for method failure. For subjects in the individual studies, the probabilities of pregnancy for overall and method failure were similar.

Table 16 Life Table Estimates of the Probability of Pregnancy

Cycle 6 and Cycle 13 for All Subjects Who Received EVRA
(All Subjects Evaluable for Efficacy; Studies CONT-004, CONT-003, and CONT-002)

	Study CONT-004 N=811	Study CONT-003 N=844	Study CONT-002 N=1664	Total N=3319
Probability of Pregnancy[a]: Overall (95% CI)				
Cycle 6	0.6% (0, 1.2%)	0.5% (0, 1.0%)	0.4% (0, 0.7%)	0.5% (0.2%, 0.7%)
Cycle 13	1.3% (0, 2.7%)	0.5% (0, 1.0%)	0.7% (0, 1.4%)	0.8% (0.3%, 1.3%)
Probability of Pregnancy[a]: Method Failure[b] (95% CI)				
Cycle 6	0.4% (0, 1.0%)	0.4% (0, 0.9%)	0.4% (0, 0.7%)	0.4% (0.2%, 0.6%)
Cycle 13	1.1% (0, 2.5%)	0.4% (0, 0.9%)	0.4% (0, 0.7%)	0.6% (0.2%, 0.9%)

[a] Kaplan-Meier estimates of the cumulative probabilities of pregnancy.
[b] Method failure index: numerator = method failures, denominator = all cycles.

The overall 13 cycle Life-Table cumulative pregnancy probability for EVRA™ is estimated as 0.8% . Cumulative pregnancy rates for cycle 6 and 13 are provided above by the sponsor. These data are based on the Pivotal Efficacy Analysis Group, which included all subjects who contributed evaluable information on pregnancy exposure.

Reviewer's comment: the above table shows the probability of pregnancy for the individual three trials and the pooled data. The results show no clinically significant difference between the three studies and further demonstrate the acceptable contraceptive efficacy of the patch.

Method Failure ("Perfect Use") Evaluation

Reviewer's comment: although the data presented by the sponsor in the preceding sections for the "method failure" population is slightly better than the overall trial population [method + user failures], it is the Pearl Index of the All-Subjects-Treated Group that is traditionally considered by the FDA, because it felt to be more clinically meaningful. Since the study protocols are virtually identical, pooled data from the three trials may be used for approval and labeling.

4.8.5 Potential Predictors of Pregnancy

From the ISE: the results of the exploratory analyses performed using proportional hazards models to assess the association between age, baseline weight (kg), race (white vs. non-white), and site of patch application (abdomen, buttock, upper outer arm, and upper torso [excluding breast tissue]) were summarized for 1) each potential predictor considered individually, and for 2) a stepwise fit of all potential predictors. The population of interest is comprised

of the 3,319 efficacy-evaluable subjects in the Pivotal Efficacy Analysis Group. In each proportional hazards model, the dependent variable for each of the 15 subjects who became pregnant on therapy was the cycle in which she became pregnant. For the 3,304 efficacy-evaluable subjects who did not become pregnant on therapy, the dependent variable was censored at the subjects' last cycle on study medication.

In the single-predictor model, patch application site was analyzed in two ways. First, application site was analyzed to determine whether pregnancy was associated with any particular site; second, application site was analyzed to determine whether pregnancy was associated with the abdomen application site vs all other sites combined. Each of these analyses showed that the abdomen application site was not significantly associated with pregnancy. This finding should, however, be interpreted with caution, because patch application is a less reliable covariate than baseline age, body weight, and race. Unlike these potential predictors, application site is time-dependent: **for each subject, the application site used in the analysis was the first patch applied at the start of the last cycle** . In addition, the application site was changed with each application, and the site of patch application was not always recorded on the diary card. **Of the potential predictors tested in the single-predictor model, only baseline weight was significantly associated with pregnancy.** Both body mass index (BMI) and body surface area (BSA) were subsequently investigated to confirm this significant finding, and both were also significantly associated with pregnancy.

Reviewer comment: the three studies collected a large amount [>70,000 patches over >22,000 cycles] of patch application data. Subjects recorded the patch site for each cycle (three patch applications per cycle). No explanation is offered for using the application site for only the first patch and not all three patches of the last cycle. In any case, the reviewer looked at the patch sites for the last six applications (two full cycles) and could find no association between the patch sites and pregnancies.

Baseline weight was a significant factor as a potential predictor of pregnancy. Thirty-three percent (5/15 of the sponsor's failures) of the pregnancies with EVRA™ occurred in women with a baseline body weight ≥ 198 pounds (90 kg), yet this group comprised ≤ 3% of the study population. Special attention to this finding is found in the label for the product. The distribution of pregnancies by baseline weight is shown in sponsor Table 17 below.

Table 17 Distribution of Pregnancies by Baseline Body Weight Deciles

(Studies -004, -003, and -002)

Decile	Weight Range (kg)	Number of Pregnancies
1	<52	1
2	52 - <55	2
3	55 - <58	0
4	58 - <60	0
5	60 - <63	2
6	63 - <66	0
7	66 - <69	1
8	69 - <74	0
9	74 - <80	2
10	≥80	7
Subsets in Decile 10	(80 – 85)	1
	(85 – 90)	1
	(≥90)[a]	5

Reviewer comment: it is clear that contraceptive effectiveness is reduced for women weighting ≥ 90 kg. In addition, 27% (4/15) of the pregnancies while using EVRA™ occurred in women weighing 74 to 94 kg at baseline; this weight range comprised 17% of the study population. It is unclear how this fact should be used in the labeling for this product, but it is probably not significant.

4.8.6 Secondary Efficacy Parameter: Cycle Control (Bleeding patterns)

From the sponsor's ISE: the primary efficacy endpoint of interest for the evaluation of cycle control is the incidence of breakthrough bleeding and/or spotting in Cycle 3 in Study -004. Bleeding information was also available from Study CONT -001. To assess cycle control, diary cards were used to record daily bleeding information from each of the 28 "on-therapy" cycle days.

Valid Cycles

Bleeding summaries and analyses included only data from "valid" cycles, (those cycles that met the validity criteria established for bleeding summaries) in the Pivotal Efficacy Analysis Group. The number of cycles that were valid for the bleeding summaries are presented by cycle for Studies CONT-004, CONT-003, CONT-002 and overall in Table 18 below.

Table 18 Number of Cycles Valid for Bleeding Information

All Subjects Evaluable for Efficacy; Studies CONT-004, CONT-003, and CONT-002

	Study CONT-004 N=811		Study CONT-003 N=844		Study CONT-002 N=1664		Total N=3319	
Cycle	Total Cycles	Valid Cycles	Total Cycles	Valid Cycles	Total Cycles	Valid Cycles	Total Cycles	Valid Cycles
1	810	755	844	803	1664	1564	3318	3122
2	731	686	795	760	1512	1435	3038	2881
3	697	657	775	730	1462	1374	2934	2761
4	649	618	739	708	1357	1274	2745	2600
5	626	600	728	700	1333	1274	2687	2574
6	615	583	719	694	1306	1252	2640	2529
7	175	160	203	196	374	353	752	709
8	167	157	200	192	359	349	726	698
9	162	150	195	187	348	327	705	664
10	155	149	185	179	329	308	669	636
11	154	151	182	177	324	312	660	640
12	153	147	181	175	321	303	655	625
13	152	146	176	175	315	300	643	621
14	--	--	--	--	3	1	3	1
Total	5246	4959[a]	5922	5676	11007	10426	22,175	21,061

[a] Number of subjects with diary card information.

Reviewer comment: the three studies collected a large amount [21,061 valid cycles] of cycle control data. Studies -003 and -004 were comparative, using an oral contraceptive pill, and collected bleeding data also from the pill users. The proportion of cycles considered invalid for bleeding analysis is similar in all three studies as well as for the two comparator contraceptive pills.

Bleeding pattern results

From the ISE: The primary efficacy endpoint for the evaluation of cycle control was the incidence of breakthrough bleeding and/or spotting (BBS) at Cycle 3. The incidence of BBS at representative cycles is summarized in Table 19 below for all efficacy-evaluable subjects in the Pivotal Efficacy Analysis Group who received EVRA. Breakthrough bleeding and breakthrough spotting were each defined in two ways. For the in-text summary tabulations of BBS, breakthrough bleeding, and breakthrough spotting, breakthrough bleeding was defined as requiring at least one pad or tampon per day, and breakthrough spotting was defined as requiring no pads or tampons per day.
At Cycle 3, the incidence of BBS for EVRA subjects in the three pivotal studies was similar, ranging from 10% in Study -004 to 14% in Study -003. In the other representative cycles, the incidence of BBS was highest in Study -003 at Cycle 9 (14% compared with 7% in Studies -002 and -004). By Cycle 13, however, the incidence of BBS in Study -003 was 8%, compared with 5% in Study -004 and 9% in Study -002. Overall, the incidence of BBS tended to decrease over time (from 11.6% at Cycle 3 to 8% at Cycle 13).

Table 19 Summary of Breakthrough Bleeding and/or Spotting (BBS) by Cycle

All Subjects Evaluable for Efficacy; Studies CONT-004, CONT-003, and CONT-002

	Study -004 (USA) N=811			Study -003 (EURO) N=844			Study -002 (Mixed) N=1664			Total N=3319		
Cycle	N[a]	n[b]	%[c]	N[a]	n[b]	%[c]	N[a]	n[b]	%[c]	N[a]	n[b]	%[c]
3	650	65	**10.0**	710	100	**14.1**	1339	148	11.1	2699	313	**11.6**
6	582	55	9.5	681	63	9.3	1231	90	7.3	2494	208	8.3
9	149	10	6.7	182	25	13.7	323	21	6.5	654	56	8.6
13	146	8	**5.5**	171	14	**8.2**	294	27	9.2	611	49	**8.0**

[a] Number of subjects with diary card information and valid cycle.

[b] Number of subjects with breakthrough bleeding and/or spotting.

[c] Percentage of subjects with breakthrough bleeding and/or spotting.

Reviewer's comment:
The sponsor has focused on BBS, especially during Cycle 3, as the most important event 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 removal of the third patch], amount of bleeding [compared to the subject's usual menses], and prolonged bleeding. Elizabeth Belsey [15], 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 combination OC pills] have usually been associated with "regular, shorter, lighter menses" with a predictable onset relative to a 28-day cycle, data of this type would be very useful for the prescribing healthcare provider and the consumer. Analysis of the additional cycle control data requested by the Division from the sponsor showed the following findings for EVRA™ users during cycles 2-12:

The median day for onset of wi

- **Withdrawal bleeding lasted an average of 5.6 days (the 2 comparators averaged 4.7 days)**
- **Breakthrough bleeding ranged from 3.1 to 5.2% of patch users each cycle**
- **Breakthrough spotting ranged from 6 to 7.7% of patch users per cycle**
- **On average, 2.2% of patch users experienced amenorrhea each cycle [range from 1 to 4%]**
  - **One OC comparator averaged 7.5% per cycle; the other comparator averaged 3.9% per cycle**
- **Bleeding/spotting days ≥ 7 per cycle: 26.4% of patch users per cycle [range 22 to 34%]**
  - **The OC comparators showed 16.3% and 13.7% on average per cycle [range 11 to 20%]**
- **Bleeding/spotting days ≥ 10 per cycle: 4.7% of patch users per cycle [range 3 to 8%]**
  - **The OC comparators showed 2.4% and 3.5% on average per cycle [range 1 to 7%]**

These findings suggest that EVRA™ users can expect withdrawal bleeding to start one day later in the drug-free interval than is seen with the two COC comparators, to last 5-6 days on average, and to extend into the next cycle of patch use. EVRA™ users can expect breakthrough bleeding and/or spotting in 9-13% of cycles and ≥ 7 days of total bleeding/spotting in ~26% of cycles. After the first cycle of use, there appears to be little change over the next 12 cycles of use. The 2.2% incidence of amenorrhea per cycle is lower than that observed with the comparators.

4.8.7 Patch acceptability (wearability and reasons for patch change)

Patch-wearability data (the percentage of subjects with at least one patch that detached) are summarized overall in sponsor Table 20. These data were summarized by cycle from diary card information provided by the 3,319 efficacy-evaluable subjects in the Pivotal Efficacy Analysis Group who used EVRA. For individual cycles, the percentage of subjects with at least one patch that detached ranged from 2% to 6%. Only 2% of all patches applied during the study detached; and the percentage of patches that detached tended to decrease over time.

Table 20 Number and Percentage of Patches that Fell Off

All Subjects Evaluable for Efficacy; Studies CONT-004, CONT-003, and CONT-002

	Total Number of Subjects[a]	Number of Subjects With At Least One Patch That Fell Off		Total Number of Patches	Number of Patches that Fell Off	
Cycle	No.	No	(%)	No.	No.	(%)
1	3302	196	(5.9)	11059	234	(2.1)
2	3030	191	(6.3)	9789	212	(2.2)
3	2959	169	(5.7)	9348	195	(2.1)
4	2744	137	(5.0)	8662	161	(1.9)
5	2692	128	(4.8)	8462	142	(1.7)
6	2648	143	(5.4)	8305	165	(2.0)
7	751	34	(4.5)	2343	40	(1.7)
8	729	36	(4.9)	2267	39	(1.7)
9	711	31	(4.4)	2189	34	(1.6)
10	668	24	(3.6)	2064	25	(1.2)
11	660	20	(3.0)	2046	21	(1.0)
12	655	14	(2.1)	2016	16	(0.8)
13	643	12	(1.9)	1990	12	(0.6)
14	3	1	(33.3)	12	1	(8.3)
All[b]	**3319**	**826**	**(24.9)**	**70552**	**1297**	**(1.8)**

[a] Numbers are based on diary card information.

[b] Numbers of subjects with diary card information at any time during the study.

Reviewer comment: the compliance per cycle was very good throughout the 13 cycles of use. Only 1.8% of all patches applied during the three pivotal studies detached; and the percentage of patches

that detached tended to decrease over time. For individual cycles 1 through 13, the percentage of subjects with at least one patch that detached ranged from 1.9% to 6.3%.

A summary of reasons for patch change for all subjects evaluable for efficacy is shown in the sponsor's table below. In each study and overall, over 90% of the patches were changed as scheduled.

Table 21 Summary of Reasons for Patch Change

All Subjects Evaluable for Efficacy; Studies CONT-004, CONT-003, and CONT-002

	Study CONT-004		Study CONT-003		Study CONT-002		TOTAL	
Total Number of Patches	16,673		18,677		35,202		70,552	
	n	%	n	%	n	%	n	%
Reason for Patch Change[a]:								
Scheduled Change	15,300	91.8	17,371	93.0	32,401	92.0	65,072	92.2
Skin Reaction	136	0.8	103	0.6	216	0.6	455	0.6
It Fell Off	300	1.8	317	0.7	680	1.9	1,297	1.8
Partially Lifted	470	2.8	531	2.8	1,049	3.0	2,050	2.9
Accidentally Pulled Off	143	0.9	113	0.6	301	0.9	557	0.8
Other	312	1.9	217	1.2	521	1.5	1,050	1.5
Missing Reason[b]	12	0.1	25	0.1	34	0.1	71	0.1

[a] Reason for patch change was recorded on the weekly diary page of the CRF.
[b] Reason for patch change and/or date of patch change, was not recorded on the weekly diary page of the CRF.

Reviewer comment: over 92% of the patch changes were for the normal scheduled change; otherwise, the most common reason (2.9%) was that the patch was partially lifted. In this case, the subjects were specifically instructed to change the patch. Only 0.6%, 455 of 70,552 patches, were changed because of a local skin reaction. The patch wearability, acceptance, and compliance are favorable for this new delivery system for combination hormonal contraception.

4.9 Safety analyses (see Sponsor's Integrated Summary of Safety: ISS)

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-therapy, on-therapy, or post-therapy. 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.

The ISS for EVRA includes 24 studies: three Phase 3 efficacy and safety studies, five specialized safety, dose-ranging, and/or supportive efficacy studies, four dermal safety studies, and 12 pharmacokinetic and bioavailability studies. Analyses are ongoing for two more pharmacokinetic studies (PHI-017 and -018). Overall, safety information has been collected for 6,254 women who have participated in the clinical investigations, including 3,330 subjects who wore the EVRA patch in the three Phase 3 studies with a planned duration of 6 or 13 cycles (total 22,176 treatment cycles). The results of these clinical trials demonstrate that EVRA is an effective contraceptive agent that is safe and well tolerated by women who are candidates for hormonal contraception.

Overview of the ISS:

In the ISS, the 24 studies have been classified into two sets of safety analysis groups: (1) a set comprised of all 24 studies, with each study categorized into one of three analysis groups (principal, supportive, or other) based on the relevance of the standard safety results (adverse events, clinical laboratory evaluations, vital signs, findings of physical and gynecologic examinations) of the study to the overall safety profile of EVRA, and (2) a set comprised of selected studies that provide results of additional safety evaluations (assessments of dermal safety, lipid data, and coagulation data), or data that contributed to dose selection. The studies included in each analysis group are listed in Table 22 along with the safety information included in the ISS from each group.

Table 22 ISS Safety Analysis Groups and Type(s) of Safety Information Provided

Safety Analysis Groups	
Studies	Type of Safety Information
ANALYSIS GROUPS FOR STANDARD SAFETY EVALUATIONS: ALL STUDIES	
Principal Safety Analysis Group[a] N = 3,330	
CONT-002, CONT-003, and CONT-004	Adverse events[b] Standard clinical laboratory tests Vital signs/weight Physical examination results Gynecologic examination results
Supportive Safety Analysis Group[c] N = 377	
PHI-013, CONT-001, CONT-005, CONT-006, CONT-007, and CONT-008	Adverse events Standard clinical laboratory tests[d] Vital signs/weight Physical examination results Gynecologic examination results Vaginal bleeding complications (-001)
Other Studies Providing Supportive Safety Data[e] N = 624	
PHI-001, PHI-003, PHI-004 PHI-005, PHI-006, PHI-007, -008 PHI-009, PHI-011, PHI-012, -014 PHI-015, PHI-016, PHI-017, -018	Adverse events Standard clinical laboratory tests Vital signs/weight Physical examination results Gynecologic examination results

ANALYSIS GROUPS FOR SUMMARIZATION OF ADDITIONAL (SPECIAL) SAFETY EVALUATIONS: SELECTED STUDIES

Studies Providing Special Safety Data	
PHI-007, PHI-008, PHI-009, -011	Dermal safety data
CONT-005 **N = 99**	Lipid data
CONT-006 **N = 36**	Coagulation and fibrinolysis data
Studies Providing Dose-Ranging Data	
CONT-001 and PHI-006	Dose-ranging data

[a] Safety summaries presented for all subjects who received EVRA in these studies and by regimen (patch versus oral comparator) for the two comparative trials (CONT-003 and CONT-004).

[b] Summaries of all adverse events (including skin irritation at the EVRA application site and vaginal bleeding complications) and adverse events summarized by subject age, race, and weight are presented in the ISS for the Principal Safety Analysis Group.

[c] Safety summaries presented for subjects who received EVRA in Studies PHI-013, CONT-001, CONT-005, CONT-006, CONT-007 and -008, and by study and regimen for the placebo-controlled study (CONT-005) and the active-controlled studies (CONT-001, -006, -007, and -008).

[d] Studies CONT-007 and CONT-008 did not include clinical lab evaluations.

[e] Safety information from these analysis groups is presented by study and regimen (where appropriate); no pooled summaries are provided.

Reviewer's comment: treatment-emergent adverse event (TEAE), serious adverse event (SAE), treatment-limiting adverse event (TLAE), standard clinical lab tests, vital sign (VS), weight, and Pap smear data are pooled and summarized for subjects who received the 20 cm ^{2} transdermal contraceptive system for EVRA™ in the six studies included in the Supportive Safety Analysis Group. Safety data are also presented separately by study and regimen for the three active-controlled studies in the Principal Safety Analysis Group. This review will concentrate on the pooled safety data from these two Analysis Groups, unless otherwise indicated, as it represents a large and acceptable database from which to draw conclusions.

Deaths

One death (27 year old Caucasian women with a self-inflicted gunshot wound) was reported in the EVRA™ subjects in the clinical studies. The death was not related to study drug in the opinion of the investigator and the sponsor. One of 605 subjects who received Triphasil in Study CONT-004 experienced depression and died of a drug overdose.

Reviewer comment: The CRF was reviewed. This subject was a non-smoker, weight 135 #, G0P0, current barrier method user, with an entirely normal medical history, regular menstrual cycle and normal 4-day periods. Throughout the study she recorded no AEs except some breast tenderness, occasional headaches, and occasional BBS. The patients satisfaction questionnaire pre-study stated excellent emotional and physical well-being, and "the same" overall emotional well-being at four follow-up visits. In the CRF, there is no explanation or details concerning the suicide.

Serious Adverse Events (SAEs)

The incidence of treatment-emergent SAEs in the Principal Safety Analysis Group was 1 to 2%, and the incidence of individual SAEs showed no apparent differences between treatments. Of the two frequently reported adverse events that occurred with a higher incidence in subjects who received EVRA versus Triphasil in Study -004 (application site reaction and breast symptoms), there were no SAEs in EVRA subjects. Most of the serious adverse events that occurred during the clinical trials were considered unrelated or of doubtful relationship to the study drug, most did not result in discontinuation of study drug treatment, and the vast majority resolved either spontaneously or with appropriate treatment.

Seven of the 3,330 EVRA subjects in Studies CONT-002, CONT-003, and CONT-004 experienced SAEs that the investigators judged to be possibly, probably, or very likely related to study drug treatment. These events included pulmonary embolus, which was experienced by two subjects, and one case each of thrombosis, menorrhagia, pain, hypoesthesia, paresthesia, migraine, cholecystitis, and carcinoma in situ of the cervix. For six subjects, the serious adverse events resolved; the outcome of one subject's serious event was unknown.

Table 23 Summary of Treatment-Emergent Serious Adverse Events for EVRA Subjects

Studies CONT-002, CONT-003, and CONT-004

Total Subject (N=3,330) Incidence, n(%)	**50 (1.5%)**

Serious Adverse Events Reported for > One Subject

Adverse Event (Preferred Term)	No. of Subjects
Abdominal Pain	8
Injury	6
Cervical Smear Test Positive	3
Cholecystitis	2
Embolism Pulmonary	2
Meningitis	2
Pneumonia	2
Pyelonephritis	2

SAEs (Preferred Terms) Each Reported for One Subject

Abscess	Migraine
Aneurysm	Nausea
Bronchitis	Ovarian Disorder
Cervix Carcinoma In Situ	Pain
Cholelithiasis	Paresthesia
Dehydration	Pharyngitis
Depression	Pheochromocytoma
Diabetes Mellitus	Psychosis Manic-Depressive
Gastritis	Renal Calculus
Gastroenteritis	Sinusitis
Hemiplegia	Skin Neoplasm Malignant
Hypoesthesia	Sleep Disorder
Infection	Suicide Attempt
Infection TBC	Thrombosis
Leg Pain	Tooth Disorder
Melanoma Malignant	Uterine Disorder NOS
Menorrhagia	Vomiting

Abbreviations: NOS, not otherwise specified; TBC, tuberculosis.

Reviewer comment: As noted above, 1.5 % (total of 50) of the 3,330 subjects in the Principal Safety Group experienced serious adverse events. The three women with either pulmonary emboli (2) or thrombosis (1) will be discussed in detail later.

4.9.1 Discontinuations Due to AEs (so-called "treatment-limiting adverse events" or TLAEs)

The incidence of adverse events that led to the discontinuation of subjects in the Phase 3 studies is summarized in the sponsor table below for all EVRA subjects in Studies CONT-002, CONT-003, and CONT-004. A listing of subjects in the three studies who discontinued treatment because of TLAEs is provided and narrative descriptions of these subjects are included in the submission.

Three hundred ninety-nine (12.0%) of 3, 330 EVRA subjects discontinued study drug because of TLAEs. No individual adverse event led to the discontinuation of more than 2% of EVRA subjects. The most common TLAEs reported among the subjects who received EVRA treatment included application site reaction, breast symptoms, nausea, and headache (see Table 24). With the exception of application site reactions, adverse events that most frequently led to the discontinuation of EVRA treatment in the Phase 3 studies were similar to those reported for other hormonal contraceptives. Most of the treatment-limiting adverse events were mild or moderate in severity and not serious.

Table 24 Treatment-Limiting Adverse Events Reported for ≥ 0.5% of EVRA Subjects

Studies CONT-002, CONT-003, and CONT-004

	N=3,330	
Preferred Term	n	(%)
Application Site Reaction	62	(1.9)
Breast Symptoms[a]	63	(1.9)
Nausea	58	(1.7)
Headache	38	(1.1)
Emotional Lability	32	(1.0)
Dysmenorrhea	26	(0.8)
Vomiting	23	(0.7)
Weight Increase	23	(0.7)
Depression	17	(0.5)
Pruritus	17	(0.5)
Intermenstrual Bleeding	16	(0.5)
Menorrhagia	16	(0.5)
Migraine	16	(0.5)
Any Treatment-Limiting Adverse Event[b]	**399**	**(12.0)**

[a] Includes breast symptoms recorded as breast discomfort, breast engorgement, and breast pain female.

[b] Subjects may have discontinued treatment in association with one or more adverse events.

Reviewer comment: as noted above, a total of 399 of the 3,330 subjects (12.0%) discontinued from the three large clinical studies due to adverse events, called TLAEs. In the sponsor's table above, the most common AEs causing discontinuations were application site reactions and breast symptoms. If nausea

and vomiting are combined, however, there were 58 + 23 = 81 discontinuations. This would represent 2.45% of all evaluable subjects, or 20% (81/399) of all the discontinuations. If 62 women with site reactions and 63 with breast symptoms were added to the 81 women with nausea and vomiting, this would comprise over 50% of the TLAEs.

In the comparative USA/Canada study -004, subject discontinuations due to treatment-limiting AEs were 12.8% of EVRA™ users compared to 5.6% of Triphasil users. Part of the explanation is that there were obviously no Triphasil discontinuations due to application site reactions. In the equally large, comparative Euro/South Africa Study -003, subject discontinuations due to AEs were 9.7% of EVRA™ users compared to 4.5% of Mercilon [150 µg desogestrel/20 µg EE] users. In three other recently approved combination hormonal contraceptive products, subject discontinuations due to AEs ranged from 4.2 to 15.1%. These figures are hard to interpret because with one product 6.5% of the subjects were lost to follow-up and 11.6% chose to discontinue the study without listing an AE as the reason. The TLAEs and percentages listed above for EVRA™ users are comparable to those seen in other NDA reviews.

4.9.2 Overall Incidence of Adverse Events (TEAEs)

From the ISS: In general, the adverse events reported for EVRA subjects in the Principal Safety Analysis Group are similar to those associated with the use of other marketed hormonal contraceptives. One exception was application site reactions, which occurred only in subjects who received the EVRA patch. Overall, 80.0% of the EVRA subjects in this analysis group experienced at least one TEAE. Most adverse events, including the most commonly reported events, were mild or moderate in severity, not serious or treatment limiting, and most resolved either spontaneously or after appropriate treatment.

Individual adverse events (preferred terms) reported most frequently by 2,665 (80.0%) of the 3,330 EVRA subjects included breast symptoms (22.0%), headache (21.1%), application site reaction (17.4%), and nausea (16.8%). In the comparative trial -004, the incidence rates for most individual adverse events (not including application site reaction) were similar among subjects who received EVRA and those who received Triphasil. Breast symptoms were reported by a higher percentage of EVRA versus Triphasil subjects. The breast symptoms reported for subjects in either treatment group were mild to moderate in severity, occurred early in the treatment period (primarily in Cycle 1), and were generally not treatment limiting.

In general, the type of adverse events observed among EVRA subjects in the Supportive Safety Analysis Group studies (PHI-013, CONT-001, CONT-005, CONT-006, CONT-007, and CONT-008), as well as the severity and relationship to study treatment of these events, were similar to the adverse events reported among EVRA subjects in the studies that comprise the Principal Safety Analysis Group.

Adverse events that occurred in the Principal Safety Analysis Group with a subject incidence greater than 5% are summarized by preferred term in Table 25 below:

Table 25 Treatment-Emergent Adverse Events Reported with an Incidence >5%

Summarized by WHOART Preferred Term for Subjects Who Received EVRA
Studies CONT-002, CONT-003, and CONT-004

	(N=3,330)		USA Study -004 (N=812)		Euro Study -003 (N=846)	
Adverse Event (Preferred Term)	n	(%)	n	(%)	n	(%)
Breast Symptoms[a]	734	(22.0)	153	(18.8)	212	(25.1)
Headache	704	(21.1)	178	(21.9)	171	(20.2)
Application Site Reaction	581	(17.4)	**164**	**(20.2)**	**117**	**(13.8)**
Nausea	559	(16.8)	**166**	**(20.4)**	**103**	**(12.2)**
Upper Respiratory Tract Infection	336	(10.1)				
Dysmenorrhea	335	(10.1)	**108**	**(13.3)**	**45**	**(5.3)**
Abdominal Pain	302	(9.1)	66	(8.1)	93	(11.0)
Influenza-like Symptoms	238	(7.1)				
Vaginitis	180	(5.4)				
Sinusitis	180	(5.4)				
Pharyngitis	173	(5.2)				
Vomiting	171	(5.1)				
Back pain			**55**	**(6.8)**	**26**	**(3.1)**
Any Adverse Event	**2,665**	**(80.0)**	**698**	**(86.0)**	**612**	**(72.3)**

[a] Includes breast symptoms recorded as breast discomfort, breast engorgement, and breast pain

Reviewer comment: It is interesting to note the differences in the incidence of certain common symptoms among EVRA™ users in the USA vs. European studies. The TEAE data (# and % of total subjects) for site reaction [20 vs. 14%], nausea [20 vs. 12%], dysmenorrhea [13 vs. 5%], and back pain [7 vs. 3%] are much higher in the USA/Canada study, whereas breast symptoms [19 vs. 25%] and abdominal pain [8 vs. 11%] are somewhat higher in EVRA™ users in the European Study -003. Overall, however, the reviewer agrees with the sponsor that the TEAEs reported for the EVRA™ users are similar to those associated with the use of "other marketed combination hormonal contraceptives."

It is difficult to explain certain individual discrepancies in the two large comparative studies -003 and -004. In Study -004, women taking Triphasil (containing 30-40 µg EE per pill) had 1/3 the incidence of breast symptoms [6 vs. 19%] as women using EVRA™; yet the incidence of headache, nausea, and vomiting were almost the same for the two products. In Study -003, women taking Mercilon (containing 20 µg EE per pill) had a 9% incidence of breast symptoms compared to women using EVRA™ who had a 25% incidence of breast symptoms; unlike the Triphasil data, the incidence of nausea + vomiting was ~9% for Mercilon users and 17% for EVRA™ users.

4.9.3 Serious Adverse Events

In the three large efficacy trials, during the on-therapy period, 50 subjects had SAEs, 19 in Study -002, 15 in Study -003 and 16 in Study -004. All subjects recovered from their SAEs with or without sequelae, and the majority did not result in discontinuation of study drug treatment. See Table 23 (page 36) listing the 50 SAEs.

From the ISS: the sponsor has reviewed the list of coagulation abnormalities in detail. Six of 3,330 EVRA subjects, 1 of 643 subjects who received Mercilon, and 1subject using a 15 cm^2 patch in Study CONT-001 experienced coagulation-related adverse events. Each of these cases is reviewed below.

Reviewer comment: the sponsor uses the term "coagulation abnormalities," but each of the six women experienced a VTE (venous thrombotic event), commonly subdivided into either a thrombophlebitis, deep vein thrombophlebitis (DVT), or pulmonary embolus (PE). Reviewer comments will follow each subject's synopsis, and further comments will follow at the end of this section.

Subject 1181 (Study CONT-003), a 30-year-old white South African non-smoking female G2P2, was randomized to EVRA for 13 cycles as a direct switch from Mercilon. Her entry weight was 72 kg and her height was 166 cm. This subject began study drug 16DEC97, and on Day 254 she developed a cough and pleuritis; she was diagnosed with a pulmonary embolus on Day 277 (Cycle 10). Although a noninvasive venous assessment with a Doppler technique showed normal veins in both legs, a ventilation perfusion scan conducted on 19SEP98 revealed normal ventilation scan and an abnormal perfusion scan compatible with the diagnosis of pulmonary embolism. Study drug had been stopped on 15SEP98 and anticoagulation administered to the subject. She recovered without sequelae.

Reviewer comment: no hospital discharge summary is available for this woman, but the submission includes reports from a series of four spiral CT chest studies with IV contrast performed on 9/19/98 (initial diagnosis), 11/5/98, 12/9/98, and 2/18/99. All four studies are compatible with an initial pulmonary embolus and its subsequent resolution with residual scarring at the left costophrenic corner. According to the MedWatch form, she was discharged from the hospital on Day # 7 on Warfarin (coumadin) and Clexane (enoxaparin) 40 mg injections. Enoxaparin is a low molecular weight heparin that is usually given subcutaneously every 12-24 hours. No further information is available on this subject, except to note that a coagulation profile on 6/12/99 was normal.

This is a well-documented case of a pulmonary embolus without a documented peripheral DVT in a healthy 30-year-old woman with no predisposing factors. She had used EVRA™ for 10 consecutive cycles after switching directly from using Mercilon (21-day monophasic desogestrel 150 mg/EE 20ug).

Subject 21022 (Study CONT-002), a 34-year-old white American non-smoking female G2P2, was randomized to EVRA for six cycles as a direct switch from Triphasil. Her entry weight was 190 lbs and her height was 64 inches. This subject began study drug 20MAR98 and was withdrawn from the study on 4JUN98 for elective surgery, which was performed on 5JUN98. The surgery included bilateral breast implants, liposuction, and abdominoplasty. According to the protocol, subjects were to be removed from study drug at least four weeks prior to elective surgery that involved intubation or an incision larger than 2 cm. Postoperative pulmonary embolus was reported. In the opinion of the investigator, the pulmonary embolus was probably related to the study drug. It should be noted that this case was also initially coded with "thrombosis arterial leg," a finding that is not consistent with a typical postoperative pulmonary embolus. The study site was unable to obtain copies of the hospital records as the subject was lost to follow up. Through a review of all available data, including notes from telephone conversations with the subject, the investigator determined that "thrombosis arterial leg" was likely an error because there was no history or finding of heart disease nor mention of "arterial" by the subject. This case, although associated with the use of EVRA, occurred when the instructions for the proper use of EVRA were not followed.

Reviewer comment: unfortunately there are no operative note, hospital discharge summary, diary data from Cycles 2 or 3, or follow-up visits for this subject. The CRF does contain notes from three phone calls with the subject on 6/4/98, 6/17, and 6/30. She probably used the EVRA™ patch for three full cycles, as 6/4/98 would have been patch Day 20 or 21 of Cycle 3. We do not know when she was discharged from her initial hospital stay, but she was re-admitted from 6/24 to 29 for treatment of a pulmonary embolus. She received IV heparin from 6/24-28, plus Coumadin starting on 6/27 (for 6 months), and Lovenox (enoxaparin) 80 mg subcutaneous every 12 hours from 6/28 for 6 days. She failed to keep follow-up appointments on 6/15, 6/17, and in July '98.

This is a patient-only documented case of pulmonary embolus in a 190-pound non-smoking woman, switching directly from Triphasil OCs, with a past medical history (no dates are given) of asthma, pneumonia, scapula fracture, and depression. We do not know what surgery was actually

performed, the anesthesia used, the operating time, or any of the post-operative course. The sponsor argues that this SAE occurred in a subject with a protocol violation (EVRA™ should be discontinued 4 weeks prior to major surgery). The fact remains, however, that this subject used EVRA™ for three cycles, had major surgery, and had a post-op pulmonary embolus. Because of the morbidity and mortality associated with a pulmonary embolus, this reviewer remains concerned that this was the second case of pulmonary embolus associated with use of EVRA™, a combination hormonal contraceptive containing a newer progestin [new molecular entity] with a new (transdermal) delivery system. Some caution is warranted.

Subject 23027 (Study CONT-002), a 25-year-old white American non-smoking female G0P0, was randomized to EVRA for 13 cycles as a direct switch from Ortho Novum 7/7/7. Her entry weight was 187 lbs and her height was 70 inches. This subject began study drug 28JAN98. On 30MAR98, Day 6 of Cycle 3, the subject developed symptomatic venous varicosities and was initially treated with aspirin and ibuprofen. On 21APR98, the end of Cycle 3, the subject was withdrawn from the study for the symptomatic venous varicosities and possible phlebitis. On 23APR98, noninvasive venous testing was performed with a Doppler technique. The results were normal with no evidence of deep venous thrombosis.

Reviewer comment: the MD notes in the CRF on 4/7 and 4/20/98 state that this subject was a smoker with a history of varicose veins without any phlebitis, and whose father who recently died of a DVT complicated by a pulmonary embolus. The reviewer agrees that this subject had a superficial left popliteal phlebitis and should have been withdrawn from the study. Of interest, she consulted a vascular surgeon and was treated with an IV sclerosing agent on 4/23/98, one month after withdrawing from the study.

Subject 2040 (Study CONT-003), a 26-year-old white Belgian non-smoking female G0P0, was randomized to EVRA for six cycles as a direct switch from Mercilon. Her entry weight was 75 kg and her height was 170 cm. This subject began study drug 13FEB98. On 23FEB98, the subject sustained a leg fracture and a cast was placed on the broken limb. On 6MAR98, the subject was placed on prophylactic heparin-like medication. No thrombotic event was ever diagnosed. The subject completed the study on 10AUG98.

Reviewer comment: the heparin-like medication was Fraxiparine 10,000 units subcutaneous. It is surprising that this subject was continued in the trial as she had a relative contraindication to hormonal contraception (immobilization due to a leg fracture requiring a cast). In any case, she completed the 6-cycle trial without further problems. The reviewer agrees that no VTE event was diagnosed in this subject.

Subject 5155 (Study CONT-003), a 37-year-old white Finnish non-smoking female G1P1, was randomized to EVRA for six cycles as an indirect switch from Femilar. Her entry weight was 63 kg and her height was 162 cm. This subject began study drug 31MAY98. On 9SEP98, Cycle 4, the subject developed a superficial thrombophlebitis, which was considered mild and not serious and was treated with a heparin-like medication; the event resolved eight days later. The subject completed the study on 14NOV98 at the end of Cycle 6. This was a case of superficial phlebitis.

Reviewer comment: this subject was actually 38 years old at the start of the study. She had a mild, superficial thrombophlebitis, was not hospitalized, was given only a topical treatment, and continued on the EVRA™ patch to complete the 6-cycle study. The treatment was Trombosol forte® 1% cream containing "heparine 250 Ky and bentzyline cotinate 2.5 mg/g." The phlebitis resolved without additional treatment.

Subject 71032 (Study CONT-002), a 42-year-old white Swedish non-smoking female G3P2, was randomized to EVRA for six cycles as a fresh start subject. Her entry weight was 79.6 kg and her height was 172 cm. This subject began study drug 20FEB98. On 06MAR98, Day 15 of Cycle 1, the subject developed a thrombophlebitis of the left thigh; this adverse event was considered moderately severe and not serious. No diagnostic tests were performed and

study medication was not stopped. The subject was treated with a nonsteroidal anti-inflammatory medication and the event resolved eight days later. The subject completed the study at the end of six cycles on 06AUG98 without problems.

Reviewer comment: the affected area was described as red, very superficial, and above the knee on the posterior medial aspect of the left thigh. A topical cream (? name and ingredients) was used locally and the subject had a normal exam 1 week later. There was no recurrence of the findings and the subject completed the 6-cycle study. In light of the woman's age, weight (175 pounds), and "moderately severe" symptoms, it is surprising that this subject was continued in the trial.

Subject 5063 (Study CONT-003), a 37-year-old white Finnish non-smoking female G4P3, was randomized to Mercilon for 13 cycles. Her entry weight was 66 kg and her height was 168 cm. This subject began study drug on 6FEB98. On 17NOV98, Day 5 of Cycle 11, the subject developed a thrombophlebitis of the left leg; this adverse event was considered mild and not serious and was treated with a heparin-like medication. No diagnostic tests were performed, study drug was not stopped, and the subject completed the study on 4FEB99.

Reviewer comment: this subject was using Mercilon throughout the study. This is another example of a participant in the European trial -003 who was treated with a "heparin-like medication" with resolution of her symptoms, and continuation in the trial. The reviewer did not find a CRF for this subject.

Subject 11020 (Study CONT-001), age 38, non-smoking, in the 15 cm^2 transdermal patch group was discontinued on Day 36 due to thrombosis. On Day 27 she reported right leg pain which was treated with acetaminophen. The leg pain was diagnosed by standard duplex ultrasound techniques, in addition to color flow, as a non-occlusive thrombus of the greater saphenous vein. It was marked in severity and considered probably drug related. The thrombosis resolved eight days after onset.

Reviewer comment: the treatment was local therapy for the pain and swelling. There was no history of clotting events although the subject had a history of a saphenous vein ligation with injections in 1993. Because of the AE, the subject was discontinued from the study. The reviewer agrees with the diagnosis and discontinuation from the study.

From page 92 of the ISS: in the Phase 3 trials, there have been a total of 22,176 cycles of experience with EVRA, which equates to 1,706 women-years of experience with EVRA. A final disposition of the above cases shows two confirmed cases of thrombotic events, both pulmonary emboli (Subjects 1181, and 21022). Case 21022, while associated with EVRA, was a case of improper use of EVRA. There was also a case in association with Mercilon, which is not believed to be a true case because no diagnostic procedures were performed, study drug was not stopped, and the subject successfully completed the study.

The observed cases of clotting attributable to EVRA and associated with the proper use of EVRA therefore number one (Subject 1181) during 1,706 women-years of observation. For EVRA, with 1,706 women-years of observation and one attributable case of clotting associated with proper use of EVRA, the estimated rate of deep vein thrombosis/pulmonary embolus is [1x100,000/1706] 59 cases per 100,000 women-years. The 95% confidence interval on this observed rate is 0 to 174. The published incidence rates of nonfatal venous thromboembolism (VTE) from a recent review [Drugs 2000; 60 (4):721-869] of currently marketed oral contraceptives ranged from 18 to 41 cases per 100,000 women-years. In the same review, the incidence of VTE associated with pregnancy ranged from 59 to 90 cases per 100,000 women-years across studies; and the incidence of VTE in women not taking OCs is not more than 11 cases per 100,000 women-years. OC formulations containing ≥50 mcg EE are associated with a VTE rate of 82 cases per 100,000 women-years.

Reviewer comment: THE REVIEWER DOES NOT AGREE WITH THE SPONSOR'S ABOVE CONCLUSIONS. The two cases of pulmonary embolus, a serious and potentially fatal condition, must be counted as two cases in the primary safety group. In actual use many women [such as

Subject 21022] may not always use a drug approved for chronic use according to the proper or labeled directions. So we cannot ignore this case just because of a protocol violation.

The incidence rates quoted by the sponsor may be misleading. The Committee for Proprietary Medicinal Products (CPMP), the scientific group for human drug use in Europe, just published on 9/28/01 its assessment on the risk of VTEs associated with the use of so-called third generation combination oral contraceptives (COCs). It must be emphasized that some experts consider norelgestromin (17d-NGM) to be a third generation progestin. The CPMP concludes in its report that:

- **The risk of VTE is highest within the first year a woman ever uses a COC of any type**
- **There are currently insufficient epidemiological data on the risk of VTE for COCs containing progestins other than levonorgestrel, desogestrel, or gestodene**
- **The risk of VTE can be summarized as follows:**
  - 5-10 cases per 100,000 women-years for healthy women between 15-44 years old not taking COCs
  - 20 cases per 100,000 women-years for women taking COCs with <50 μg EE in combination with levonorgestrel
  - 30-40 cases per 100,000 women-years for women taking COCs containing at least 20 μg EE in combination with desogestrel or gestodene
  - 60 cases per 100,000 pregnancies for women while pregnant

The four SAE reports of cases of thrombosis or phlebitis [Subjects 23027, 5155, 71032, 11020] are of less importance because all four were superficial, treated symptomatically, resolved easily, and no DVTs were documented. Subject 2040 was placed on prophylactic SC anticoagulation because of a leg fracture and cast, and completed the study, so this is a case of VTE prevention in a woman at risk. It is surprising that she was not withdrawn from the study by the investigator.

The CPMP's report states that the risk of VTE is highest within the first year a woman ever uses a COC of any type. In the Phase III trials, only 26.6% of the women were "fresh starters," and presumably at higher risk of VTE. Many of these subjects, however, could have been previous COC users, but by sponsor definition not within the previous two months. Once marketed, EVRA™ may have a much higher percentage of true starters [first-time-ever users] who will be in the CPMP's group at highest risk of VTE. The two cases of PE occurred in women who were "direct switchers" from a marketed combination oral contraceptive and therefore presumably at lower risk of VTE.

The sponsor's estimated rate of deep vein thrombosis/pulmonary embolus for EVRA™ is 59 cases per 100,000 women-years [1 case x 100,000/1706 with 95% CI 0,174]. The reviewer's rate is 118 per 100,000 women-years, double the sponsor's rate, because both cases of PE must be counted. The 95% CI around the reviewer's rate is 14.2, 424. Although this rate is not statistically significant compared to the sponsor's estimated rate of VTE, it is still clinically important and of potential concern. Further discussion is found in the Reviewer's Summary of Safety at the end of this review.

4.9.4 Adverse Events by Subgroups of Subjects

From the ISS, for the Principal Safety Analysis Group, the incidence of treatment-emergent adverse events (TEAEs) is summarized by age, race, and weight. These summaries are provided for all subjects in the analysis group who received EVRA and by treatment regimen for subjects in the comparative studies -004 and -003. The incidence of most of the individual adverse events was too low to evaluate any potential associations between these demographic characteristics and adverse event frequency.

Among the frequently reported treatment-related adverse events, the incidence of gastrointestinal complaints (primarily abdominal pain and nausea) and dysmenorrhea tended to be higher among the younger versus older subjects. Application site reactions among EVRA subjects tended to be reported with a higher incidence by younger

compared to older subjects. Although the evaluation of the influence of race on adverse event incidence is of limited value because of the predominance of white subjects in the three Phase 3 studies, common gastrointestinal complaints, breast symptoms, and dysmenorrhea appeared to occur more frequently among white compared with non-white subjects who received EVRA. Few differences in the incidence of individual adverse events were observed between subjects with low and high body weights. However, a somewhat higher incidence of nausea and breast symptoms in subjects with lower versus higher weights was a relatively consistent finding. Taken together, an examination of adverse event incidence by age, race, and weight revealed some apparent differences in the incidence of various treatment-related adverse events, but the results did not suggest a notable increase in risk for any demographic subgroup who received EVRA treatment. Results of a population pharmacokinetic analysis, which examined the effects of age, race, and weight on 17d-NGM and EE pharmacokinetics, are summarized in the biopharmacology section of the NDA submission and in the Division's biopharmacology review.

Reviewer comment: this reviewer agrees with the sponsor's overview and assessment of AEs in the three subgroups [age, race, and weight]. Although there are some small differences, they do not appear to be clinically significant and are therefore not a concern. Median ages were 28 years for the EVRA™ subjects in the Primary Safety Group. Racial distribution showed 91% Caucasian and 9% non-Caucasian. Median weights were 63 kg (~139 pounds). It is interesting to note that a population PK analysis revealed that non-white subjects who received EVRA™ tended to have higher steady-state plasma concentrations of 17d-NGM, but not EE, than did Caucasian subjects. The same study showed that increasing body weight in EVRA™ subjects was associated with decreasing steady-state plasma concentrations and AUCs of both 17d-NGM and EE.

4.9.5 Clinical Laboratory Evaluations

Overview from ISS:

In the Principal and Supportive Safety Analyses Groups, up to 13 cycles of EVRA treatment were not associated with clinically important mean changes in hematology or chemistry laboratory analytes. In these studies, treatment-emergent markedly abnormal laboratory findings were rarely observed, and there was a low incidence of laboratory abnormalities reported as adverse events, regardless of treatment (EVRA, placebo, or oral contraceptive comparators).

Lipid metabolism: In Study CONT-005, treatment with EVRA resulted in a significantly ($p<0.001$) greater increase in total HDL cholesterol than placebo from baseline to Cycles 3, 6, and 9. Neither EVRA nor placebo treatment resulted in clinically significant changes from baseline in the LDL/HDL ratio when calculated using LDL by direct measurement. These findings indicate that EVRA treatment does not result in changes in serum lipid profiles associated with increased cardiac morbidity and mortality. When LDL is assessed by methods used in the development of the NCEP lipid criteria (Friedewald calculation), an improvement in the lipid profile was suggested. Results of adverse event monitoring and serum lipid laboratory evaluations performed for EVRA subjects during other clinical studies are consistent with the absence of deleterious effects on serum lipid profiles observed in Study CONT-005.

Coagulation: In Study CONT-006, EVRA, like Mercilon or Triphasil, increased the conversion of prothrombin to thrombin and resulted in increased levels of fibrin degradation products d-dimer; there were no statistically significant differences between the three treatments in these effects. Moreover, no case of clinical thrombosis occurred in this six-cycle study.

Reviewer comments: mean changes in lab values or any other parameter are not very helpful as the increases and decreases often tend to balance out, therefore resulting in "no significant change" in the parameter being measured from baseline to the last time point. What is often more meaningful is the change over time for individual subjects, and not the mean change for the entire group collectively.

It is somewhat illogical that if EVRA™ resulted in a significantly greater increase in HDL than placebo, that it did not result in a clinically significant change in the LDL/HDL ratio. In any case, no special claims can be made based on Study -005. The reviewer agrees, however, with the statement about "the absence of deleterious effects of EVRA™ on serum lipid profiles."

In Study -006 it should be noted that the sample size was ~35 subjects in each of the three arms. The sponsor notes that no case of clinical thrombosis occurred in the 6-cycle study [total women-years exposure was < 50], but the much larger Principal Safety Analysis Group had two cases of pulmonary embolus.

4.9.5.1 Markedly Abnormal Changes in Lab Findings (hematology, chemistry, and lipid profiles)

Hematology and chemistry:
The incidence of EVRA subjects in the Principal Analysis Group who had markedly abnormal laboratory findings is summarized in Table 9.2.2 in the submission. For all five hematology and seven chemistry analytes evaluated, the incidence of markedly abnormal test results was low, ranging from 0 to 4.0% and 0 to 1.0% in the hematology and chemistry parameters respectively. In most cases, the abnormal findings did not have any clinically significant consequences. There was a low incidence of markedly abnormal laboratory test results observed in the comparative studies that comprise this analysis group, regardless of treatment (EVRA or Triphasil in Study CONT-004 and EVRA or Mercilon in Study CONT-003).

Reviewer comment: the reviewer concurs with the sponsor's range of "markedly abnormal values" and finds no abnormal hematology or chemistry findings that are a clinical or safety concern.

Lipid metabolism:
In a randomized, double-blind, Phase 3 study, CONT-005, lipid evaluations were performed for all subjects who took study drug (EVRA or placebo) for at least one day, and provided measurements at baseline and at least one post-baseline measurement. For each parameter in the lipid profile (total HDL, calculated LDL, calculated LDL/HDL ratio, measured LDL, measured LDL/HDL ratio, total cholesterol, HDL $_2$ cholesterol, HDL $_3$ cholesterol, and total triglycerides), the changes from baseline (with standard error [SE]) to Cycle 3, Cycle 6, and Cycle 9, and to the last available visit, was calculated. For apolipoproteins (A-1, A-2, B), the change from baseline to Cycle 9 was calculated. Results of these evaluations are summarized in Table 9.3.1 in the submission.

The EVRA group had greater mean values and significantly greater mean increases from baseline ($p<0.05$) for several lipid parameters (total HDL cholesterol, measured LDL cholesterol, total cholesterol [except Cycle 6], and total triglycerides) compared with the placebo group. The mean increases in total HDL cholesterol values in the EVRA group were entirely in the HDL $_3$ cholesterol subfraction, which is supported by the mean increases in apolipoproteins A-1 and A-2. When the calculated LDL cholesterol is assessed (Friedewald method), there is no clinically meaningful change in the LDL level during treatment with either EVRA or placebo and no significant difference between the two treatments. The calculated LDL/HDL ratio shows a favorable decrease for EVRA and an unfavorable increase for placebo. The difference in the change from baseline for the calculated LDL/HDL ratio between EVRA and placebo was statistically significant. Although the measured LDL/HDL ratio was slightly greater in the EVRA than placebo group at all timepoints, the mean change from baseline in the measured LDL/HDL ratio was not significantly different between the two groups up to nine cycles of treatment.

Reviewer comment: Study CONT-005 was a double-blind group-comparative evaluation of 99 EVRA™ and 47 placebo patch users over 9 cycles. The statements about the calculated LDL/HDL ratio made in the overview and in the subsequent analysis are contradictory. The overview states "neither EVRA nor placebo treatment resulted in clinically significant changes from baseline in the LDL/HDL ratio when calculated using LDL by direct measurement," whereas the above states "the calculated LDL/HDL ratio shows a favorable decrease for EVRA and an unfavorable increase for placebo. The difference in the change from baseline for the calculated LDL/HDL ratio between EVRA and placebo was statistically significant." As commented earlier, much of the analysis is

comparing mean changes from baseline for the entire group of EVRA™ users and not for individual subjects. Furthermore, the study was not designed to show superiority, and had only one comparative group when additional groups 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 no special claims can be made based on the -005 study. As stated above, the reviewer agrees, however, with the statement about "the absence of deleterious effects of EVRA™ on serum lipid profiles."

Coagulation/Fibrinolytic activity:
Oral contraceptive use is associated with a variety of changes in concentrations of hemostatic factors and in the results of in vitro coagulation and fibrinolysis function tests. The general view is that oral contraceptive use activates both coagulation and fibrinolytic pathways, perhaps in a balanced fashion. The relationship between these changes and the propensity to clot has not been definitively established. Study CONT-006 was designed to evaluate and compare the effects of EVRA, Mercilon, and Triphasil on coagulation parameters.

The primary coagulation parameter used in Study CONT-006 was Prothrombin Fragment 1+2, which was selected because it appears to be the most sensitive marker for the effects of oral contraceptives and the least sensitive to blood sampling and handling artifacts. The primary endpoint for statistical purposes was the comparison of EVRA versus Mercilon and EVRA versus Triphasil (or Trinordial in Europe) for the change in baseline to Cycle 6/Day 20 for Prothrombin Factor 1+2. Additional parameters evaluated in Study CONT-006 included factors explaining changes in prothrombin fragment 1+2 (protein S, PT, activated protein C resistance, antithrombin III, glucose, and SHGB), fibrinolysis activity markers (fibrin degradation products d-dimer [FDP d-d] and plasmin- α_2-antiplasmin), and factors related to liver metabolism (C-reactive protein, fibrinogen) or extrinsic system activity (APTT).

Reviewer comment: taken together, the reviewer agrees with the sponsor's conclusions that the results of the primary evaluations showed that EVRA™, like Mercilon and Triphasil, increases the conversion of prothrombin to thrombin and results in increased levels of FDP d-d; and that there were no significant differences between the three hormonal drugs in these effects. The observed changes in the primary markers and the other coagulation markers and factors related to liver metabolism and extrinsic activity are expected findings during treatment with combination hormonal contraceptives. The changes in these secondary factors were similar for subjects who received EVRA™ or one of the two oral contraceptive comparators (Mercilon and Triphasil).

4.9.6 Dermal Safety Evaluations

From the ISS: four clinical studies (PHI-007, PHI-008, PHI-009, and PHI-011) were conducted specifically to evaluate aspects of the dermal safety of the EVRA patch and various control patches (vehicle [placebo] and positive and negative controls). In these studies, transdermal application of both the EVRA and vehicle (placebo) patches showed evidence of mild primary irritation potential. Compared with the vehicle patch, the EVRA patch did not demonstrate any potential for producing phototoxicity, delayed contact sensitization, or photoallergic reactions. Overall, the results of the four clinical dermal safety studies, which suggest that EVRA use is associated with only mild irritation potential, were consistent with the findings from animal dermal irritation and sensitization studies and with the skin irritation data obtained during the Phase 3 clinical studies. In the Phase 3 studies, there was a low incidence of patch changes resulting from skin irritation, and an even lower incidence of treatment-limiting application site reactions.

Reviewer comment: the four dermal studies demonstrated the safety of the patch. The use of over 70,000 patches in the Phase 3 studies is further demonstration of both the safety and acceptance of the 20 cm^2 transdermal delivery system for combination hormonal contraception. For all cycles combined in the Phase 3 studies, 9.0% of the 3,330 EVRA™ subjects changed at least one patch because of skin irritation. Most of the reactions at the application sites were mild or moderate in severity and none of the reactions were serious.

Changes in vital signs, weight, Pap smears

Overview: vital sign and body weight data obtained in the Phase 2 and 3 studies were examined for mean changes from baseline to the end-of-study visit, and to identify subjects who had markedly abnormal values during study drug treatment. In these studies, systolic and diastolic blood pressure, pulse rate, and weight showed mean changes from baseline to the end-of-study visit that were not clinically significant. There was also a low incidence of markedly abnormal findings at the end-of-study visit, regardless of treatment (EVRA or comparators). Among EVRA subjects in the Principal Analysis Group (Studies -002, -003, and -004), the incidence of end-of-study systolic blood pressure, diastolic blood pressure, or pulse rate measurements that were markedly abnormal was less than 1%. Only 69 subjects (2.2%) had >10% increases from their baseline body weights at the end-of-study visit. The incidence of markedly abnormal vital sign or weight measurements was low and comparable for subjects who received EVRA or Triphasil in Study -004. Vital sign and weight results in the Supportive Safety Analysis Group were consistent with those observed in the three Principal Safety Analysis Group. Further, the low incidence of markedly abnormal vital sign and weight results observed in all of these studies is consistent with the low incidence of vital sign/weight abnormalities reported as adverse events.

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 TLAE (reason for discontinuing from the study). It is interesting to note from the sponsor's data that 7.2% of subjects experienced at least a 5% increase in weight and 10.0% had at least a 5% decrease in weight. With other combination hormonal contraception products weight gain can be a troublesome side effect. The percentage of women who had an increase in their weight is represented in the following reviewer Table 26 by actual pounds gained and not as a percentage change of their baseline weight:

Table 26 Weight gain during Phase III Studies

Category	n	% of total N (3,088)	
[redacted]	[redacted]	[redacted]	6.9%
[redacted]	[redacted]	[redacted]	
10-15 lb. Increase	147	4.8	
5-10 lb. Increase	430	13.9	
Within 5 lb. of baseline	2,015	65.2	

Looking at the above data, a total of 211 women (6.9%) using EVRA™ had at least a 10 pound weight gain and over 2% [redacted] had at least a 15 pound weight gain. Stating the data in this manner is more meaningful to the reviewer and consumer than the sponsor's statement that "only 69 subjects (2.2%) had >10% increases from their baseline body weights at the end-of-study visit" or that "there were no clinically important mean changes in body weight during the studies, regardless of treatment." As noted before, mean changes tend to balance the increases with the decreases and can be very misleading. The final label should not use the expression "mean change in body weight from baseline to end of treatment." Including specific data such as presented in Table 26 above would be more informative for the prescribing healthcare provider and the consumer (user).

Pap smear:
Based on Pap smears obtained at baseline and posttherapy, EVRA treatment was associated with a low incidence of cervical dysplasia and no malignant findings. Among the EVRA subjects in the Principal Analysis Group, the baseline incidence of abnormal Pap smear results was 6.9% (including 3.1% with benign cellular changes). At

posttherapy, the incidence was 9.6% (including 3.0% with benign cellular changes); similar results were found in the comparative Study -004, regardless of treatment (EVRA or Triphasil), and in the Supportive Safety Analysis Group in which Pap smears were obtained.

Reviewer comment:
At first impression it is of concern that there was an increase of 2.7% in the abnormal Pap smears by the end of treatment. This increase represents, however, the spectrum of changes from ASCUS (atypical squamous cells) to high-grade squamous intraepithelial lesions (HGSIL). Of major clinical significance is the incidence or change in HGSIL, which changed from 0.2 to 0.4% with the EVRA™ users. This very small increase is not unusual for this study population, namely, sexually active women ages 18-45. None of the abnormal findings were malignant.

Microbiology results: the microbiological limit test and its validation were reviewed by the microbiologist who recommended that the following comments be conveyed to the sponsor. "Concerning the quantitative portion of the Microbial Limit Test for the EVRA™ transdermal system, please note that the use of "recovery factor" and its application to results of Microbial Limit tests may not be necessary or desirable. Since variation in microbial counts are commonly accepted as normal in the aerobic plate count method, the use of "recovery factor" as described may only result in a false sense of precision."

Reviewer comment: the microbiologist's comment was sent to the sponsor on 4-17-01. No response has been received yet, but this is not a clinical or review issue.

4.9.7 Pregnancy outcomes

The pregnancy outcome for the 16 during-treatment pregnancies in the three large studies showed that at least 9 EVRA™ users continued with the pregnancy, 3 had pregnancy terminations, and the others were undecided or lost to follow-up.

Reviewer's comment: according to the sponsor, all 12 infants for whom birth reports were available were reported to be normal with normal birth weights. This included 9 pregnancies "on-therapy" with EVRA™ use and 3 pregnancies "on-therapy" with use of a comparator oral contraceptive. Review of the infant follow-up reports shows that the gestations were between 37-42 weeks and the birth weights were from 2,727 to 4,885 grams. No congenital anomalies or other problems were noted.

4.10 Annual Safety Update

The sponsor's latest annual safety update was reviewed [submission N-107, CDER stamp 10-02-01] . Studies PHI-022 and -023 were still ongoing as of 4-30-01. There were no additional reported SAEs and no deaths in the trials that were either recently completed [since the NDA submission in December 2000] or are ongoing since the previous annual safety report.

5.0 REVIEWER'S SUMMARY OF EFFICACY

In summary, EVRA™ shows adequate contraceptive efficacy in three large multicenter Phase III studies. With an overall Pearl Index [combined studies, AST, all ages] of 0.94 per 100 woman-years and 13-cycle Life Table cumulative pregnancy rate of 0.8%, it is acceptable for approval for pregnancy prevention. If only women ages 18 to 35 are considered [18,296 cycles with 1,407 women-years of drug exposure], the sponsor's overall Pearl Index is 1.00 and the reviewer's overall Pearl Index is 1.07 due to one additional pregnancy in the reviewer's analysis. For women ages 36 to 45, the PI is 0.34, which is consistent with the natural decline in fertility with increasing age. Cycle control and patch compliance are also adequate and acceptable.

6.0 REVIEWER'S SUMMARY OF SAFETY

In the entire All Treated Subjects group for EVRA, there were >3,500 women who completed over 24,000 cycles of use. Although this represents a large safety database, conclusions concerning safety relate to a population of women, predominantly Caucasian (91%), mean age ~28 years, who used EVRA for up to 13 cycles and who were recent (within 2 months) or current OC users at least 75% of the time. In general, analyses of serious AEs, frequent AEs, discontinuations due to AEs, changes in lab values, changes in physical and pelvic findings show similar results for the three large trials and comparable to findings with other combination hormonal contraceptive products.

Of 3,330 EVRA-treated subjects, 399 women (approximately 12%) discontinued due to an AE, with 69% of the treatment-limiting AEs (TLAEs) due to breast symptoms, application site reactions, nausea/vomiting, headaches, or emotional lability.

The seven most commonly reported AEs in the AST group (N= 3,330) were breast symptoms (22%), headache (21%), application site reaction (17%), nausea (17%), upper respiratory tract infection (10%), dysmenorrhea (10%), and abdominal pain (9%). There did not appear to be an increased incidence of these common AEs with long-term EVRA™ 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 in this review is the increased risk of venous thromboembolism (VTE) with use of combination hormonal contraceptives containing third generation progestins, notably desogestrel and gestodene. Norelgestromin (17d-NGM), the new molecular entity progestin released from the EVRA™ patch, is considered by some experts to be a third generation progestin [1]. Many of its metabolic and coagulation properties are similar to desogestrel and gestodene. With the exception of the Burnhill article [9], all of the epidemiological studies cited in this review concerning increased risk of VTE, however, implicate only desogestrel and gestodene, partially because of the lack of epidemiological data and medical reviews with OCs containing norgestimate (NGM) or its primary metabolite norelgestromin. The Burnhill article, based on US Planned Parenthood Federation data, concluded that when desogestrel was used for the basis of comparison, norgestimate, norgestrel, and norethindrone carry a higher risk of DVT, but norgestimate and norethindrone have a statistically significant lower risk of PE, and hence a lower risk of associated death.

The combined studies with >3,500 subjects using ORTHO-EVRA™ for over 1,750 woman-years of exposure, reported two subjects with a pulmonary embolus (PE):

1. **30 year old white South African non-smoking female, G2P2, direct switch from OC use, was hospitalized during Cycle 10, diagnosed with a PE [normal leg Doppler, normal ventilation scan, 4 abnormal perfusion scans], and anticoagulated. A coagulation profile performed 6 months later was normal.**

[1] See footnote 1 on page 11.

2. **34 year old white American non-smoking female, G2P2, direct switch from OC use, who late during Cycle 3 discontinued her patch the day before elective cosmetic surgery (including breast augmentation, abdominoplasty, and liposuction); 19 days post-op she was re-admitted with a PE, treated with IV heparin for 4-5 days, and switched to subQ Lovenox (enoxaparin) for 6 days + Coumadin for 6 months.**

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 were two non-fatal pulmonary emboli in the >1,750 woman-years of exposure to EVRA. This translates to an occurrence of non-fatal VTE of ~114/100,000 woman-years (95% CI 14,424). The point estimate here is high, but the 95% CI is not significantly different from the WHO estimate of VTE risk in OC users. This may not be a valid comparison because the WHO study was based on a retrospective analysis of COC use in Europe where norgestimate-containing products are seldom used. It should also be noted that compared to the NDA submissions of OCs previously approved by the FDA, this PE occurrence is not significantly different, although PEs have rarely been reported in the NDA clinical trial databases [2 suspected and 3 confirmed pulmonary emboli in 19 previous reviews].

In studies of this size one is not likely to see a difference in safety parameters such as DVT, PE, stroke, or MI which have continued to be a subject of concern with regard to two third generation progestins (desogestrel and gestodene). In 1995, four studies found a higher risk for VTE for third generation OCs as discussed on pages 12-13 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. [16] According to epidemiology professor JP Vandenbroucke,[17] 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)."

Reviews of the increased risk of VTE with desogestrel by RMC Herings (*Lancet* '99)[18], AM Walker (*Contraception* '98)[19], 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 and gestodene 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). [20]

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).[21] 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." The European Agency for the Evaluation of Medicinal

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[16] Vanderbroucke JP. Medical journals and the shaping of medical knowledge. *Lancet* 1998; 352: p. 2001-06.
[17] Vanderbroucke JP. Competing interests and controversy about third generation OCs. *British Journal of Medicine*; 2000; 320: p. 381.
[18] Herings RMC, Urquhart J, Leufkens HGM. Venous thromboembolism among new users of different oral contraceptives. *Lancet* 1999; 354: p. 127-28.
[19] Walker AM. Newer oral contraceptives and the risk of venous thromboembolism. *Contraception* 1998;57:169-81.
[20] Bloemenkamp KWM, et. al., Correspondence: Venous thromboembolism and OCs. *Lancet* 10/23/99; 354: p. 1469.
[21] Parkin L, Skegg DCG, etonogestrel. al., Oral contraceptives and fatal pulmonary embolism. *Lancet* 6/17/2000; 355: p. 2133-4.

Products through their special CPMP committee recently (9/28/01) issued their assessment of VTE risks in combination hormonal contraceptive users as discussed in this review (page 43).

In summary, review of the literature from the past six years continues to show a safety concern of an increased risk of VTE, especially deep vein thrombosis (DVT), in third generation progestin-containing oral contraceptives compared to second generation OCs. The two cases of PE in these three large trials is not statistically significant compared to approved third generation progestin-containing OCs marketed in the United States. In this reviewer's opinion, however, there remains a definite clinical concern about the possibility of an increased risk of VTE events with EVRA™, containing norelgestromin, a NME not yet universally classified as to its progestin generation. The concern is based on both the literature and the results from the EVRA™ trials. With approval of this product, the label should clearly reflect this reviewer's safety concern about a potential increased risk of VTE in EVRA™ users.

7.0 REVIEWER'S COMMENTS ON PROPOSED LABELING

The proposed labeling is a combination of the old class labeling for OCs, the June 1999 *draft* guidance for OC class labeling, the recent NuvaRing® label [because it is an NME and the first transvaginal delivery system for hormonal contraception], and other special considerations.

Class labeling for OCs is being revised and should generally apply to this new combination hormonal contraceptive. **The possible increased VTE risk should be incorporated into the EVRA label. This could be effectively accomplished by adding a statement similar to the third generation oral contraceptive VTE statement found in subsection 1. a. Thromboembolic Disorders and Other Vascular Problems in the WARNINGS section or by stating the clinical finding of the two cases of pulmonary embolus.**

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 norelgestromin. These changes will be incorporated into the final label.

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

- EVRA™ application and removal
- WHEN to start the FIRST patch
- Day 1 start vs. later start vs. Sunday start
- What to do during the month
- What to do if the patch is inadvertently removed or partially loose
- What to do if any patch is used for > 7 days
- When to use a "back-up" method of contraception
- Disposal of a used EVRA™ patch

The final EVRA label may include the following clinical statement placed after Table II, (from Hatcher et al., *Contraceptive Technology*, 1998):

> **In three large clinical trials in North America, Europe and South Africa, 3,330 women (ages 18-45) completed 22,155 cycles with EVRA™ use and approximately 1 pregnancy occurred for every 100 women-years of use. About 17% of the women were age 36 to 45. These rates include women who did not use the EVRA™ patch as directed (per protocol).**

8.0 REVIEWER'S RECOMMENDATIONS FOR REGULATORY ACTION

Approval of EVRA™ as the first transdermal combination hormonal contraceptive in the USA is recommended for prevention of pregnancy. The Final Printed Label (FPL) should reflect the possible increased risk of venous thromboembolism (VTE) associated with this new transdermal combination hormonal contraceptive containing the new molecular entity progestin, norelgestromin (17d-norgestimate). 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 three large clinical trials, such as number of subjects, cycles of exposure, pregnancies or Pearl Indices, common AEs and discontinuations due to AEs. Limited, specific information about bleeding patterns (cycle control) with initial use and extended use (up to 13 cycles) is included in the label. 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 patch are well illustrated and acceptable. The FPL also addresses issues that are unique to this new delivery system, such as partial separation of the patch, prolonged use of the patch, and accidental removal.

Post-marketing surveillance for DVT and PE events will be important, as these are potential serious adverse risks (with two cases of pulmonary emboli in the clinical trials) with this new delivery system for contraception containing a NME progestin that is the active metabolite of norgestimate.

11/06/2001

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

Dena Hixon, M.D.
Team Leader, DRUDP

cc: Daniel Davis, M.D.
Dena Hixon, M.D.
Dan Shames, M.D.
Johnny Lau, Ph.D.
Amit Mitra, Ph.D.
Moh-Jee Ng, M.S.
NDA 21-180
Division file
DFS: to be electronically submitted by the medical officer

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ON ORIGINAL

Table 27 LIST OF NDA 21-180 ABBREVIATIONS/ACRONYMS

Commonly Used Abbreviations and Acronyms in Medical Officer Review	
AE	adverse event
AST	All-Subjects-Treated
BMI	body mass index
CDER	Center for Drug Evaluation and Research
CI	Confidence Interval
COC	combined oral contraceptive [estrogen + progestin]
CRF	case report form
DRUDP	Division of Reproductive/Urologic Drug Products
DSG	desogestrel
DVT	deep vein thrombophlebitis
EC	emergency contraception
EDC*	estimated date of conception*
EE	ethinyl estradiol
ENG	Etonogestrel
EURO	European [usually refers to study CONT-003]
FDA	Food and Drug Administration
FPL	Final Printed Label
GSD	gestodene
IND	Investigational New Drug
IRB	Institutional review board
ISE	Integrated summary of efficacy
ISS	Integrated summary of safety
ITT	Intent-to-treat
LMP	Last menstrual period
LNG	Levonorgestrel
MOR	medical officer review
NDA	New Drug Application
NME	New molecular entity
Ob/Gyn	Obstetrics and gynecology
OCs	oral contraceptives
PE	Pulmonary embolus
PP	Per Protocol
RWJPRI	Robert Wood Johnson Pharmaceutical Research Institute; the NDA sponsor
SAE	serious adverse event
STDs	sexually transmitted diseases
TEAD	Treatment-emergent adverse event
TLAD	Treatment-limiting adverse event
US	United States
VTE	venous thromboembolism

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

/s/

Daniel Davis
11/8/01 07:43:22 PM
MEDICAL OFFICER

Dena Hixon
11/19/01 01:22:08 PM
MEDICAL OFFICER
I concur.

Daniel A. Shames
11/20/01 11:10:01 AM
MEDICAL OFFICER

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ON ORIGINAL

NDA 21-180

ORTHO EVRA®
(norelgestromin/ethinyl estradiol) Transdermal Patch

R.W. Johnson Pharmaceutical Research Institute
1, 4S

PM: Jennifer Mercier
HFD-580
7-4260

Submission Date: December 21, 2000
Primary Goal Date: October 21, 2001
Secondary Goal Date: December 21, 2001

/S/

Safety Update

See Medical Officer review page 48

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA Number: N 021180
Trade Name: ORTHO EVRA(NORELGESTROMIN/ETHINYL ESTRAD
Generic Name: NORELGESTROMIN/ETHINYL ESTRADIOL
Supplement Number. 000 **Supplement Type**: N
Dosage Form:
Regulatory Action: ~~OP~~ AP **Action Date**: ~~12/21/00~~ 11/20/01
COMIS Indication: PREVENTION OF PREGNANCY

Indication #1: Prevention of pregnancy.
Label Adequacy: Does not apply
Formulation Needed: Other
Comments (if any) Safety and efficacy of Ortho Evra have been established in women of reproductive age. Safety and efficacy are expected to be the samefor post-pubertal adolescents under the age of 16 and for users 16 years and older. Use of this product before menarche is not indicated.

Lower Range	Upper Range	Status	Date
Adult	Adult	Waived	
11/21/01			

This page was last edited on 10/19/01

Signature /S/ Date 10/19/01

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ON ORIGINAL

ITEM 20: OTHER
REQUEST FOR WAIVER OF REQUIREMENT TO PROVIDE PEDIATRIC USE INFORMATION ON ORTHO EVRA™ AS PER 21 CRF 314.55

ORTHO EVRA™ is indicated for the prevention of pregnancy.

The development of the ability to conceive is the defining event in human biology that separates adults from children. The development of the ability to conceive is associated with endocrinological maturity and the attainment of maximum height. From a strictly biologic point of view, anyone who is in need of a product to assist in the "prevention of pregnancy" is an adult. In spite of these biologic facts all subjects age 16 years or less are classified as "pediatric" for labeling purposes. This means that for certain individuals between the ages of 10 and 16 biologically mature "adults" will be classified as "pediatric".

ORTHO EVRA™ was studied in biologically mature women who desired contraception. The subjects with the lowest age in the study population were 18 years old. The safety and efficacy of ORTHO EVRA™ is expected to be the same for all biologically mature women whether 18 years or older, or 17 years and younger.

Therefore a full waiver of the pediatric requirements [21 CFR 314.55(C.2.)] is hereby requested. The basis for this request is that the product is for prevention of pregnancy and that the indication defines the correct population of biologically mature individuals who are eligible for its use. Those eligible for the prevention of pregnancy are separated from their immature counterparts not based on age but on biology. This product would be unsafe if prescribed to pediatric patients based only on age because below age 16 there are individuals who have not attained their maximum height and who could be harmed by a reduction in maximum height through prolonged exposure to an estrogen product.

The safety and efficacy of ORTHO EVRA™ has been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents under the age of 16 and for users 16 years and older. Use of this product before menarche is not indicated.