (page 117) weight increase was reported as an AE for 116 subjects (5.0%) in the two adequate and well controlled studies [N= 2,096]. When the sponsor includes the metabolic and local effects trials [N= 2,254], weight increase was reported as an AE for 122 subjects (4.9%). These figures refer only to the percentage of women who reported weight gain as an AE. The more revealing facts are the following:**
>
> - **18.1% of all subjects in the large US study had a clinically significant weight gain, defined as a ≥ 7% increase from baseline to end of treatment**
> - **10.2% of all subjects in the large European trial had a significant weight gain**
>
> **From the above findings, weight gain must remain in the label as a common AE. If deleted from this list, then the sponsor should include in the label the data from the bullets above. Obviously the majority of women with a clinically significant weight gain did not report it as an AE.**

Non-contraceptive Health Benefits:

A statement in the label about non-contraceptive health benefits should not be included because to date there does not exist an epidemiological database to support such a claim. NuvaRing® is a new product containing a new molecular entity (NME) and a new delivery system (vaginal ring). The statement found in the class labeling for oral contraceptives is based on several large epidemiological studies of oral contraceptives. The sponsor argues that they are "being required to include all contraindications, warnings and precautions, which are based on the data obtained from these same OC studies," so they should be allowed to include the health benefits as well.

> **Reviewer comment: The primary reason for including all the contraindications, warnings and precautions in the label is to cover all the safety concerns associated with combination hormonal contraception. It is not appropriate to include unsubstantiated benefits in the label.**

VTE risk:

Etonogestrel, the progestin in NuvaRing®, is the active metabolite of desogestrel, the progestin contained in Mircette®. Therefore, the Division requires that the NuvaRing® label include the text that is required for all desogestrel-containing OCs regarding an approximate 2-fold increased risk of VTE with desogestrel-containing OCs compared with certain second generation OCs.

Phase IV Commitments:

A teleconference with the sponsor was held on 12/11/00 to discuss chemistry issues and clinical Phase 4 commitments. The sponsor made commitments addressing the following three Division clinical concerns:

- Concomitant use of miconazole nitrate [single high dose] and NuvaRing® results in a 16-17% increase in serum etonogestrel and ethinyl estradiol levels
- Any potential effect of tampon use on efficacy of NuvaRing® or changes in serum etonogestrel and ethinyl estradiol levels [due to tampon absorption of the hormones] are unknown
- Follow-up data on pregnancies conceived while using/continuing NuvaRing® are very limited

The Division has received submissions addressing these concerns and has proposed a study addressing the first two issues.

Reviewer's comments:
The sponsor has submitted a protocol plus a revised protocol for a clinical study addressing the issue of increased serum levels of etonogestrel and ethinyl estradiol with the use of NuvaRing® and use of both a cream-based and suppository vaginal products containing miconazole nitrate. Serum hormone levels will be the primary focal points. Safety information will also be collected. The protocol has been reviewed and is acceptable.

The sponsor's proposed protocol also addresses the issue of potential changes [possible decrease] in serum hormone levels with the use of NuvaRing® and use of vaginal tampons. Serum hormone levels and ovulation inhibition will be the primary focal points. Safety information will also be collected.

Pregnancy outcomes for the 22 pregnancies occurring during treatment in the two large studies included three live births, nine pregnancies continued (no stated results), eight abortions, and two unknown outcomes. No congenital anomalies, stillbirths, or major newborn problems were reported. The sponsor agreed to a Phase 4 commitment to collect as much data as possible on pregnancy outcomes from conceptions occurring during NuvaRing® use. Information on spontaneous miscarriages, preterm births, full term births, stillbirths, and congenital anomalies will be of particular interest.

Final Reviewer Comments:

NuvaRing® (etonogestrel/ethinyl estradiol vaginal ring) as a vaginal combination hormonal contraceptive for prevention of pregnancy is shown to be safe and effective. On 4/26/01 the sponsor informed our division that they could not accept the FDA labeling sent to the sponsor on 4/17/01. The primary areas of disagreement were the Carcinogenesis section, the Bleeding Irregularity section under Warnings, and the Non-Contraceptive Health Benefits section. It can be approved if the sponsor accepts the label changes recommended by the division in response to this latest submission.

This is the first FDA-reviewed hormonal contraceptive product containing the progestin etonogestrel and the first vaginal delivery system for combination hormonal contraception. The PI and PPI should reflect the increased risk of venous thromboembolism (VTE) associated with combination hormonal contraceptives containing desogestrel. Etonogestrel, the active progestin released directly from NuvaRing®, is the active metabolite of oral desogestrel.

Etonogestrel is a NME and the delivery system continually releases etonogestrel and ethinyl estradiol [with relative steady state levels] as compared to the once daily oral dose with

traditional combination hormonal contraception resulting in daily serum peak and trough hormone levels. For this reason, the current safety profile on NuvaRing® is based solely on the data submitted with the NDA and with use of the product for up to 13 months. Although no future problems with AEs or SAEs are anticipated, postmarketing surveillance will be important.

The reviewer's overall impression from the original NDA review and review of the sponsor's 10/06/00 submission is that the cycle control due to NuvaRing® is acceptable and not clinically or significantly different from that expected with most oral contraceptives. There are definite differences in the cycle control (bleeding) data from the two large clinical studies, and any statements in the label should not be from pooled data. Data from the USA/Canada Study 68003 should be used, or separate statements from the two studies may be included. The instructions to patients about how and when to use the ring are somewhat complicated, but are well illustrated and acceptable. The label also addresses issues that are unique to this new delivery system, such as expulsion of the ring, prolonged use of the ring, and accidental removal. Statements are made, when appropriate, that "it is unknown whether NuvaRing® is distinct from combination oral contraceptives with regard to" several items discussed in the standard OC labeling.

Finally, the label should include weight gain as one of the most common adverse events. The label should not include any specific statements concerning non-contraceptive health benefits associated with use of NuvaRing® for the reasons stated earlier in this review.

/S/ 9/17/01

Daniel Davis, M.D.
Medical Officer, HFD-580
DRUDP

9/17/01
Date

Dena Hixon, M.D.
Team Leader, DRUDP

cc: Daniel Davis, M.D., Jennifer Mercier, B.S., Dena Hixon, M.D., Johnny Lau, Ph.D., David Lin, Ph.D., Susan Allen, M.D., NDA 21-187, Division file, DFS: to be electronically submitted by the MO

HFD-580: DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS

Medical Officer's Review of Complete Response to Approvable Letter

NDA 21-187: NuvaRing

Sponsor's Complete Response
Date submitted: 2/28/01
CDER stamp: 3/01/01
MOR completed: 4/27/01

Original NDA Dates:
Date submitted: 12/28/99
CDER stamp: 12/29/99
PDUFA date: 10/29/00, extended to 12/29/00
Original MOR: 10/06/00

MOR Addendum #1 completed 12/12/00

Key words: contraception, NuvaRing, etonogestrel, ethinyl estradiol, contraceptive vaginal ring, combination hormonal contraception

Sponsor: Organon Inc.
375 Mt. Pleasant Avenue
West Orange, NJ 07052

Drug names:
Generic: etonogestrel and ethinyl estradiol
Trade: NuvaRing® (etonogestrel/ethinyl estradiol ring)
Chemical: etonogestrel chemical name:
13-ethyl-17-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one,
ethinyl estradiol chemical name:
19-nor-17α-pregna-1,3,5(10)-trien-20-yne-3, 17-diol

Drug class: Progestin and estrogen (steroids)
Route of administration: Vaginal
Dosage form: Ring, one compartment, flexible
Strength: Ring contains 11.7 mg etonogestrel and 2.7 mg ethinyl estradiol:
Release ~ 0.120 mg/day of etonogestrel + ~0.015 mg/day of ethinyl estradiol for 21 days

Proposed indication: Prevention of pregnancy (hormonal contraception)

Related NDAs:

NDA 20-071 CTR 04 - Desogen® (desogestrel and ethinyl estradiol) Tablets - marketed product - Organon Inc.

NDA 20-301 CTR 04 - Ortho-Cept 21 and 28 (desogestrel and ethinyl estradiol) Tablets - marketed product - R.W. Johnson Pharmaceutical Research Institute, Raritan, NJ

NDA 20-713 CTR 25 - Mircette ™ (desogestrel/ethinyl estradiol and ethinyl estradiol) Tablets - marketed product - Organon Inc.

[redacted]

Background Regulatory History:

The original NDA received an Approvable Action on 12/22/00 because the sponsor was unable to reach an agreement with the Division on acceptable labeling. The current submission, a major multidiscipline amendment [CDER stamp date 3/1/01], represents the sponsor's Complete Response to the Approvable Letter. The submission includes proposed labeling and a safety update.

Safety Update:

The sponsor submitted their first 120-day safety update on April 27, 2000, stating that there were no further adverse events to report and that the product has not yet been marketed anywhere in the world. An additional safety submission was received on November 1, 2000, covering the time period to 10/1/00 and there were no further AEs, SAEs, or deaths to report.

The current safety update covers the period of 10/1/00 to 1/1/01. The only ongoing trial is a European trial (Protocol 34224) to evaluate the effects of NuvaRing® on endometrial histology and on bone mineral density. The current submission includes all safety data on 82 subjects from trial start until the cutoff date of January 1, 2001 for this document. Since Trial 34224 is ongoing [final N = 100], complete data validation has not yet occurred. To date, there are no deaths or SAEs in the 82 subjects using NuvaRing®. The discontinuation rates and reasons, and the incidence of AEs are similar to those seen in the two large clinical trials with NuvaRing®.

There is no postmarketing safety information because NuvaRing® is not yet marketed in any country. On February 14, 2001, N. V. Organon (Oss, The Netherlands) received Marketing Authorization for NuvaRing® from the Dutch Medicines Evaluation Board and is now proceeding with the Mutual Recognition Procedure within the European Union.

> **Reviewer comment: There are no additional safety concerns for NuvaRing®. The potential increased incidence of venous thromboembolism (VTEs) associated with desogestrel-containing OCs remains the major safety concern. Etonogestrel, the progestin in NuvaRing®, is the active metabolite of desogestrel. No safety data exists on long-term use (> 13 cycles) of NuvaRing®, and it is unknown whether the increased incidence of VTE will be found with NuvaRing® use.**

Labeling Update:

General:

In November 2000, the Division sent to the sponsor major revisions to the original PI and PPI label. The original label proposed in the NDA contained the basic information and format found in the guidance document for class labeling for all oral contraceptives. The sponsor proposes a label very similar to that for their desogestrel-containing oral contraceptive Mircette®, substituting the name NuvaRing® for Mircette. Like Mircette, NuvaRing® is a combination hormonal [estrogen and progestin] contraceptive, but unlike Mircette, it is a vaginal delivery system with a constant release of hormones for 21 days, rather than an oral dose of hormones administered every 24 hours. Therefore, throughout the final label, the Division recommends appropriate changes when using terms such as "combination oral contraceptives," "hormonal contraceptives," etc. Another issue is the sponsor's use of the statement, "In the absence of data, it is unknown whether NuvaRing® is distinct from combination oral contraceptives with regard to ....". In many places, because the sponsor has data from over 2,500 women using NuvaRing® for up to 13 cycles, the sponsor has accepted the Division's recommendation that the statement should simply read, "It is unknown whether NuvaRing® is distinct from combination oral contraceptives with regard to ....".

VTE risk:

Etonogestrel, the progestin in NuvaRing®, is the active metabolite of desogestrel, the progestin contained in Mircette®. Therefore, the Division requires that the label include the text that is required for all desogestrel-containing OCs regarding an approximate 2-fold increased risk of VTE with desogestrel-containing OCs compared with certain second generation OCs.

Efficacy statement:

The Division does not recommend including in the PI and PPI label specific efficacy data from the two, large, non-comparative 13-cycle clinical trials because clinical contraceptive trials included in various NDA submissions differ in several respects:

- Length of product use in the trial(s): 6-12 months
- Comparative vs. non-comparative trial design
  - Choice of the active comparator if one is used
- Age range of trial subjects: inclusion criteria cut off at 35, 38, 40, 45, 50 years of age
- Number of cumulative woman-months (or woman-years) of product use
- Accuracy of determining date of conception and calculating product failure rates (# pregnancies during treatment; differing Pearl Index rates)
- Per protocol [perfect or PP] use vs. Typical [actual or non-PP] use
  - Different definitions for per protocol use populations
- Different requirements for pregnancy testing

NuvaRing® has an acceptable Pearl Index (pregnancies per 100 women-years of use) and cycle control pattern, but such specific data in the PI and PPI should not be included. This would avoid the issue of misleading or unsubstantiated comparative marketing claims. The section **How effective is NuvaRing®?** says; "If NuvaRing® is used according to the directions, your chance of getting pregnant is about 1 to 2% a year. That means every year, for every 100 women who use it, about 1 to 2 will become pregnant." This statement is acceptable to the reviewer and may stay in the label.

Bleeding patterns:

The reviewer's overall impression from the original NDA review and review of the sponsor's 10/06/00 submission is that the cycle control due to NuvaRing® is acceptable and not clinically different from that expected with most oral contraceptives. The bleeding pattern over one year of use of NuvaRing® was examined in the non-comparative US trial with 1,177 women for a total of 11,188 cycles. Bleeding patterns were originally analyzed for each of the 13 cycles and analyzed further, per our Division's 9/20/00 request, on a more cumulative basis for cycles 2-12. The discontinuation rate related to unacceptable bleeding patterns was less than 1%.

Reviewer comment: The bleeding patterns seen in the equally large European trial were significantly better than those seen in the US trial. The sponsor proposes to use the combined data to describe bleeding patterns in the label. This would make the overall bleeding pattern appear better than was seen in the US trial alone. The label should contain the US data alone because of the differences in the two large trials. European and combined data is found on page 44 of the original MOR. The following patterns in the large US trial were observed from cycle 2 through 12:

- **Average onset of withdrawal bleeding: Day 24 ± 1 day**
  Per cycle range not given
- **Median duration of withdrawal bleeding: 5 days**
  Per cycle range: data not available
- **Heavy bleeding [menorrhagia]: data not available**
- **Prolonged bleeding (at least 1 episode ≥ 10 days): 11.3%**
- **Early withdrawal bleeding (≥ 1 episode): 28%**

Per cycle range:

- **Cumulative chance of ≥ 1 episode of amenorrhea: not given**
  Per cycle amenorrhea range:
  Amenorrhea > 60 days: 1.4%
- **Breakthrough bleeding/spotting (≥ 1 episode): 46%**
  Per cycle range

Lipid statement:

In the Warnings section on carbohydrate and lipid metabolic effects, the text concerning ten different lipoprotein metabolic parameters cannot be included. The sponsor evaluated changes from baseline to cycle 6 in 33 women using NuvaRing® compared to the changes seen in a similar group of 37 women on a combination OC for 6 cycles. This text cannot be included in the label because the trial had a small sample size, was not designed to show superiority, and was not blinded (a double-dummy design could have been easily used). Furthermore, the sponsor has added all the subjects together to show geometric mean average changes by treatment group [NuvaRing® vs. OC comparator], rather than individual subject's or percentile changes, or a range of changes. Laboratory parameters were evaluated at baseline, 3 months and 6 months. The interim values were not included in the sponsor's primary analysis or conclusions. The statistical and clinical significance of the results as presented is questionable. **[For further discussion, see page 54 of the original 10/06/00 MOR.]**

Likewise, the sponsor proposes to change Precautions Section 9e. [Interactions with laboratory tests], concerning lipid changes. This section is part of class labeling for combination hormonal contraception, and cannot be changed.

Pharmacology and Drug/Drug interactions:

The Division recommends changes to the sponsor's original proposed label to provide clinically relevant pharmacology (PK and PD) information regarding drug/drug interactions that may affect serum levels of the active progestin and estrogen and may influence contraceptive effectiveness of hormonal contraceptives. New information concerning griseofulvin, anti-HIV protease inhibitors, St. John's wort (hypericum perforatum), and atorvastatin is incorporated.

The Precautions Section #8 Drug Interactions is edited to include the following new subsections:

- Changes in Contraceptive Effectiveness Associated with Co-Administration of Other Drugs
- Increase in Plasma Hormone Levels Associated with Co-Administered Drugs
- Changes in Plasma Levels of Co-Administered Drugs

Chemistry:

Chemical stability of the ring in its foil sachet at room temperature has been established. The actual serum levels of the steroids, however, are noted to be highest (burst effect) in the first 24 hours after ring insertion, after which the serum levels fall back to steady state and remain relatively constant for the next 20 days of normal ring use. It is uncertain if the burst effect may be altered by improper storage of the ring by a consumer after purchase from a pharmacy (where NuvaRing® is stored under refrigeration). Appropriate language about storage and temperature ranges is addressed in the label. The PPI label states: "Avoid exposure to direct sunlight or storage at temperatures above 86 ^{0}."

Dosage and Administration:

The Dosage and Administration section of the PI and the entire PPI are extensive. NuvaRing® is a new delivery system and a new molecular entity, so both providers (prescribers) and users will initially be unfamiliar with the product and its correct use. The PPI has been extensively revised by DDMAC to make the text and instructions more easily read and understood. The instructions to patients about how and when (and when not) to use the ring are somewhat complicated, but are well illustrated and acceptable. The label

also addresses issues that are unique to this new delivery system, such as expulsion of the ring, prolonged use of the ring, and accidental removal.

Non-contraceptive Health Benefits:

A statement in the label about non-contraceptive health benefits should not be included because to date there does not exist an epidemiological database to support such a claim. NuvaRing® is a new product containing a new molecular entity (NME) and a new delivery system (vaginal ring). The statement found in the class labeling for oral contraceptives is based on several large epidemiological studies of oral contraceptives.

Phase IV Commitments:

A teleconference with the sponsor was held on 12/11/00 to discuss chemistry issues and clinical Phase 4 commitments. The sponsor made commitments addressing the following three Division clinical concerns:

- Concomitant use of miconazole nitrate [single high dose] and NuvaRing® results in a 16-17% increase in serum etonogestrel and ethinyl estradiol levels
- Any potential effect of tampon use on efficacy of NuvaRing® or changes in serum etonogestrel and ethinyl estradiol levels [due to tampon absorption of the hormones] are unknown
- Follow-up data on pregnancies conceived while using/continuing NuvaRing® are very limited

So far, the Division has not received submissions addressing these concerns. The sponsor has committed to submit draft proposals for the first two commitments within 6 months of the Action date.

Reviewer's comments:
The sponsor agreed to submit within 6 months a protocol for a clinical study addressing the issue of increased serum levels of etonogestrel and ethinyl estradiol with the use of NuvaRing® and prolonged use [perhaps 4-7 days] of oil-based vaginal products such as miconazole nitrate. Serum hormone levels will be the primary focal points. Safety information will also be collected.

The sponsor agreed to submit within 6 months a protocol for a clinical study addressing the issue of potential changes [possible decrease] in serum hormone levels with the use of NuvaRing® and prolonged use [perhaps 4-7 days] of vaginal tampons. Serum hormone levels and ovulation inhibition will be the primary focal points. Safety information will also be collected.

Pregnancy outcomes for the 22 pregnancies that occurred during treatment in the two large studies included three live births, nine pregnancies continued (no stated results), eight abortions, and two unknown outcomes. No congenital anomalies, stillbirths, or major newborn problems were reported. The sponsor agreed to a Phase 4 commitment to collect as much data as possible on pregnancy outcomes from conceptions occurring during NuvaRing® use. Information on spontaneous miscarriages, preterm births, full term births, stillbirths, and congenital anomalies will be of particular interest.

Final Reviewer Comments:

NuvaRing® (etonogestrel/ethinyl estradiol vaginal ring) as a vaginal combination hormonal contraceptive for prevention of pregnancy is approvable. On 4/26/01 the sponsor informed our division that they could not accept the FDA labeling sent to the sponsor on 4/17/01. The primary

areas of disagreement are the Carcinogenesis section, the Bleeding Irregularity section under Warnings, and the Non-Contraceptive Health Benefits section.

This is the first FDA-reviewed hormonal contraceptive product containing the progestin etonogestrel and the first vaginal delivery system for combination hormonal contraception. The PI and PPI should reflect the increased risk of venous thromboembolism (VTE) associated with combination hormonal contraceptives containing desogestrel. Etonogestrel, the active progestin released directly from NuvaRing®, is the active metabolite of desogestrel.

Etonogestrel is a NME and the delivery system continually releases etonogestrel and ethinyl estradiol [with relative steady state levels] as compared to the once daily oral dose with traditional combination hormonal contraception resulting in daily serum peak and trough hormone levels. For this reason, the current safety profile on NuvaRing® is based solely on the data submitted with the NDA and with use of the product for up to 13 months. Although no future problems with AEs or SAEs are anticipated, postmarketing surveillance will be important.

The reviewer's overall impression from the original NDA review and review of the sponsor's 10/06/00 submission is that the cycle control due to NuvaRing® is acceptable and not clinically or significantly different from that expected with most oral contraceptives. Detailed information about bleeding patterns (cycle control) with initial use and extended (up to 13 cycles) use is not needed in the label. The instructions to patients about how and when to use the ring are somewhat complicated, but are well illustrated and acceptable. The label also addresses issues that are unique to this new delivery system, such as expulsion of the ring, prolonged use of the ring, and accidental removal. Statements are made, when appropriate, that "it is unknown whether NuvaRing® is distinct from combination oral contraceptives with regard to" several items discussed in the standard OC labeling.

Finally, the label should not include any specific statements concerning lipid changes or non-contraceptive health benefits associated with use of NuvaRing® for the reasons stated earlier in this review.

4/27/01

Daniel Davis, M.D.
Medical Officer, HFD-580
DRUDP

Date

Dena Hixon, M.D.
Team Leader, DRUDP

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NDA 21-187
Division file
DFS: to be electronically submitted by the medical officer