CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-180

MEDICAL REVIEW(S)

NDA 21-180
ORTHO EVRA (norgestimate/ethinyl estradiol) Tablets

3S

R.W. Johnson

PM: Jennifer Mercier
7-4260
HFD-580

Submission Date: August 25, 2000
Goal Date: June 25, 2001

Clinical Section

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 20, 2001

FROM: Florence Houn MD MPH

SUBJECT: Office Director's Memo

TO: NDA 21-180 ORTHO EVRA (norelgestromin and ethinyl estradiol transdermal system)
The R.W. Johnson Pharmaceutical Research Institute

This memo documents my concurrence with the Division of Reproductive and Urologic Drug Products to grant marketing approval for ORTHO EVRA, a combination hormonal transdermal contraceptive indicated for preventing pregnancy. Three contraceptive efficacy studies support the effectiveness of the product and are thoroughly reviewed by the primary medical officer, team leader, and acting division director. Overall PEARL index for this product is similar to oral contraceptives. Safety was comprehensively reviewed by the division. Careful consideration was given to the two cases of venous thromboembolic events. This product increases the risk of venous thromboembolic events, as do other combined hormonal forms of contraception, and this fact is included in the labeling. This product has skin adherence and irritation problems, not found with oral contraceptions, but are not unexpected or unreasonable for the product. The advantages of this form of oral contraceptive are it may offer convenience and compliance over daily administration.

I've reviewed the action package. On November 2, 2001 I presented the Division my labeling comments: inclusion of the racial breakdown of the efficacy database and moving statements about efficacy failure in obese women forward to highlight this observation in the professional labeling and the patient labeling. The Division transmitted these comments to the sponsor and final labeling was agreed upon.

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/s/

Florence Houn
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ON ORIGINAL

HFD-580: DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS

Medical Officer's Review

NDA: 21-180 Ortho EVRA™

Date submitted: 12/21/00
CDER stamp: 12/21/00
CDER due date: 10/21/01, extended to 11/21/01
MOR completed: 11/06/01
Key words: contraception, EVRA patch, norelgestromin, ethinyl estradiol, transdermal contraceptive patch

Sponsor: R. W. Johnson Pharmaceutical Research Institute
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Drug names:
Generic: norelgestromin (NGMN) and ethinyl estradiol (EE)
Trade: Ortho EVRA™ (norelgestromin/ethinyl estradiol transdermal system)
Chemical: 17-deacetylnorgestimate (17d-NGM):
(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); combination hormonal contraception
Route of administration: transdermal patch
Dosage form: patch, matrix-type, three compartments (layers), flexible
Dosing regimen: each patch is worn for 7 days, then replaced with a new patch, to complete 21 days of continuous use, followed by a 7-day drug-free interval
Strength: patch contains 6.0 mg norelgestromin and 0.75 mg ethinyl estradiol **(EE)**
Days 1-7 release: ~ 150 µg/day of norelgestromin + ~20 µg/day of ethinyl estradiol

Proposed indication: Hormonal contraception

Related INDs:

Related NDAs:

NDA 19-653: Ortho-Cyclen (norgestimate 250 µg/EE 35 µg), a monophasic oral combination hormonal pill (COC) that gives similar exposure to the EE and norelgestromin (the active metabolite of the norgestimate contained in Ortho-Cyclen) released by the EVRA™ patch. Submitted 3/87; approved 12/89.

NDA 19-697: Ortho Tri-Cyclen, a triphasic COC (norgestimate 180-250 µg/EE 35 µg).

There have been no prior NDA submissions for a combination hormonal patch for contraception. Several submissions have been reviewed for a combination hormonal patch for estrogen replacement therapy in postmenopausal women. Recently NDA 21-187 was approved for a combination hormonal 21-day vaginal ring (etonogestrel/ethinyl estradiol) for contraception.

Table of Tables

TABLE OF CONTENTS

SECTION AND TOPIC **PAGE**

Executive Summary for NDA 21-180, Ortho EVRA™ transdermal system

I. Recommendations

A. Approvability:

Approval of EVRA™ as a transdermal combination hormonal contraceptive is recommended for prevention of pregnancy. The final printed label (FPL) should reflect the possible increased risk of venous thromboembolism (VTE) associated with this combination hormonal contraceptive based on the occurrence of two cases of pulmonary embolus in the clinical trials. Norelgestromin, the active progestin released from the transdermal patch, is the primary active metabolite of 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 demographic information, number of subjects, cycles of exposure, pregnancies, bleeding patterns (cycle control), common AEs and discontinuations due to AEs. 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 where to place the patch, prolonged use of the patch, partial detachment of the patch, and accidental removal.

B. Phase 4 Studies Recommendations

Public Outreach or Information: no specific Phase 4 studies are recommended. The reviewer's primary concern, however, is the possible increased risk of VTE and/or PE associated with the transdermal delivery of norelgestromin (17deacetyl-norgestimate) for combination hormonal contraception This issue is addressed in the review and the FPL.

II. Summary of Clinical Findings

A. Brief overview:

EVRA™ is a new delivery system for combination hormonal contraception using transdermal patches for the prevention of pregnancy. It utilizes three 7-day patches, each a 20 cm^2 patch applied to the abdomen, buttock, upper arm or torso for a total of 21 consecutive days followed by a 7-day patch-free interval.

This current NDA submission includes three large Phase 3 studies, CONT-002, -003, -004, each designed to accumulate information about the contraceptive efficacy, vaginal bleeding patterns, and safety of the EVRA™ regimen in generally healthy women, age 18 to 45, who elected to use transdermal hormonal contraception for the prevention of pregnancy. Each study was multicenter, open-label , 6 or 13-cycle, for efficacy and safety with the transdermal patch. Study 002 was non-comparative and conducted in 31 centers in the United States and 42 outside the US, while Study 003 was comparative (Mercilon OCs), conducted in 65 centers in European countries and South Africa, and Study 004 was comparative (Triphasil OCs), conducted in 39 US and 6 Canadian centers. **Since these studies were similar in design and the protocols were almost identical, the data from these three clinical studies have been primarily pooled for a combined analysis, but sometimes analyzed separately in the NDA submission and in the medical officer's review.**

Study -002 enrolled a total of 1,754 female subjects and treated (i.e. subject received at least one day's use of the study patch) 1,664 women for a total of 10,994 28-day cycles. Study -003 enrolled a total of 861 female subjects and treated 844 women for a total of 5,921 cycles. Study -002 enrolled 856 women and treated 811 for a total of 5,244 cycles. The agency goal of a total of at least 10,000 evaluable cycles was achieved. The total extent of EVRA™ use (evaluable for efficacy) in all the studies was 3,319 women treated for 22,159 cycles, comprising 1,704 woman-years of exposure.

B. Efficacy

The primary efficacy endpoint is on-therapy pregnancies in the sponsor's ITT evaluation group. This is in fact the all-subjects-treated (AST) group. One post-treatment pregnancy is reclassified by the medical officer as an on-therapy pregnancy. With this additional pregnancy, the Pearl Indices for the principal AST efficacy group increase from the sponsor's 0.88 to the reviewer's 0.94 calculation. For the 2,778 women age 18-35 years, the Pearl Indices increase from 1.00 to 1.07 for the three combined studies. The sponsor and reviewer Pearl Index for the combined 552 women age 36 to 45 years is 0.34; as expected, this result is lower compared to the younger age group because of lower fecundity (fertility) as women become older.

The primary efficacy results [combined and by individual study; overall and by subsets for age and per protocol use] are within an acceptable range compared to other approved combination hormonal contraceptives. Use as directed per protocol (the sponsor's "method failure" on-therapy) for the three AST groups results in a range of 0.6 to 1.0 pregnancies per 100 women per year, with an overall average of 0.7, which is similar to the pregnancy rates observed with use of COCs.

In spite of identical study designs and protocols, the discontinuation, efficacy, and cycle control results from the predominantly European Study 003 were slightly better than the US/Canadian Study 004. The demographic categories noted in the first 6 rows in the table below probably reflect population differences between the 12 European/ South African countries versus the US/Canada. It is difficult to know whether these differences would influence compliance, discontinuation rates, and efficacy. Some of the demographic and outcome differences are shown in the reviewer's table below:

Table 1 EVRA™ users (All-Subjects Treated) in Studies -004, -003, -002.

DIFFERENCES Category	**US Study 004** N= 811 treated	**EURO Study 003** N= 846 treated	**Multinational Study 002** N= 1672 treated
Caucasian subjects	85.7%	96.7%	91.1%
Black subjects	5.0%	1.2%	6.8%
Asian subjects	3.9%	0.4%	1.1%
Smoking- yes	21%	25.5%	25%
Baseline body mass index	23.8	22.6	23.3
Switch from OC use	73.3%	77.7%	75%
Switch from non-OC use	26.6%	22%	25%
Compliant cycles	90.5%	91.4%	91.8
Discontinued study	30%	20%	28%
% Subjects at Cycle 3 with Breakthrough bleeding/spotting	10%	14%	11%
% Subjects at Cycle 6 with Breakthrough bleeding/spotting	9.5%	9.3%	7.3%
Pregnancies during study	5	4	6 (7 per reviewer)
Overall Pearl Index (AST group)* **per Sponsor**	1.24	0.88	**0.71**
Overall Pearl Index (AST group)* **per Reviewer**	1.24	0.88	**0.83**

*The total is N= 3,319 with a combined overall Pearl Index of 0.88 (sponsor) and 0.94 (FDA reviewer)

Cycle control claims: the sponsor's primary analysis centered on per cycle breakthrough bleeding/spotting data rather than cumulative data per subject [called reference period analysis]. The sponsor's primary endpoint is Cycle 3. Daily recordings of vaginal bleeding were made for each of the 3,330 women who were treated from 1 to 13 cycles in the three large clinical trials. The sponsor had ample data from which to make non-comparative statements about expected menstrual bleeding (cycle control) and abnormal bleeding (breakthrough bleeding- spotting, amenorrhea, early withdrawal bleeding, and prolonged bleeding) while using EVRA™, so the Division requested specific information which was submitted in late October. **Analysis of the cycle control data showed the following findings for EVRA™ users during cycles 2-12:**

- The median day for onset of withdrawal bleeding was Day 25 (the fourth patch-free day)
- 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
  - 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
  - The OC comparators showed 16.3% and 13.7% on average per cycle [range
- 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 [

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/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.

C. Safety

With 3,330 women exposed to at least one day of EVRA™ use and 655 women completing 12 or 13 cycles of EVRA™ use, there is a solid database of safety information. Subjects were seen at 3-month intervals during the three major 6 to 13-cycle trials. Most (83.4%) of these 3,330 women using EVRA™ in the large clinical trials were 18 to 35 year-old Caucasians in good health. The smaller studies added safety information from 1,001 additional women exposed to EVRA™ for variable periods of time. Women in the 17 combined studies accumulated a total of 1,870 woman years of exposure to EVRA™.

The single death reported among EVRA™ subjects was a suicide. Of the 50 EVRA™ subjects with serious adverse events (SAEs) reported during the on-therapy period (extended to 30 days after last pill or patch use), 10 subjects had SAEs that were considered by the investigator or the sponsor to be possibly, probably, or definitely drug-related. **Two of the EVRA™ users had a pulmonary embolus (PE), although there were no documented deep vein thromboses (DVTs):**

1. During Cycle 10, a 30 year old white South African non-smoking female, G2P2, was hospitalized, diagnosed with a PE [normal leg Doppler, normal ventilation scan, abnormal perfusion scan], and anticoagulated. She went home on Coumadin and had a normal coagulation profile 6 months later.
2. Late during Cycle 3; a 34-year-old white American non-smoking female, G2P2, discontinued her patch one day before major elective cosmetic surgery (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.

Of EVRA™-treated subjects (N=3,330), approximately 12% discontinued due to an AE. The most frequent AEs (reported by ≥ 1% of subjects) leading to discontinuation included specifically: breast symptoms (N=63), application site reaction (N=62), nausea (N= 58), headache (N=38), and emotional lability (N=32).

The most commonly reported AEs in the AST group (≥9% in the trials, 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.

Few subjects had clinically significant abnormal values for hemoglobin, hematocrit, leukocyte count, and platelet count. Most of the clinically significant abnormal hematology values reported were for changes in lymphocyte and neutrophil differential count parameters, but these changes were not considered to be clinically relevant. Very few (2.7%) subjects had clinically significant abnormal blood chemistry values. In the combined studies, the most frequently occurring notable shifts in blood chemistry parameters were upward and downward shifts in blood glucose. For all other parameters the incidence of notable shifts in blood chemistry values was very low (≤ 0.5%).

The majority of subjects in all studies had no major changes in blood pressure during the studies compared to the screening assessment.

An increase or decrease ≥ 10% from the baseline weight was considered to be clinically significant by the sponsor. The reviewer considered an increase or decrease of ≥ 10 pounds from the baseline weight to be clinically significant. Using the reviewer's criteria, 211/3088 or 6.8% of EVRA™ users had a ≥ 10 pounds increase, and 134/3088 or 4.3% had a ≥ 10 pounds decrease. Using the sponsor's criteria, only 1.9% and 1.3% of subjects had a clinically significant increase or decrease, respectively.

The majority of subjects who received EVRA™ had normal pelvic examinations at screening and last visit. The majority of EVRA™-treated subjects had a cervical Pap class I at screening (92%) and at last assessment (89%). Clinically relevant shifts of note occurred for a total of 11 subjects with a normal Pap result at screening and a Pap class IIIb-IV (high grade SIL) at last assessment. At first impression this looks serious, but this represents only 0.33% of the 3,330 women in the three large trials. This low percentage is acceptable in a population of sexually active women age 18-45.

In the randomized, double-blind, Study CONT-005 several parameters of lipid metabolism were assessed during 9 cycles of EVRA™ use in a comparative placebo patch double-blind study in 138 women (93 EVRA™ and 45 placebo). For each lipid profile parameter, the changes from baseline to Cycles 3, 6, 9, and to the last available visit were calculated. For apolipoproteins (A-1, A-2, B) the change from baseline to Cycle 9 was calculated. EVRA™ had generally favorable effects on HDL-cholesterol [entirely due to increases in the HDL_3 cholesterol subfraction] relative to the placebo comparator. The sponsor's analysis, however, focused exclusively on mean changes for the EVRA™ subjects collectively relative to the placebo group, and not relative to baseline values of each drug. This study was not designed to show superiority, showed no clinically meaningful change in the LDL or triglyceride levels with either EVRA™ or placebo. The calculated LDL/HDL ratio "shows a favorable decrease for EVRA™ and an unfavorable increase for placebo" based on the increases in HDL_3 with EVRA™. The statistical and clinical significance of the results can 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 FPL.

In Study CONT-006 the small increases on coagulation parameters prothrombin fragment 1+2, fibrin degradation products d-dimer [FDP d-d], and plasmin α-2-antiplasmin seen in the EVRA group (N= 36) compared to Mercilon (N= 34) and Triphasil (N= 33) were similar and not statistically different. Taken together, the study results showed that EVRA™, like Mercilon and Triphasil, increases the conversion of prothrombin to thrombin and results in increased levels of FDP d-d, but without significant differences between the three treatment arms. The sponsor's analysis here is again comparative; more important, no major changes of concern were seen in these coagulation/fibrinolytic parameters in any of the three groups.

Pregnancy outcome data 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 lost to follow-up. The data for pregnancy outcome showed 9 term deliveries of healthy normal newborns with no anomalies.

The standard warnings and precautions for combination hormonal contraceptives should be followed in the FPL, with special attention to the fact that this will be the first transdermal delivery system marketed in the world for pregnancy prevention. Therefore, the FPL needs to state that it is unknown whether EVRA™ is distinct for many of the specific parameters listed in the class label for oral contraceptives. Special information should be included concerning the possible increased risk of venous thromboembolism (VTE or DVT) with this combination hormonal contraceptive.

D. Dosing

The dose and regimen have been adequately studied.

Unresolved efficacy questions are:

1) At what subject weight is the contraceptive efficacy unacceptable; 33% of the pregnancies occurred in women with a baseline weight ≥ 198 pounds (90 kg), yet this group comprised ~ 3% of the study population.
2) 27% (4/15) of the pregnancies occurred in women with baseline weights between 74-90 kg; it is difficult to assess the clinical and statistical significance of this finding, but the sponsor has readily acknowledged the increased risk of pregnancy in women weighing 198 pounds or more.

Unresolved safety questions are:

1) Is the transdermal delivery system and the relative steady-state serum hormone concentrations for 17d-norgestimate and ethinyl estradiol a factor in the two cases of pulmonary emboli seen in the three pivotal studies;
2) will the larger 20 cm^2 patch be as well tolerated with widespread use as it was in the clinical trials, and
3) does the sequential location of the three patches per cycle make a difference in terms of AEs and SAEs;

It is of note that there is limited data in African (Black) and Asian women as these racial groups comprised only 4.9% and 1.6%, respectively, of the 3,330 women in the combined three large clinical trials held throughout the US, Canada, Europe, and South Africa.

E. Special Populations

No studies were carried out in special populations. The 3,330 women enrolled in the 3 large clinical studies were generally healthy, ages 18-45, and Caucasian (91.0%). Post-marketing data will be needed for any meaningful conclusions concerning special populations, women under age 18, and non-Caucasian ethnic groups.

Daniel Davis, MD
Medical Officer, HFD-580
Reproductive/Urological Division

Clinical Review

1.0 INTRODUCTION

Transdermal delivery systems have been successfully developed for drugs to treat a variety of conditions; until now, none has been developed for contraception. Although estrogen-only patches and combination estrogen/progestin patches are available for the treatment of menopausal symptoms, transdermal delivery of sufficient levels of hormones for contraception has been difficult to achieve. A transdermal contraceptive system that can be worn for seven days should be convenient to use, and may increase subject compliance relative to traditional daily oral contraceptive use.

The sponsor, the R.W. Johnson Pharmaceutical Research Institute (RWJPRI), has evaluated the feasibility of delivering transdermally a combination of two contraceptive steroids. The progestin norelgestromin, the generic name for 17d-NGM, can be combined with the estrogen EE, and delivered from a transdermal system (patch) developed by [redacted] The seven-day EVRA transdermal contraceptive system is a square, flexible 20 cm^2 patch with radius corners. Each patch contains 6 mg of 17d-NGM and 0.75 mg of EE and, according to the sponsor, each day delivers to the systemic circulation 0.15 mg 17d-NGM and 0.02 mg (20 µg) EE. The laminated matrix system is composed of three distinct layers, as described below:

- a backing layer composed of a colored, flexible, occlusive backing film which provides protection and support to the drug-contact adhesive mix. The backing material is a two-layer barrier film, which consists of a low-density polyethylene pigmented layer, and a polyester layer.
- a contact adhesive layer consisting of polyisobutylene/polybutene (PIB) adhesive, 17d-NGM, EE, micronized crospovidone (PVP), and lauryl lactate.
- a disposable polyester film with a release coating of polydimethylsiloxane on one side which protects the drug-contact adhesive layer, and is removed by the wearer before use.

The sponsor's goal for the transdermal administration of contraceptive steroids is to provide contraceptive efficacy equivalent to that achieved with oral contraceptives, but with improved user compliance. Three patch sizes (10 cm^2, 15 cm^2, and 20 cm^2) have been investigated in clinical studies. EVRA is the 20 cm^2 patch. This size was selected for the Phase 2 and 3 clinical studies and contains 0.75 mg of EE and 6.0 mg of 17d-NGM. At the inception of clinical development, it was anticipated that the 20cm^2 patch would deliver a daily dose of 250 µg 17d-NGM/ 25 µg EE. The results of Study PHI-014 subsequently showed that the daily dose delivered to the systemic circulation by the 20 cm^2 patch is 150 µg 17d-NGM/ 20 µg EE. The results of the three pivotal contraceptive efficacy studies show that the EVRA™ patch provides contraceptive efficacy equivalent to that achieved with ORTHO-CYCLEN, a monophasic hormonal oral contraceptive containing 250 µg NGM and 35 µg EE in each pill.

> **Reviewer comment: the two products, EVRA and Ortho-Cyclen, were not compared directly in the same study for contraceptive efficacy. The sponsor is using the efficacy achieved with Ortho-Cyclen in its original Phase 3 clinical trials, which enrolled 1,647 women exposed to a total of 22,237 cycles. Ortho-Cyclen was approved in December 1989 with an overall Pearl Index of 1.02.**

The clinical program for Ortho EVRA™ was designed and performed in accordance with the relevant FDA guidelines for oral hormonal contraceptive formulations. This provided the basis for the total number of cycles of exposure, the number of subjects exposed for 13 cycles, as well as monitoring of major clinical endpoints (pregnancy, bleeding patterns).

There are six clinical studies that provide direct evidence of either the effectiveness of EVRA or pharmacodynamic data related to effectiveness. All six studies were conducted under [redacted] These include three Phase 2 studies (CONT-001, CONT-007, and CONT-008), providing pharmacodynamic data related to effectiveness, and three large Phase 3 studies (CONT-004, CONT-003, and CONT-002). The Phase 2 studies (see Table 2) evaluated

follicular development and cycle control, the effect of EVRA on endocrine endpoints, cervical mucus only, endometrial wall thickness and/or histology, and follicular development.

Table 2 Phase II Studies

Study objectives	Study Name		
	CONT-001	CONT-007	CONT-008
PK data	Yes	Yes	Yes
Follicular development	Yes		Yes
Cycle control	Yes		
Endocrine endpoints	Yes		Yes
Cervical mucous		Yes	
Endometrial changes		Yes	Yes

Phase 3 studies: two of the studies (CONT-003 and CONT-004) compared EVRA with an oral contraceptive (Triphasil® or Mercilon®) in contraceptive efficacy, safety, cycle control, compliance, and subject satisfaction. The third study (CONT-002), a large (N = 1,664) open-label, non-comparative trial, also provided effectiveness and safety data for EVRA. See Table 3 below listing the Phase III studies. The effectiveness data obtained from these investigations and relevant dose-ranging information from the pharmacokinetic and pharmacodynamic studies are summarized in the sponsor's Integrated Summary of Effectiveness (ISE). Subject listings (case report forms: CRFs) of all pertinent data are provided electronically for the three pivotal studies.

Reviewer comment: these studies were very similar in design and the protocols were almost identical. The data from the three clinical studies have been analyzed separately and also pooled for a combined analysis by the sponsor in the NDA submission. Where there are notable differences in the three major clinical trials, specific "Reviewer comments" will be made throughout this review. In general, however, the combined (pooled) data are acceptable.

Table 3 Phase III Efficacy/Safety Studies

Study Identifier Investigator(s)* (Country) Start Date	CONT-004 39 USA/ 6 Canada Oct. 17, 1997	CONT-003 54 Europe/ 11 South Africa Oct. 18, 1997	CONT-002 42 Europe/ 31 USA Nov. 7, 1997	Medical Officer Comment
Study Description/Design	Randomized, open-label, multicenter, 6 or 13 cycles	Randomized, open-label, multicenter, 6 or 13 cycles	Randomized, open-label, multicenter, 6 or 13 cycles	3 large open-label multicenter trials
# Subjects enrolled/evaluated	EVRA™ 856/ 811	EVRA™ 861/ 844	EVRA™ 1754/ 1664	3,319 women evaluable for efficacy with EVRA
	Triphasil 639/ 605	Mercilon 656/ 640		
Total cycles of exposure to EVRA	5,240	5,921	10,994	Total = 22,155
Total women-years of exposure	403	455	846	Total = 1,704
Comparator oral contraceptive (OC)	Triphasil triphasic with levonorgestrel/ ethinyl estradiol	Mercilon mono phasic with deso-gestrel/EE	NONE	Study -002 is non-comparative
Race	85.7% Caucasian	96.7% Caucasian	91.1% Caucasian	Predominantly Caucasian
Mean age	27.9 years	28.6 years	28.7 years	Range 18-45

2.0 BACKGROUND

Combination hormonal OCs are divided into three generations:

1. First generation: high dose OCs with greater than 50 mcg estrogens were developed first in the 1960s (Enovid in 1960 contained 150 mcg mestranol and 9.85 mg norethynodrel).
2. Second generation: in the1970s, the dose-response relationship between adverse events and the amount of steroids in the pill was appreciated and "low dose" OCs with the progestins norethindrone or levonorgestrel (LNG) + 30-50 mcg of estrogens were developed.
3. Third generation: were introduced in the late 1980s; these low dose estrogen OCs seemingly offered the androgenic metabolic effects (less adverse lipid profiles, especially in terms of cardiovascular disease) with new progesterone components involving variations on norgestrel (primarily gestodene or desogestrel). *The terms "third generation progestin" and "third generation OCs" derives from the fact that they appeared on the market at roughly the same time rather than from any pharmacological resemblance. Norgestimate is classified as second or third generation by various investigators.* [1]

The progestin component of Ortho EVRA™ is norelgestromin (the generic name for 17-deacetyl-norgestimate), a new molecular entity (NME), not yet classified, but sometimes called a third generation progestin because it is newer (see footnote[1]). Norelgestromin is the active metabolite of norgestimate (used in three approved Ortho COC formulations). It has the unique property that it can be absorbed cutaneously along with ethinyl estradiol, through the sponsor's transdermal patch, in quantities sufficient to provide contraception.

Medical officer Table 4 shows the total amount of NGM or 17d-NGM + EE administered orally during one 21-day cycle of the following combination hormonal contraceptive products. The EVRA™ data shows the total amounts presumed to be released during 21 days of patch use, thereby making it, according to the sponsor, the lowest dose of the four current NGM-containing hormonal contraception products.

Table 4 **Total Cycle NGM/17d-NGM and EE Content:**

NGM-Containing OCs and Ortho EVRA™

Brand name	Total Cycle Dose NGM (in descending order)	Total Cycle Dose EE
Ortho-Cyclen	5,250 mcg	735 mcg
Ortho-Tri-Cyclen	4,515 mcg	735 mcg
Ortho Tri-Cyclen Lo	4,515 mcg	525 mcg
EVRA™	**~3,150 mcg**	**~420 mcg**

Reviewer comment: Exact comparisons of EVRA™ to oral contraceptives cannot be made here because of several factors:

- **all OCs have daily serum peak and trough levels, while the C_{max} level of EVRA™ is sustained throughout a week without obvious daily peak and trough levels**
- **transdermal bioavailability and oral bioavailability are not similar for 17d-NGM and EE due to different absorption and metabolism**
- **the appropriate comparison is in systemic exposure, but limited dose-ranging data is available from PK studies for serum concentrations and AUC values for EVRA™ and norgestimate containing COCs**

[1] Edwards RG and Cohen J, The recent saga of cardiovascular disease and safety of oral contraceptives. *Human Reproduction Update* 12/99; Vol. 5, #6, p. 566.

Increased risk of venous thromboembolism (VTE): an on-going controversy

Late in 1995, epidemiology reports were published linking combined oral contraceptives (COCs) containing desogestrel and gestodene with venous thromboembolism (VTE). VTE includes both deep vein thrombosis (DVT) and pulmonary embolism (PE). The WHO Study [2] (21 centers in 17 countries) matched controls to cases within 5-year age bands. This study found an Odds Ratio (OR) of 2.4 (CI 1.3-4.6) or a 2.4 :1 increase in VTEs in COC users containing third generation progestins compared to first or second-generation progestins. The Transnational Study [3] used a protocol similar to that of the WHO study, but was specifically designed to compare the cardiovascular risks of combination OCs containing different progestins matched within 5-year age bands. The Transnational Study reported an OR of 1.5 (CI 1.1-2.2) or a 1.5 :1 increase in VTEs when comparing desogestrel (DSG) to levonorgestrel (LNG) users. The Boston Collaborative Study [4] investigated the risks of cardiovascular death and nonfatal VTE among women who used different OCs through the General Practice Research Data Base of over 4 million people in the UK. Here the adjusted matched relative risk from a nested case-control analysis was 2.2 (CI 1.1-4.4) or a 2.2 :1 increase in VTE when comparing DSG to LNG users.

Table 5 below summarizes the odds ratio for VTE risk comparing OCs containing either DSG or LNG (a second generation progestin):

Table 5 **VTE and OCs: Study Descriptions and Main Results** [5]

Study	WHO[1]	Transnational[2]	Boston Collaborative[3]
Design	Case-Control	Case-control	Cohort
No. of centers	21 in 17 countries	10 in Germany and UK	370 general practices in UK
Cases/controls (n)	1143/2998	471/1772	75/300*
Odds Ratio (95% CI) DSG vs. LNG	2.4 (1.3-4.6)	1.5 (1.1-2.2)**	2.2 (1.1-4.4)

*nested case-control subgroup analysis

**compared with OCs containing all progestins other than DSG or gestodene (GSD)

In November 1997, The World Health Organization convened a meeting of scientific experts to consider the safety of the new progestins. They concluded that, "COC preparations containing desogestrel and gestodene probably carry a small risk of venous thromboembolism beyond that attributable to COCs containing levonorgestrel. **There are insufficient data to draw conclusions with regard to COCs containing norgestimate** ." In addition, the group concluded, "The suggestion that gestodene- or desogestrel-containing low dose COC may carry a lower risk of myocardial infarction compared with low dose formulations containing levonorgestrel remains to be substantiated." [6]

[2] World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception, effects of different progestagens in low estrogen OCs on venous thrombolic disease. *Lancet* 1995; 346: p. 1582-88.

[3] Spitzer WO et al., Third generation oral contraceptives and risk of thromboembolic disorders: an international case-control study. *BMJ* 1996; 312: p. 83-88.

[4] Jick H et al., Risk of idiopathic cardiovascular death and non-fatal venous thromboembolism in women using oral contraceptives with differing progestagen components. *Lancet* 1995; 346: p. 1589-93.

[5] Ory H, Epidemiology of Venous Thromboembolic Disease and OC Use. *Dialogues in Contraception* Fall 1996; Vol. 5, No. 1, p. 4.

[6] WHO Scientific Group on Cardiovascular Disease and Steroid Hormone Contraception, Report of a WHO scientific group. *WHO Tech Rep Ser* 1998; No. 877.

Of 16 regulatory decisions reviewed by Dr. Michael Lewis in 1998, 3 agencies (UK, Germany, and Norway) restricted the use of third-generation oral contraceptives, 6 issued warnings, and 7 (including EMEA, the European agency) took no action. [7] With their publications, it was apparent that the above 3 studies with their subsequent publications showed the incidence of venous thromboembolism among women who used third generation OCs containing desogestrel or gestodene to be higher than that among women who used second-generation products. Subsequently, the interpretation of the results of the 3 studies has been criticized primarily for bias and confounding factors [causal relationship vs. selection bias]. [8]

In February 1999, Burnhill's article assessed the risk of thromboembolic events in 2,265,087 woman-years of OCs use in a group of Planned Parenthood Federation of America patients and found 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.**[9] In July 1999, Herings reported new use of third generation oral contraceptives was associated with a four-fold increased risk of VTE compared with users of second-generation oral contraceptives, particularly among young, healthy women. [10] He had examined data from the PHARMO system, which included information of hospital admissions and drug dispensing for all 450,000 residents of eight Dutch cities, to identify exclusive use of second or third generation oral contraceptives among new users. Bloemenkamp offered the biological explanation for the differences to be an interaction between types of oral contraceptives and an unidentified susceptibility factor that might be a prothrombotic mutation, such as factor V Leiden mutation. [11] In September 1999, Mellemkjaer reported a 16% increase in admission rates for VTE in a population study from Denmark that correlated with the increase in prescription of third generation contraceptives. [12] In June 2000, Parkin reported that in a national New Zealand case-control study of fatal pulmonary embolism in women of childbearing age, current users of OCs had a relative risk of 9.6; the relative risk was 5.1 for levonorgestrel OCs, and 14.9 for desogestrel or gestodene OCs. [13]

A meta-analysis published recently (BJM 7/21/01) [14] by a clinical epidemiology group in Utrecht, Netherlands, supports that third generation oral contraceptives are associated with a 1.7-fold increases risk of VTE compared with second generation oral contraceptives. The risk is highest in first time users. After stratifying by various factors and examining selected subgroups, the increase remained.

> **Reviewer comment: it appears that all the above references are drawn from European or New Zealand data except for Burnhill's study of over 2,265,000 woman-years of oral contraceptives prescriptions through Planned Parenthood Clinics in the United States. Gestodene is not available in the US, but fortunately the Burnhill study has a large database of four different progestins including products containing norgestimate. Norgestimate accounted for 21% of the total OC use and 18% (8/45) of the reported DVTs (7 of 25) and PEs (1 of 20).**

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[7] Lewis M, The epidemiology of oral contraceptive use: A critical review of the studies on oral contraceptives and the health of young women. *Am J Obstet Gynecol* Oct. 1998: Vol. 179, No. 4, p.1096-97.

[8] Lidegaard O and Milson I, Oral contraceptives and Thrombotic Diseases: Impact of new epidemiological studies. *Contraception* 1996; 53: p. 135-39.

[9] Burnhill MS, The use of a large-scale surveillance system in Planned Parenthood Federation of America clinics to monitor cardiovascular events in users of combination oral contraceptives. *Int J Fertil Womens Med* 1999 Jan-Feb; 44 (1): p. 19-30.

[10] Herings R et al., Venous thromboembolism among new users of different oral contraceptives. *Lancet* 1999; 354: p. 127-28.

[11] Bloemenkamp K et al., Venous thromboembolism and oral contraceptives. (Letter), *Lancet* 1999; 354: p. 1469.

[12] Mellemkjaer L et al., Admission for and mortality from primary venous thromboembolism in women of fertile age in Denmark, 1977-95. *BJM* 1999; 319: p. 820-21.

[13] Parkin L et al., Oral contraceptives and fatal pulmonary embolism. *Lancet* 2000; 355: p. 2133-34.

[14] Kemmeren JM et al., Third generation oral contraceptives and risk of venous thrombosis: meta-analysis. *BJM*

2.1 Regulatory history

Pre-NDA meetings were held on 7/7/99 and 7/27/99 with the sponsor. The following major agreements were reached:

- the preclinical program and oral NGMN/EE data is sufficient to support the NDA
- the toxicology bridging data in the background package is sufficient
- sponsor could cross-refer to OC NDAs for Ortho-Cyclen (NDA 19-653) and Ortho Tri-Cyclen (NDA 19-697) for relevant human ADME reports
- sponsor needs to provide clinical PK justification and quantitative information from oral norgestimate/EE studies to demonstrate the comparability of norelgestromin from OCs containing norgestimate to the contraceptive patch containing norelgestromin
- efficacy results in the background package are sufficient to support the NDA
- sponsor will make a request for waiver for the Pediatric Labeling Requirement

2.2 Preclinical studies

The pharmtoxicology review of 5 toxicity studies [3 dermal, 1 developmental, and a battery of genotoxicity studies] showed no abnormal findings or new concerns. Results from pre-clinical toxicity studies for the three currently approved oral contraceptives on the US market containing norgestimate [the active metabolite of norgestimate is the hormone 17d-norgestimate in the EVRA™ patch], were accepted as supportive data.

2.3 Human pharmacology studies

The clinical pharmacology and biopharmaceutics review by DJ Chatterjee does not demonstrate any major issues. The sponsor studied three patch sizes (10 cm^2, 15 cm^2, and 20 cm^2); Study PHI-006 found the three patch sizes to be dose proportional. Finally, the 20 cm^2 patch was selected for the Phase 2 and 3 studies and contains 0.75 mg EE and 6.0 mg of 17-deacetyl-NGM. The results of Study PHI-014 showed that the daily dose delivered by the EVRA™ patch is 150 µg 17D-NGM and 20 µg EE. The PK studies showed that both 17d-NGM and EE appear rapidly in serum, reach a plateau by ~48 hours after patch application, and are maintained at an approximate steady state throughout the wear period. Serum concentrations of 17d-NGM and EE are approximately 0.8 ng/mL and 50 pg/mL, respectively. Studies were performed to show that all four application sites were therapeutically equivalent based on C^{ss}; although one study showed higher and another showed lower values for the abdominal site, the conclusion was that the abdomen is equivalent to the buttock, upper outer arm, and upper torso.

Following application of EVRA™ under conditions of extreme wear (high heat, humidity, cold and exercise), PK parameters for 17d-NGM were not significantly different from those observed during normal activity, while slight differences were observed for EE. The steady state values for EE during extreme wear, however, were within the reference range.

In summary, an approximate steady state is maintained throughout the period of wear and for at least an additional two days of wear. The C^{ss} for EVRA is similar to the C_{avg} at steady state following oral administration of ORTHO-CYCLEN. The C^{ss} and AUC are increased only slightly following multiple-dose applications. Elimination kinetics following patch removal are 28 hours for 17d-NGM ($t_{1/2}$) and 17 hours for EE ($t_{1/2}$). Absorption profiles under conditions of high heat, humidity, cold and exercise had no effect on the level of 17d-NGM and were associated with a slight increase in EE. Finally, although significant trends toward slightly decreasing C^{ss} for both 17d-NGM and EE were associated with increasing age, body weight, and body surface area, only 10% to 20% of the variability in the data is explained by these parameters.

2.4 International and US marketing experience

EVRA™ is not approved in any country and therefore not currently marketed in any country.

3.0 NDA CLINICAL SECTION

Evaluation of Financial Disclosure: the medical reviewer agrees with the conclusions reached by Jeanine Best in her review of financial disclosure documents, dated June 14, 2001. Adequate documentation was submitted to comply with 21 CFR 54.

3.1 Summary of Phase III trials for efficacy and safety- see table below, tabulated by the MO:

Table 6 **Phase III Studies incorporated into NDA 21-180 submission**

Study CONT #	# Sites Location	1^0 Objective (2^0 objective)	Study design	# subjects with evaluable cycles (woman-years exposure)	Age range (Mean)	Medical Officer Comments
-002	73 USA- 31 Europe- 42	Efficacy/Safety (Cycle control)	Open-label Non-compare Multicenter	N= 1,664 (846)	18-45 (28.7)	Multinational; Enrollment 2X -003 or -004
-003	65 Europe- 54 S.Africa-11	Efficacy/Safety (Cycle control)	Open-label Comparative Multicenter	N= 844 (455)	18-45 (28.8)	Predominant European
-004	45 USA- 39 Canada- 6	Efficacy/Safety (Cycle control)	Open-label Comparative Multicenter	N = 811 (403)	18-45 (28.0)	Predominant USA
TOTAL # →	183 SITES	Same objectives		N = 3319 1,704 women-years exposure	18-45 28.5	22,155 evaluable cycles

Reviewer comment:
There were no blinded, large Phase III clinical trials submitted in this NDA. It would be very difficult to have a blinded study, as each subject would additionally need either an inactive patch or a placebo pill. The design of the Phase III trials is acceptable. None of the trials were designed by protocol to show superiority, so no superiority claims should be made in the Final Printed Label or marketing of EVRA™.

3.2 Summary of Sponsor's Clinical Development Program

Findings from the above Phase 3 trials were submitted in this NDA. The first subjects were enrolled starting in October 1997 in all 3 trials and the last subjects completed the studies in 1999. The objectives, entry criteria, and treatment and evaluation schedules used in the 3 trials were similar. Most of the protocol differences between studies were related to the inclusion of the comparator oral contraceptive pills in Studies -003 and -004. The DRUDP requirement of a total of at least 10,000 evaluable cycles for efficacy and safety was more than doubled.

The EVRA clinical development program also included five specialized safety, dose-ranging, and/or supportive efficacy studies, four dermal safety studies, and 12 pharmacokinetic and bioavailability studies. Overall, safety information was collected from 6,254 women [this includes comparator OC subjects] who participated in the clinical investigations, including 3,330 subjects who wore the EVRA patch in Phase 3 studies for a planned duration of 6 or 13 cycles.

4.0 PROTOCOLS -002, -003, -004: Open-Label, Multicenter Phase 3 Studies in Healthy Female Subjects

4.1 Objectives

The study objectives were to evaluate the safety, contraceptive efficacy, and cycle control seen with the use of EVRA™ for a duration of treatment of 6 or 13 consecutive cycles. Each cycle consisted of a 21-day period with the administration of either three 7-day patches or 21 pills, followed by a 7-day period with no patch or active oral contraceptive pill.

4.2 Design

Study -002 was open-label, non-comparative, conducted in 73 centers in the United States and Europe. Studies -003 and -004 were open-label, comparative studies conducted in 65 centers in Europe/South Africa (-003) and 45 centers in the United States/Canada (-004). With a 4:3 randomization, monophasic Mercilon 21-day [identical to Days 1-21 in Mircette® in the US] was the comparator oral contraceptive in the -003 study, while triphasic Triphasil-28 was used in the -004 study.

4.3 Study population

A total of 3,330 female subjects were treated at 183 different centers in the 3 Phase III studies. The subjects were recruited and treated between October 1997 and 1999. These subjects received at least one day of the study medication.

4.3.1 Demographics

Demographic data including date of birth, race, height, body weight, and a general medical and gynecological history (including menstrual cycle characteristics, gravidity, and parity) were recorded during the screening period. Descriptive summaries of demographic characteristics (age, race, body mass index [BMI]), obstetric history (gravidity, parity), and contraceptive history (last contraceptive method used) are presented for the three studies individually and for the three studies combined.

For the three studies combined, the subjects had a mean age of 28.5 years (range of 18 years to 45 years). The majority of subjects (83.4% in combined studies) ranged in age from 18 years to 35 years of age. A lower percentage of Caucasians in Study -004 (85.7%) than in Study -003 (96.7%) reflected a greater percentage of Blacks (5.1%) and Asians (3.9%) in Study -004 than in Study -003 (1.2% and 0.4%, respectively). Study -002 had 90.7% Caucasian, 6.7% Black and 1.1% Asian. All three combined, EVRA™ racial distribution was Caucasian 91.0%, Black 4.9%, Asian 1.6%, and Other 2.4%. Mean BMI for the combined studies was 23.6 kg/m^2. The three studies were comparable to each other with respect to age. Women in Studies -002 (Mixed) and -004 (USA) tended to be heavier than women in Study -003 (EURO); the mean weight was 65.7 kg in Study -002 and 64.4 kg in Study -004, compared to 62.8 kg in Study -003. The average coital frequency was not reported.

Under Ob/Gyn History, the screening history asked for the "usual length of menstrual cycle and the usual length of menstrual period." Menstrual bleeding characteristics, such as amount of pain/discomfort, amount of flow and number of pads/tampons used, was **not** recorded at screening, but was recorded each cycle throughout the three studies.

Admission information gave the following choices for contraceptive method used during **60 days prior to admission: None, Oral Contraceptive, Non-hormonal IUD, Hormonal IUD, Barrier, or Other, specify.** The next item asked was "most recent oral contraceptive used: None , Product , and Date of Last Active Pill.

Reviewer's comment: the two smaller Phase III studies were well matched with regard to age and number of subjects enrolled. Despite this fact and identical study protocols, it is interesting to note the following small differences in the two study populations (US study -004 versus Euro study -003):

- **higher proportion of Black subjects——— 5.1% vs. 1.2%**
- **lower proportion of Caucasian subjects ——— 85.7 vs. 96.7%**
- **higher mean baseline BMI (heavier subjects)——— 23.8 vs. 22.6**
- **lower proportion with previous OC use ——— 73% vs. 78%**

It is difficult to know if some of these above differences were major contributing factors in the differences in compliance, discontinuation, and treatment-emergent adverse event results that are discussed later in this review.

4.4 Inclusion and exclusion criteria: similar for the three clinical studies

Inclusion Criteria

1. Women in good health at risk for pregnancy and asking for contraception
2. Between 18-45 years of age at the time of screening
3. Cycles with a usual length of between 25 and 35 days
4. Not lactating or pregnant within 42 days prior to study admission
5. An "acceptable" Body mass index [not clearly defined in the ISE]
6. Systolic blood pressure <140 mmHg and diastolic < 90 mmHg
7. Willing to give written informed consent to participate in the study

Exclusion Criteria

1. A cervical smear Papanicolau Class III, IV, or V, in the history or diagnosed in the screening phase [US study: smear of low grade SIL or higher in the Bethesda System]
2. Any disorder that is a contraindication to steroid hormonal therapy
3. Use of an injectable hormonal contraceptive within the past six months
4. An uncontrolled thyroid disorder
5. History or presence of dermal hypersensitivity in response to topical application
6. Use of any experimental drug, device, or hepatic enzyme-inducing drugs within 30 days prior to the prestudy visit
7. A history of (within 12 months) alcohol or drug abuse
8. If local regulatory requirements restricted the use of oral contraceptives in women who smoke, women over the age of 35 who smoke were to be excluded

Reviewer's comment:
The inclusion criteria "women within the age range of 18-45 years inclusive" differs from the majority of previous United States OC investigations, which have studied women in the age range of 18-35 (or 38) years inclusive. Accepting females up to age 45 into the clinical trial potentially introduces the bias of decreased fertility due to maternal age. The value, however, is the information gained concerning efficacy and safety in women > 35. The combined number and percentage of all-subjects-treated (AST) from age 18-35 and ages 36-45 are shown below.

Table 7 **Demographics by Age Group (AST)**

Trials -002, -003, -004 Combined		
	N	%
Age < 36	2778	83.4
Age ≥ 36	552	16.6
TOTAL	3330	100%

4.5 Procedures/Visits

4.5.1 Screening period

The study design and purpose were explained at the Prestudy Visit, and the volunteers were assessed for eligibility. Written informed consent was obtained. The requirements of participation were thoroughly explained to the subject, including the use of home pregnancy testing, compliance with back-up contraceptive methods (if used), and availability for scheduled visits. A medical and gynecological history, and pretrial medications history (recreational, prescription and OTC) were obtained. General characteristics including smoking, alcoholic beverage consumption and need for contraception were recorded. Vital signs and a complete physical examination (including breast, pelvic exam, and cervical Pap smear) were performed. Subjects had blood drawn for β-hCG level (pregnancy), routine biochemistry and hematology (CBC) testing at a central laboratory.

Reviewer comment: per protocol, there were three categories under previous OC use- direct switchers, indirect switchers, and fresh starters. Direct switchers were currently using hormonal contraception and could start study drug without interruption; indirect switchers had used hormonal contraception within the last two months, but not at study enrollment; fresh starters had not used hormonal contraception within the two months prior to study enrollment but might have used oral contraceptives previously. Thus, a small number of the women enrolled in the three clinical trials were "never-users" of oral contraceptives.

4.5.2 Admission period: there was an official admission visit after the screening visit.

At this visit study drug and diary cards for Cycle 1 and reserve patches for Cycles1-6 were dispensed. An in-office urine pregnancy test was performed, and patient satisfaction questionnaires were completed.

4.5.3 Treatment period

Subjects were seen on approximately Day 28 of Cycles 1, 3, 6, 9, and 13. At each of these visits, an interim history was taken, the daily diaries and study drug were collected, and AE and concomitant therapies were reported. A gynecological exam was repeated at the Cycle 6 and 13 Visits and also in case of early discontinuation. Routine laboratory parameters and a PAP smear were repeated after completion of Cycle 6 or 13, or in case of early discontinuation.

A pregnancy test was also done whenever pregnancy was suspected during the study period. Pregnancy testing was prompted by failure of withdrawal bleeding. Testing was not done at each visit, but was performed 10 days after each subject's final visit. All pregnancies reported during the study and post-treatment period were followed for pregnancy outcome and a pregnancy follow-up form completed.

Reviewer comment: see page 48 for further comments. There were no congenital anomalies; 9 of 16 women continued their pregnancy to 37-42 weeks gestation and delivered normal healthy babies. The other women were either lost to follow-up or had a pregnancy termination.

The sponsor table below shows the flow chart of subject assessments:

Table 8 Assessment (Visit) Schedule for Phase III Studies

Assessment	Pre-study	Cycle 1	Cycle 3	Cycle 6 (if FINAL VISIT)	Cycle 9	Cycle 13[a]	10 Days Post[b]
Informed consent	•						
Medical and gynecological history	•						
Physical examination	•			•		•	
Vital signs[c]	•			•		•	
Gynecological examination	•			•		•	
Cervical cytology	•			•[d]		•[d]	
Routine laboratory parameters	•			•		•	
EVRA™ acceptability		•	•	•		•	
Serum pregnancy test	•			•		•	Urine
Vaginal bleeding		•	•	•	•	•	
EVRA™ compliance		•	•	•	•	•	
Drug accountability	•	•	•	•	•	•	
Pre-trial and concomitant medication	•	•	•	•	•	•	
Pre-treatment signs and symptoms	•		•				
Adverse events		•	•	•	•	•	•

[a] Assessments were to be performed after completion of Cycle 13 and also in case of early discontinuation.

[b] The post-treatment evaluation was to be performed by interviewing the subjects. Inquiries were to be made regarding menstrual cycle, possible return of fertility, and possible use of contraceptives. This evaluation was to be performed within 1 month following completion of Cycle 13, but preferably in the last week (fourth week) of this period.

[c] Blood pressure, body weight, pulse, temperature, and (at screening only) height.

[d] Repeat PAP smear completed at study discontinuation

4.6 Evaluation criteria (methods)

4.6.1 Contraceptive Efficacy

The sponsor classified pregnancies into four categories: pre-therapy, on-therapy method failures, on-therapy user failures, or post-therapy. Pre-therapy pregnancies were those in which conception occurred prior to the first start of study drug (patch or pill). On-therapy pregnancies were those in which conception occurred after study drug was first started. Post-therapy pregnancies were those in which conception occurred after discontinuation of the study drug (patch or pill). Pregnancy tests were not done at every visit. Pregnancy tests were performed only at Screen Visit, at home immediately before applying the first patch for the first cycle, at Cycle 13 Visit or in case of early discontinuation. If pregnancy was suspected during the study period, then pregnancy testing was performed.

Reviewer's comment: many contraceptive trials include subjects who become pregnant within 7-14 days of the last study dose as "on-therapy" pregnancies. This issue is briefly discussed later in this review in the Section titled Pregnancies conceived POST discontinuation of study drug.

The date of conception was determined by using the following information, if available:

1. ultrasound,
2. estimation of gestational age based on pelvic and/or abdominal examination,
3. daily diary information (e.g. absence of withdrawal bleeding, subjects LMP),
4. determination of gestational age at pregnancy outcome
5. quantitative serum β-hCG determination,
6. investigator's estimation in the absence of the above criteria for the determination of the conception date.

Reviewer's comment: this is not the best hierarchy to use, but is acceptable to the medical reviewer. All pregnancies are carefully reviewed for estimated date of conception; the one disagreement between this reviewer and the sponsor is noted and discussed later.

In the case of conflicting information, the more accurate method of estimation was used. If a range was reported (e.g. 18-20 weeks on ultrasound), the midpoint was used. In the case of multiple ultrasounds, the results of an ultrasound performed between 5 and 12 weeks of gestational age was recorded on the Pregnancy Determination Form and used for calculating the estimated date of conception (EDC).

4.6.2 Bleeding patterns

The evaluation of bleeding patterns was based on bleeding and spotting information recorded by the subjects on daily diary cards. Bleeding was defined as any bloody discharge requiring at least one sanitary napkin or tampon per day. Spotting was any bloody discharge that did not require more than one napkin or tampon per day. For definitions of additional bleeding/spotting terms, see pages 26-27 and 32-33 of the sponsor's ISE. Bleeding patterns were evaluated by individual cycle control analysis. Duration of latent period, menses, withdrawal flow, early withdrawal flow, continued withdrawal flow, and the number of breakthrough bleeding-spotting days were also defined in the ISE. Breakthrough bleeding/spotting was distinguished from the withdrawal flow (menses) that is expected to occur during the treatment-free intervals. Amenorrhea was defined as two consecutive cycles without bleeding or spotting in the absence of pregnancy.

The primary efficacy endpoint of interest for the evaluation of cycle control is the incidence of breakthrough bleeding and/or spotting at Cycle 3 in Study -004 (USA). Bleeding information was also available from Studies 003, -002, and -001. To assess cycle control, diary cards were used to record daily bleeding information from each on-therapy cycle day in the Phase III trials.

Reviewer comment: one other method of bleeding or cycle analysis is called "reference period analysis" where the data is evaluated in a block of time such as three menstrual cycles [e.g., a "reference period" of 90 days]. Both methods are valid, but the reference period data allows for much better information over time. The sponsor's cycle control analysis gives information for what happened each cycle 1 through 13, but no insight into whether the same subjects are having the same bleeding patterns each cycle or different subjects are contributing each cycle.

The choice of Cycle 3 as the primary endpoint is certainly arbitrary and limited. No special claims will be allowed from such an analysis. In general, however, the patterns of cycle control seen with short-term and extended use of EVRA™ are acceptable. See pages 31-32 for further comments.

4.6.3 Safety evaluation

Safety evaluation was based on the incidence of adverse experiences (AEs), discontinuations due to AEs, changes from screening to last assessment in vital signs, weights, cervical Pap smears, laboratory results and pregnancy outcome. Adverse experiences and serious adverse experiences 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 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: it is not likely that repeated exposure would occur in the context of this study. Therefore, the designation of "definitely related" is not likely to have been made in most cases. Thus, those events which are "probably related" may be more meaningful.

4.7 All-Subjects Disposition: enrollment, withdrawals, compliance and discontinuations

A total of 3,471 subjects were assigned to treatment with EVRA in Studies CONT-004, CONT-003, and CONT-002. Of these, 3,330 were treated with EVRA and were evaluable for safety; 3,319 were evaluable for efficacy. Study completion status and reasons for withdrawal are summarized by study and overall in Table 9 for the 3,330 subjects who were treated with EVRA and were evaluable for safety in the three pivotal studies. Seventy-four percent of all subjects completed, and 26% withdrew prematurely from the studies. Overall and within each study, the incidence of premature withdrawal from treatment with EVRA was highest for adverse events (12%) and subject choice (7%).

Table 9 **Study Completion and Reasons for Withdrawal**

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

	Study CONT-004 USA N=812		Study CONT-003 EURO N = 846		Study CONT-002 US/EURO N=1672		Total N=3330	
Status	n	%	n	%	n	%	n	%
Completed	571	70.3	678	80.1	1210	72.4	**2459**	**73.8**
Withdrawal	240	**29.6**	168	**19.9**	462	**27.6**	**870**	**26.1**
Lost to Follow-up	32	3.9	14	1.7	84	5.0	130	3.9
Adverse Event	102	12.6	81	9.6	213	12.7	396	**11.9**
Subject Choice	77	9.5	49	5.8	108	6.5	234	**7.0**
Protocol Violation	6	0.7	6	0.7	18	1.1	30	0.9
Pregnancy	4	0.5	3	0.4	5	0.3	12	0.4
Death	0	0.0	0	0.0	1	0.1	1	0.0
Other	19	2.3	15	1.8	33	2.0	67	2.0
Unknown	1	0.1	0	0.0	0	0.0	1	0.0

Reviewer's comment: in the All-Subjects Treated Group from the combined data, 870 (26.1%) of the subjects discontinued prematurely from the study. This is a relatively good [low] discontinuation rate given the fact that these three studies were either a 6-cycle or a 13-cycle trial. The percentage of subjects who discontinued was greater in the predominant US study -004 (29.6%) than the predominant European study -003 (19.9%). There is no specific explanation for this fact except to note that in the US trial there was a higher percentage of women who were categorized as "lost to follow-up, AEs, or subject choice", suggesting that the US subjects were not as compliant or committed to the trials as the European counterparts.

4.7.1 Dosing compliance

The number and percentage of subjects with compliance data were summarized for all subjects contributing efficacy data to the pivotal Phase 3 studies. Compliance was defined as 21 consecutive days of drug-taking, followed by a seven-day, drug-free period; for EVRA users, no patch could be worn for more than eight days (summaries based upon no patch worn for more than seven days are also presented). For subjects who were discontinued from the study for reasons other than loss to follow-up, the cycle in which the discontinuation occurred was included in the denominator for calculation of compliance as long as there were 21 days of drug-taking data. Compliance data are summarized in sponsor Table 10 within and across the pivotal studies for all subjects treated with EVRA. Overall 91% of subjects treated with EVRA™ were compliant throughout their study.

Table 10 Number and Percentage of Subjects with Patch Compliance

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	N[a]	n[b]	%	N[a]	n[b]	%	N[a]	n[b]	%	N[a]	n[b]	%
1	774	692	89.4%	805	725	90.1%	1606	1454	90.5%	3185	2871	90.1%
2	714	656	91.9%	778	696	89.5%	1486	1357	91.3%	2978	2709	91.0%
3	685	616	89.9%	760	683	89.9%	1439	1294	89.9%	2884	2593	89.9%
4	640	579	90.5%	728	670	92.0%	1347	1239	92.0%	2715	2488	91.6%
5	622	560	90.0%	722	647	89.6%	1326	1219	91.9%	2670	2426	90.9%
6	603	543	90.0%	712	659	92.6%	1291	1202	93.1%	2606	2404	92.2%
7	170	153	90.0%	202	190	94.1%	373	355	95.2%	745	698	93.7%
8	163	146	89.6%	198	185	93.4%	356	339	95.2%	717	670	93.4%
9	160	138	86.3%	195	183	93.8%	345	309	89.6%	700	630	90.0%
10	152	144	94.7%	185	171	92.4%	326	303	92.9%	663	618	93.2%
11	154	145	94.2%	180	171	95.0%	322	300	93.2%	656	616	93.9%
12	153	145	94.8%	180	172	95.6%	316	295	93.4%	649	612	94.3%
13	151	138	91.4%	176	171	97.2%	313	294	93.9%	640	603	94.2%
14	--	--	--	--	--	--	3	3	100.0%	3	3	100.0%
Total Cycles	5141	4655	**90.5%**	5821	5323	**91.4%**	10849	9963	**91.8%**	21811	19941	**91.4%**

[a] N=Number of subjects per cycle who supplied diary cards

[b] **n=number of subjects with compliance**. Compliance was calculated using the following rules: 21 consecutive days of drug-taking followed by a seven-day drug free period; no patch could be worn for more than 8 days.

Reviewer's comment: a detailed daily diary recording system was used throughout the trials, and an acceptable analysis plan used to determine patch compliance. This level of compliance is very good for a 13-cycle hormone contraceptive study involving the use of 3 consecutive 7-day transdermal patches. For subjects treated with EVRA™, compliance per cycle ranged from 86.3% to 97.2%, and the overall compliance in the three studies ranged from 90.5% to 91.8%, with a pooled 3-study average of 91.4%, which is excellent.

From the sponsor's ISS, for Study -004 (USA), a summary of compliance by cycle and treatment group shows the percentage of subjects who were compliant in each cycle ranged from 86% to 95% in the EVRA group and from 76% to 86% in the Triphasil group. At Cycles 1 to 6 and 10 to 13, the between-group difference (percentage of subjects) was statistically significant. In addition, the comparison of overall compliance showed that the mean percentage of compliant cycles was statistically significantly higher for subjects in the EVRA group than for subjects in the Triphasil group (89.2% compared with 77.7%; $p<0.001$, t-test; [based upon no patch worn for more than seven days]). There were no dosing errors in 95% of cycles in the EVRA group, compared with 81% of cycles in the Triphasil group.

Reviewer's comment: the sponsor would like to include in the final label a superiority claim for adherence to the EVRA™ dosing regimen using the above data. In the much smaller -001 Study, adherence to the dosing regimen was 95.9% for EVRA™ (N = 150) versus 78.3% for Ortho-Cyclen® (N = 150). Such a superiority claim will not be allowed because none of the studies were initially set up to show superiority by the protocol, endpoints, or statistical analysis plan.

4.7.2 Distribution of Patch Application Sites

From the ISE: the distribution of patch application sites is summarized overall in Table 11. The total number of subjects who applied EVRA to each application site is also presented in each table. Overall and in each of the individual studies, all application sites were used. The most frequently used site of application was the buttock, followed by the abdomen, upper outer arm, and the torso (excluding breast tissue).

Table 11 Distribution of 4 Patch Application Sites

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

Application Site	% of Total 4 sites	Total Number of Patches	Total Number of Cycles	Total Number of Subjects
Buttock	**49%**	37920	14306	2715
Abdomen	**28.5%**	19039	8335	2012
Upper Outer Arm	**17%**	10658	4936	1470
Upper Torso	**5.5%**	2819	1635	724
Other	NA*	24	10	7
Missing	NA	92	91	88

*The 4 sites total to 100%; Other and Missing are not applicable.

Reviewer comment: subjects were told to use whichever site they preferred and that the three patches during any given cycle could be placed at three totally different sites. From the above data, approximately one half of the time and one quarter of the time the subjects preferred to use the buttock and abdomen respectively. Although the PK data (serum levels of the two hormones) from the 4 sites is not exactly the same, the clinical efficacy of the 4 sites has been shown to be therapeutically equivalent. See section on Clinical Predictors of Pregnancy (page 28-9 of this review).

4.8 Contraceptive Efficacy Analysis

Contraceptive efficacy was evaluated based on the occurrence of pregnancy during the study drug administration (or "on-therapy") period. A total of 3,319 efficacy-evaluable women in the Pivotal Efficacy Analysis Group provided 22,155 cycles for the evaluation of contraceptive efficacy, with 643 women completing 13 cycles of evaluable use.

Forty-nine subjects assigned to use EVRA™ were or became pregnant in the three studies:

- 28 pregnancies occurred prior to the first patch application/pill intake (17 in the large multinational -002 Study, 3 in the -003 Study, and 8 in the -004 Study),
- 15 pregnancies occurred during the drug administration period (6 in the -002 Study, 4 in the -003 Study, and 5 in the -004 Study), and
- 6 pregnancies occurred after the discontinuation of study drug (2 in the -002 Study, 2 in the -003 Study, and 2 in the -004 Study)

Pregnancy Determination Forms were completed for a total of 80 subjects with suspected or confirmed pregnancies. This included women assigned to use the comparator oral contraceptive (Triphasil in -004 and Mercilon in -003).

Table 12 EVRA™ Pregnancies Reported by Sponsor

Study →	-004	-003	-002	Totals ↓
Total Pregnancies Confirmed	15	9	25	49
Pregnancy Prior to Start of Study Drug	8	3	17	28
Pregnancy On-therapy (On Drug use)	5	4	6	15
Pregnancy After Discontinuation of Drug	2	2	2	6
No. Subjects	811	844	1664	3319
No. Cycles	5,240	5,291	10,994	22,155
No. Women-Years	403	455	846	1,704

Reviewer's comment: the efficacy analysis includes data available from the three Phase III clinical studies called the Pivotal Efficacy Analysis Group. Each on-therapy pregnancy was classified as either a method failure or a user failure. Pregnancies were designated as user failures only if there was documentation that the subject did not use the study drug correctly. The sponsor's analysis showed 12 method failures and only 3 user failures. Reviewer analysis agrees with the sponsor's determination for the 28 pregnancies prior to start of drug and 6 pregnancies after discontinuation of drug.

4.8.1 Pregnancies conceived while on-therapy (using study drug)

From the sponsor's ISE, there were 15 pregnancies conceived during the on-therapy period [between the first day of either patch application or oral contraceptive use] and the 7 days after the last drug use]. With a total of 22,155 28-day cycles, equivalent to 1,704 women-years, the combined all subjects treated (AST) Pearl Index is calculated to be 0.88 (95% CI: 0.44-1.33).

Ultrasound data used to calculate dates for conception was available for almost all subjects who became pregnant during therapy in the three pivotal studies. A case report form (CRF) was available for every subject who was enrolled and became pregnant at any time.

Reviewer's comments: the CRFs for the 49 women who were assigned to EVRA™ and were determined to be pregnant were reviewed by the medical officer. There is only one subject for which the reviewer and sponsor disagree.

Subject 20018 at site 1025 in Study -002 used the patch for 7 cycles; her LMP was 7/26-30 [with patch #3 applied 7/21-28] and she did not use another patch until 8/11-19. A pelvic exam on 10/9 and sonogram on 10/23 are both compatible with a conception date of 8/12. This means that the subject became pregnancy while on-therapy, but is a User Failure because she did not start the patch on 8/5 per protocol.

Therefore, with the addition of Subject 20018, the reviewer counts a total of 16 pregnancies in the 3 studies. This slightly increases the Overall Pearl Index to 16 +1,704 women-years = 0.94, which is still acceptable. Because this subject was a User Failure, the Method Failure Pearl Index would remain the same as that calculated by the sponsor.

The sponsor did not submit in the ISE specific data concerning the cycle of EVRA™ use when the women on-therapy conceived. The reviewer, however, analyzed this and the results are shown in the table below.

Table 13 **Treatment Cycle for 16 Pregnancies Conceived On-therapy**

Failure ⇒ Type	User	Method	Total per cycle
Cycle 1	1		1
Cycle 2			
Cycle 3		4	4
Cycle 4			
Cycle 5		2	2
Cycle 6	1	4	5
Cycle 7	1	1	2
Cycle 8			
Cycle 9			
Cycle 10			
Cycle 11			
Cycle 12			
Cycle 13		2	2
TOTALS	**3**	**13**	**16**

Reviewer's comment: all women were enrolled for a minimum of 6 cycles, while only some of the earlier subjects were enrolled for 13 cycles. Of the initial 3,319 women evaluable for efficacy, 2,638 (79.5%) completed 6 cycles and accounted for 12 of the 16 (75%) pregnancies. Of the 752 (22.7% of 3,319) women who started Cycle 7 on EVRA™, 642 (85.4%) completed 13 cycles and accounted for 4 of the 16 (25%) pregnancies. This distribution of failures (pregnancies) with EVRA™ use is acceptable, and does not appear to be skewed.

4.8.2 Pregnancies conceived prior to administration of study drug

Pre-therapy pregnancies are those pregnancies that occurred before the first patch application /pill intake or for which dispensed study medication was returned unused to the clinic. A summary of the pre-therapy pregnancies is described below. The sponsor provided adequate details of all pre-therapy pregnancies and associated subjects' characteristics for the large Phase III studies.

In the Pivotal Efficacy Study Group, there were 28 pre-therapy pregnancies reported. Of these, some subjects were enrolled in the study but were discontinued before using any study drug. The reason for discontinuation was pregnancy. All dispensed patches or pills were returned unused. The other subjects started using study drug, but had estimated dates of conception, as recorded by the investigator, before the start of the study or were lost to follow-up.

Reviewer's comment: after careful review of the CRFs, the MO concurs with the sponsor's list of 28 pregnancies conceived prior to starting study drug. Therefore, they were not counted as pregnancies in any of the sponsor or reviewer's calculations for efficacy (Pearl Index, Life Tables, etc).

4.8.3 Pregnancies conceived POST discontinuation of study drug

From the sponsor's ISE, there were 6 post-therapy pregnancies reported in the Pivotal Efficacy Study Group.

In 4 of these 6 pregnancies, the estimated gestational age, and consequently, the estimated conception date were based on ultrasound assessment. The estimated dates, relative to the date of last EVRA™ patch use, indicate that pregnancy occurred after planned discontinuation of treatment.

Reviewer's comment: As discussed earlier in the on-therapy pregnancy section, Subject 20018 at site 1025 in Study -002 became pregnant while on-therapy per the reviewer's analysis. She is counted by the reviewer as an on-therapy User Failure, because she did not start the patch on 8/5 per protocol. The reviewer determined that the other 5 pregnancies occurred at least 14 days post-therapy.

4.8.4 Pearl Index and Life Table pregnancy rate

Pearl Index (PI)

From the sponsor's ISE, the overall and method failure Pearl Indices with 95% confidence intervals for the 3,319 efficacy-evaluable subjects who received EVRA™ are summarized in the table below. The overall and method failure Pearl Indices are 0.88 and 0.70, respectively. The indices for the individual studies ranged from 0.71 in Study -002 to 1.24 in Study -004, while the method failure PI ranged from 0.59 in Study -002 to 0.99 in Study -004. The reviewer's results are added in the right hand column.

Table 14 Overall and Method Failure Pearl Indices

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

Pearl Index	Study CONT-004 N=811	Study CONT-003 N=844	Study CONT-002 N=1664	Sponsor Total N=3319	Reviewer Analysis
Overall Failure	1.24	0.88	0.71	0.88	0.94
(95% CI)	(0.15, 2.33)	(0.02, 1.74)	(0.14, 1.28)	(0.44, 1.33)	
Method Failure[a]	0.99	0.66	0.59	0.7	0.7
(95% CI)	(0.02, 1.96)	(0.00, 1.40)	(0.07, 1.11)	(0.31, 1.10)	

[a] Method failure index: numerator = method failures, denominator = all cycles.

Reviewer's comment: the above table and calculations by the sponsor are based on the total cycles of EVRA™ exposure divided by 13 cycles per year divided by 100 to obtain the Pearl index per 100 woman-years. The only pregnancies that are counted in their calculations are those considered to have happened while on (during) study drug. The right hand column shows the reviewer's slightly higher overall PI because the reviewer considered Subject 20018 in Study -002 to be an On-therapy User Failure (pregnancy) rather than a post-therapy pregnancy.

The sponsor's Pearl Index calculations are consistently the same or lower than the reviewer's because the reviewer counted one more pregnancy during therapy (16 vs. 15 in the 3 trials). In the worst case scenario, the Pearl Index is 1.24 in the sponsor's interpretation of the All-Subjects-Treated population in Study -004 (N= 811, USA trial). In the best case scenario, the Pearl Index is 0.59 in the sponsor's calculation for the Method Failure (per protocol) population in Study -002. This is not of concern because the results were similar for all three pivotal trials, and even the highest PI is acceptable for approval of this product for contraception.

Although the data presented here by the sponsor for the "Method Failure" is better than the "overall" pregnancy rate, it is the Pearl Index of the Intent-to-Treat Group or the All-Subjects-Treated Group that is traditionally used by the FDA. Since the study protocols are virtually identical and the Pearl Indices so similar in the three pivotal studies, the pooled data for contraceptive effectiveness may be used for approval.

Efficacy by Age 18 to 35

The Division has traditionally used the Pearl Index for women age 18-35 for effectiveness approval of combination hormonal oral contraceptives. More recently, because of the widespread use of lower dose oral contraceptives in women age 36 to 50, sponsors have been including women between the ages of 36-45 in the Phase III studies. This is very helpful for overall safety evaluation, but tends to skew the Pearl Index to a lower value. The Division, therefore, takes into consideration the Pearl Index for the following three age categories: women age 18-35, women age >35, and all women combined. Table #20 presents the pooled data, and partially lists the individual study data.

Table 15 **Pearl Indices by Age Category for Studies -004, -003, and -002**

Study Ages	N (%)	Cycles	Woman -years	MO failures	Sponsor failures	MO Pearl Index	Sponsor Pearl Index	MO evaluation comments
Study -004 36-45 yr	125 (15.4%)			0	0			
-004 < 36 years	687 (84.6%)			5	5			
Study -003 36-45 yr	150 (18%)			1	1			Subject 3342
-003 <36 years	696 (82%)			3	3			
Study -002 36-45 yo	277 (17%)			0	0			
-002 <36 years	1,395 (83%)			7	6			Subject 20018 added in.
Combined 36-45 yr	552 (16.6)	3,859	297	1	1	0.34	0.34	
<36 years	2,778 (83.4)	18,296	1407	15	14	1.07	1.00	

Reviewer's comment: the reviewer counted one more pregnancy during therapy (16 vs. 15 in the pooled data). For all evaluable subjects, the combined Pearl Index for each age group is acceptable [0.34 for women age 36-45, and 1.07 for women age 18-35]. Because fertility decreases with age, especially with age > 35, we would expect the corresponding decrease in the Pearl Index as seen above.

The larger "all evaluable subjects" group clearly represents what is called "typical use" or "actual use" or "user failure," so the Pearl Index in this group is more realistic for both the patient and healthcare provider to use. The overall combined Pearl Index for the pooled data from the three large clinical trials is acceptable; the difference between the sponsor's 0.88 and the reviewer's 0.94 is not clinically significant and therefore should not affect the final label for the product.

Life Table Estimates

Life table estimates of the probability of pregnancy through 6 and 13 cycles of treatment and 95% confidence intervals are summarized in Table 16 by study and overall for all efficacy-evaluable subjects who received EVRA. Through Cycle 6, the probability of pregnancy for the entire sample of 3, 319 subjects was 0.5% overall and 0.4% for method failure. Through Cycle 13, the probability of pregnancy for the entire sample was 0.8% overall and 0.6%