**Johnson & Johnson Pharmaceutical Research & Development, L.L.C.**

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**Briefing Document for 9 December 2011 FDA Advisory Committee Meeting**

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# ORTHO EVRA®
## (norelgestromin / ethinyl estradiol TRANSDERMAL SYSTEM)

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| AUC | area under the concentration-time curve |
| BCDSP | Boston Collaborative Drug Surveillance Project |
| $C_{avg}$ | average concentration |
| CI | confidence interval |
| $C_{max}$ | maximum concentration |
| CRP | C-reactive protein |
| $C_{ss}$ | steady state concentration |
| CV | coefficient of variation |
| DRSP | drospirenone |
| DSG | desogestrel |
| EE | ethinyl estradiol |
| ETON | etonogestrel |
| FDA | Food and Drug Administration |
| GST | gestodene |
| LNG | levonorgestrel |
| MI | myocardial infarction |
| NDI | National Death Index |
| NET | norethindrone |
| NGM | norgestimate |
| NGMN | norelgestromin |
| OC | oral contraceptive |
| PK | pharmacokinetic |
| SHBG | sex hormone binding globulin |
| USPI | US Prescribing Information |
| VTE | venous thromboembolism |

# EXECUTIVE SUMMARY

## Background

ORTHO EVRA is a transdermal hormonal contraceptive patch system

This document is intended to provide information and perspective to assist the Reproductive Health Drugs and Drug Safety and Risk Management Advisory Committees in evaluating the benefit-risk profile of ORTHO EVRA (norelgestromin/ethinyl estradiol Transdermal System) at a joint meeting on 9 December 2011. This information is being provided by Janssen Pharmaceuticals, Inc., the Sponsor of NDA 21-180 for ORTHO EVRA.

ORTHO EVRA is a transdermal hormonal contraceptive patch system with a contact surface area of 20 $cm^2$ containing 6.00 mg norelgestromin (NGMN) and 0.75 mg ethinyl estradiol (EE). ORTHO EVRA is the result of years of research and was developed as a non-oral treatment option for women seeking a convenient contraceptive method with a once-a-week dosing regimen. Since its introduction in April 2002, ORTHO EVRA has been used by women of different ethnic, age, and socioeconomic groups; with more than 5.5 million woman-years of experience.

Hormonal contraceptives

All combination hormonal contraceptives (oral contraceptives [OCs], the ORTHO EVRA patch, and the vaginal ring) contain synthetic estrogen and progestins. These exogenous hormones inhibit the natural cyclic production of ovarian hormones. Pregnancy is prevented by a combination of factors, including preventing ovulation, increasing cervical mucus viscosity making it relatively impenetrable to sperm, and by making the uterine endometrial lining inhospitable for implantation. While offering multiple benefits, hormonal contraceptive options are not without risk. For example, all of the currently available products in the class, including ORTHO EVRA, carry labeling warning of the risk of venous thromboembolism (VTE), a risk that is increased with age, cigarette smoking, and other underlying risk factors.

Risk of VTE

There are several different types of OCs, and many epidemiology studies have been performed to characterize the risk of VTE associated with them. While estrogen dose is associated with VTE risk, the progestin contained in combination hormonal contraceptives also impacts VTE risk. In some studies, a number of widely used OCs are associated with VTE rates that are higher than those of "second generation" OCs (ie, OCs that contain progestins such as levonorgestrel and norgestimate). For example, for the "third generation" OCs (ie, OCs containing the progestins desogestrel, gestodene [not available in the United States], or etonogestrel that were introduced to the contraceptive market years after the second generation OCs), a majority of studies have found higher rates of VTE when compared with second generation OCs, with a published meta-analysis finding a summary relative risk of 1.7 (95% confidence interval [CI] 1.3-2.1)[34]. This is noted in the product labeling for third generation OCs as an "approximate 2-fold increased risk."[99,100] Despite the recognized increased risk of VTE among women who use third generation

OCs, these OCs are maintained on the market by health authorities and used by many women because of other product attributes.

Women and their clinicians weigh the benefits and risks of various hormonal contraceptive options and compare them with other options available to them. This briefing document provides a discussion of the data related to the need for safe and effective contraceptive options and the data on ORTHO EVRA as an important option for women and their clinicians.

**Medical Need for Contraceptive Options**

Safe and effective contraceptive options are necessary to prevent unintended pregnancies. Although advances have been made in this area, almost half of the approximately 6.4 million pregnancies in this country are unintended. Many women who conceive do so while using contraceptives. Many women acknowledge the difficulty adhering to a daily dosing regimen. In one study, the proportion of OC users who missed at least 3 birth control pills during a treatment cycle ranged from 30% to 51% over 3 cycles.[72] These facts highlight the need for alternative dosing regimens, giving women and their clinicians more contraceptive options from which to choose.

ORTHO EVRA meets an important medical need as one of many safe and effective contraceptive options. It has been shown to be effective in preventing pregnancies when used as directed and to have an acceptable safety profile. The development of ORTHO EVRA involved a comprehensive clinical program and its safety was further evaluated with large epidemiology studies. Its unique attributes make it well-suited for women desiring weekly hormonal contraception dosing rather than a daily pill. The choice to use ORTHO EVRA, or any other contraceptive, should be made by the woman and her clinician taking into account the woman's medical history, her non-medical needs, and a product's attributes.

**Clinical Pharmacology**

Since the pharmacokinetic profile of hormonal delivery via a patch (with steady state levels) differs from pills (with peaks and troughs), the first stage of product development investigated the amount of each hormone component (EE and NGMN) which should be contained in the patch in order to deliver sufficient drug to the systemic circulation for a contraceptive effect and acceptable safety profile. Initially, exposure data (plasma drug levels) from a 35 µg EE-containing OC, ORTHO-CYCLEN® (35 µg EE/250 µg NGM), were used to provide a starting point to formulate a range of doses to test with the new transdermal contraceptive system. A range of patch sizes providing different steady state exposures of EE and NGMN were evaluated in a Phase 1 study to determine which patch size would achieve concentrations within these reference ranges. Selection of hormonal exposures for EE and NGMN for definitive Phase 3 safety and efficacy clinical trials was done by studying a range of patch sizes in a Phase 2 study to identify the lowest dose patch that would achieve prespecified levels of ovulation suppression coupled with good cycle control and an acceptable risk/tolerability profile. Only the 20 $cm^2$ patch, which contained 6.0 mg NGMN and 0.75 mg EE, met the criteria and was therefore selected for Phase 3 studies.

Additional clinical pharmacology studies were conducted pre- and post-approval to further characterize the PK profile of the patch. In one post-approval study (NED-1) comparing the PK profiles of ORTHO EVRA and a 35 µg EE-containing OC, ORTHO EVRA was shown to have a 60% higher steady-state serum concentration ($C_{ss}$) and area under the concentration-time curve (AUC) for EE relative to that from the OC. In contrast, the OC had a 25% higher maximum serum concentration ($C_{max}$) for EE relative to that from ORTHO EVRA. Both products showed a high degree of inter-subject variability (based on coefficients of variation [CVs]) for all PK parameters; variability was slightly higher for ORTHO EVRA (CVs 32% to 33%) than for the OC (CVs 27% to 28%).

**Efficacy**

The results of the three Phase 3 studies in more than 3,300 women treated with ORTHO EVRA indicated that ORTHO EVRA is highly efficacious, with a Pearl Index (pregnancies per 100 woman-years) of 0.88, based on the pooled results of the three Phase 3 studies. The 2 comparative studies showed contraceptive efficacy similar to that achieved with Triphasil® (Pearl Index of 1.24 for ORTHO EVRA versus a Pearl Index of 2.18 for Triphasil) or the ex-US OC Mercilon® (Pearl Index was 0.88 for ORTHO EVRA versus a Pearl Index of 0.56 for Mercilon).

**Compliance**

The data for the Phase 3 studies demonstrated the overall percentage of ORTHO EVRA cycles with compliance was very consistent, ranging from 89-90% with no age-related trends (compliance was defined as 21 days of consecutive patch wear or pill taking, followed by a 7 day drug free interval during a 28-day cycle, with no single patch worn for more than 7 days). In the North American study the overall percentage of cycles with compliance was statistically significantly higher for ORTHO EVRA than for the OC comparator Triphasil (89% compared with 79%; $p<0.001$), and the compliance rate for Triphasil decreased with decreasing age ($p<0.001$). In contrast, in the ex-US study the overall percentage of cycles with compliance for ORTHO EVRA and the OC comparator Mercilon was similar (90% and 88%, respectively) and did not decrease with decreasing age in the Mercilon group.

**Safety**

***Clinical Safety***

<u>Treatment-emergent adverse events</u>

The types and rates of treatment-emergent adverse events experienced by ORTHO EVRA subjects in Phase 3 studies were generally consistent with types and rates reported in association with the use of combination OCs. Exceptions were breast symptoms (breast discomfort, engorgement, or pain), nausea in the ex-US study, and application site reactions. Breast symptoms were reported by 25% of ORTHO EVRA subjects versus 9% of Mercilon users in the European study, and 19% of ORTHO EVRA subjects versus 6% of Triphasil subjects in the North American study. Breast symptoms associated with the use of ORTHO EVRA occurred most commonly during Cycle 1 (17% incidence in Cycle 1 declining to <3% in Cycle 4 and later), were generally mild to moderate in severity (86%), and generally did not result in

treatment discontinuation (2% of subjects discontinued due to breast symptoms). Application site reactions were reported by 14% and 20% of ORTHO EVRA users, respectively, in these studies. Application site reactions were generally mild or moderate in severity, not serious, and resulted in a low rate of treatment discontinuation (ie, <2% in pooled phase 3 studies).

Serious adverse events

Fifty (1.5%) of the 3,330 subjects who received ORTHO EVRA in the Phase 3 studies experienced 1 or more serious adverse events. Of these 50 subjects, 7 subjects experienced a total of 10 serious adverse events that the investigators judged to be possibly, probably, or very likely related to study drug treatment. These events included 2 events of pulmonary embolus and 1 event each of thrombosis (reported in 1 of the 2 subjects who reported a pulmonary embolus), menorrhagia, pain, hypoesthesia, paresthesia, migraine, cholecystitis, and carcinoma in situ of the cervix. All of the serious adverse events that were considered at least possibly related to ORTHO EVRA treatment resolved either spontaneously or with appropriate treatment. In the 2 ORTHO EVRA subjects who experienced non-fatal pulmonary emboli, one woman had no known risk factors for VTE whereas the other woman had risk factors, including obesity and having had major surgical procedures within 1 day of terminating product use.

As is the case with all drug development programs, including those for contraceptive products, the frequency and implications of rare events cannot be fully evaluated in controlled trials.[54] To monitor and understand safety signals that may present during the post-marketing phase, the Company instituted a comprehensive safety surveillance program at product launch.

### *Post-Marketing Surveillance*

In 2003, the Sponsor's post-marketing surveillance program identified a greater than expected number of reports of multiple adverse events including VTE and 2 rare types of thromboembolic events: ischemic stroke in women ≤30 years of age and myocardial infarction (MI). With the identification of these signals, enhanced safety surveillance activities were initiated in an attempt to collect additional information about the events to better characterize the increased frequency and to understand the nature of thromboembolic events reported with the use of ORTHO EVRA. From analyses of postmarketing surveillance data, the increase in reporting of adverse events with ORTHO EVRA could not be attributed with certainty to either a true increased incidence of thromboembolic events or to stimulated reporting (ie, reporting rates that are increased over expected rates because of external stimuli, such as promotional adverting, media coverage and litigation, and not because of the drug itself). To further investigate the risk of thrombotic events related to ORTHO EVRA, a comprehensive epidemiologic evaluation was initiated.

### *Epidemiology*

Epidemiology studies of ORTHO EVRA

Four sponsor-commissioned epidemiology studies have evaluated thrombotic events in ORTHO EVRA users. The studies used similar designs. Each was a case-control study, comparing risk of thromboembolic events in women exposed to ORTHO EVRA with that in women exposed to OCs containing either 30- or 35 μg EE, and whose progestin component was either norgestimate

(NGM, the pro-drug of NGMN, the progestin in ORTHO EVRA) or levonorgestrel, progestins found in many widely used OCs. Specifically, the 4 studies were as follows:

- i3 Drug Safety used the Ingenix Research Data Mart, a US medical claims database, to study MI, ischemic stroke, and VTE and among women using ORTHO EVRA compared with women using NGM-containing OCs with 35 µg EE. This study included review of patient charts, which were available for 73% of potential events.
- Boston Collaborative Drug Surveillance Project (BCDSP) used the PharMetrics database, a US medical claims database, to study MI, ischemic stroke, and VTE among women using ORTHO EVRA compared with women using NGM-containing OCs with 35 µg EE.
- BCDSP used the PharMetrics database, a US medical claims database, to compare the VTE rate among ORTHO EVRA users relative to users of levonorgestrel-containing OCs with 30 µg EE.
- BCDSP used the MedStat database, a US medical claims database, to compare the VTE rate among ORTHO EVRA users relative to users of levonorgestrel-containing OCs with 30 µg EE.

Results for relative risk in the 4 sponsor-commissioned epidemiologic studies, for the primary composite endpoint of MI + ischemic stroke, varied among studies on both sides of the null value of 1.0, and all the studies individually had very wide confidence intervals, reflecting the small number of events. For VTE, the results of the epidemiologic studies of ORTHO EVRA were also variable among studies, with point estimates of the odds ratios ranging from 1.2 to 2.2. Methodological differences among the studies could account for some of the variability, although the expected direction of the influence of these design factors is not clear. The highest estimated odds ratio came from the one study that included chart review.

A meta-analysis of the 4 studies showed that for MI + ischemic stroke, the summary relative risk was 0.8 (95% CI 0.4-1.4), consistent with no difference between ORTHO EVRA and second generation OCs. For VTE, the summary odds ratio was 1.5 (95% CI 1.1-1.9), suggesting a 50% increase in risk. However, based on the ends of the 95% confidence intervals, the results of the meta-analyses are consistent with a 60% decrease to a 40% increase in risk for MI + ischemic stroke, and with a 10% increase to a 90% increase in risk for VTE.

In addition to the 4 sponsor-commissioned studies, results from an FDA-commissioned study were recently reported. In this study, drospirenone (DRSP)-containing OCs, ORTHO EVRA patch (abbreviated as NGMN in the FDA report), and etonogestrel/estradiol vaginal ring (ETON) were associated with a significantly higher risk of VTE relative to a combined comparator group of combination OCs containing LNG, NGM, or norethindrone acetate. Estimates of relative risk were 1.74 (95% CI 1.42-2.14) for DRSP, 1.55 (95% CI 1.17-2.07) for ORTHO EVRA (NGMN), and 1.56 (95% CI 1.02-2.37) for ETON. The results for ORTHO EVRA were based on a total of 33 events in users of ORTHO EVRA.

The results from these epidemiology studies suggest that the incidence of VTEs for ORTHO EVRA users is, as stated in the US Prescribing Information (USPI), in the “range from no increase in risk to an approximate doubling of risk”, a similar range as seen with other marketed

hormonal contraceptive products when compared to OCs containing EE and either norgestimate or levonorgestrel. Even if one were to assume that the true risk of having a VTE is approximately double that of second generation OCs, the absolute risk of VTE remains low and is lower than that observed during pregnancy and the puerperium.

Relative risks for VTE associated with combination hormonal contraception

The VTE risk associated with ORTHO EVRA should be considered in the context of the VTE risks of other hormonal contraceptives. A comprehensive review of the literature identified 22 relevant population-based studies. These include case-control and cohort studies, and describe VTE rates among users of hormonal contraceptives with second generation progestins (LNG, NGM, NGMN, and norethindrone), third generation (desogestrel, etonogestrel, and gestodene) and fourth generation (drospirenone). Four of the 22 studies included in this review were the ORTHO EVRA studies and the other 18 studies compare combination OCs having a second generation progestin with other combination OCs and allow a qualitative comparison with the findings for ORTHO EVRA, as the comparators were the same. The comparative results from the 22 studies suggests that the magnitude of the relative risks for ORTHO EVRA compared with second generation OCs is similar to the magnitude of the relative risks for third and fourth generation OCs compared with second generation OCs. This highlights the fact that many other combination hormonal contraceptive options appear to have increased VTE risks relative to second generation products that need to be discussed with the woman and weighed against the possible benefits.

**Product Labeling and Communication**

Product labeling communicates comprehensive product information to help ensure the safe and appropriate use of a product. Since the approval of ORTHO EVRA in November 2001, several revisions to the USPI have been implemented based on clinical PK or epidemiologic data obtained from studies conducted post-approval. Information about the risk of VTEs, along with information on the different PK profiles of ORTHO EVRA compared with OCs, is presented in several sections of the current USPI, including a Boxed Warning; in the Warnings, Product Description, and Clinical Pharmacology sections; and in Detailed Patient Labeling. In some instances, information was also conveyed to clinicians or the public via Dear Healthcare Professional letters or press releases. For all these labeling changes, discussions were held with the FDA regarding proposed language and all changes were submitted as prior approval supplements.

The November 2005 update to the USPI included data from a post-approval PK study on the differences in various exposure parameters between ORTHO EVRA and a 35 µg EE-containing OC. This update in ORTHO EVRA labeling included adding language to the WARNINGS section stating that exposure (ie, AUC and $C_{ss}$) to EE is 60% higher in users of ORTHO EVRA than in users of a 35 µg-EE OC but maximum blood concentration (ie, $C_{max}$) is 25% lower for ORTHO EVRA. This labeling update was accompanied by a Dear Healthcare Professional letter. A further enhancement to the labeling was made in March 2011, when this information was added to the Boxed Warning.

**Benefit-risk Assessment**

ORTHO EVRA has been marketed for almost a decade and has been safely and effectively used by millions of women to ensure their pregnancies are planned and prepared for. Many of these women have found it to be the "best option" for them based on its unique delivery system and dosing regimen. The substantial post-marketing experience confirms the findings of the clinical development program, which demonstrated ORTHO EVRA is highly efficacious, with a pooled Pearl Index from all Phase 3 studies of 0.88. This, coupled with its ability to reduce dosing frequency to once-per-week, is of benefit to some women, including those with difficulty complying with a daily pill-taking regimen.

The clinical trial and post-marketing experience also confirm the safety and tolerability of ORTHO EVRA. The frequency and types of adverse events have been found to be similar to those of other hormonal contraceptive options available to women. Nonetheless, all combination hormonal contraceptives carry a small, but real, increased risk of VTE. Multiple pharmacoepidemiologic studies, including the one recently conducted by the FDA, have demonstrated this risk and provided reasonably consistent estimates of the relative risks associated with other combination hormonal contraceptives relative to second generation combination OCs. Many of these studies have also estimated the absolute VTE rates for these products. The information on the VTE risk associated with ORTHO EVRA relative to that of second generation combination OCs is prominently displayed in ORTHO EVRA labeling and all professional and patient materials.

Although ORTHO EVRA is associated with an incremental increase in VTE risk versus the second generation combination OCs, the difference in absolute terms is small and amounts to approximately 1.5 to 4.5 events per 10,000 woman-years of use, depending on the assumed baseline risk, which varies among the studies. When compared to the widely used third and fourth generation combination oral contraceptives, the risks of VTE associated with ORTHO EVRA are essentially the same. All of these risks are substantially lower than the VTE risk associated with planned or unplanned pregnancies and during the post partum period. Thus, an unintended consequence of reducing contraceptive choice, by eliminating or limiting access to ORTHO EVRA among women for whom it is the option that works best, could be an increase in VTE risks and the other consequences of unintended or unplanned pregnancies. The health of the public will be best served by ensuring that clinicians are well informed and by encouraging clinicians to have meaningful dialogues with their patients to ensure the benefits and risks of the various contraceptive options are understood and decisions among these options are well informed.

**Concluding Remarks**

- It is important for clinicians and women to have a wide array of safe and effective contraceptive options and to be able to choose a method that is best suited for the individual woman, based on her medical history, non-medical needs, and product attributes.
- For those women who are candidates for hormonal contraception and who elect to use a transdermal patch, ORTHO EVRA is a unique contraceptive option with a favorable

benefit-risk profile. ORTHO EVRA should remain available as a contraceptive option for those women and their clinicians.

- All combination hormonal contraceptives carry a risk of VTE, which is less than the risk of VTE during pregnancy and the post-partum period. Results from the recently conducted meta-analysis and FDA-commissioned epidemiology study indicated that VTE risk associated with ORTHO EVRA:
  - is higher than that of norgestimate-containing OCs (meta-analysis data) and levonorgestrel-containing OCs (meta-analysis data and FDA-commissioned epidemiology study)
  - is in the range of other combination hormonal contraceptives.
- Since the launch of ORTHO EVRA, the Company has been diligent in generating and communicating comprehensive product information to clinicians and patients. The ORTHO EVRA labeling prominently communicates information on risk of VTE in multiple sections: Boxed Warning, Warnings, Indications and Usage and in other sections.
  - ORTHO EVRA has a unique Indication and Usage section that advises clinicians to balance the higher estrogen exposure and "the possible increased risk of VTE with ORTHO EVRA against the chance of pregnancy if a contraceptive pill is not taken daily." It is the only combination hormonal contraceptive that is indicated "for the prevention of pregnancy in women who elect to use a transdermal patch as a method of contraception."
  - The labeling will continue to be updated appropriately as new information becomes available, including the Company's recently completed meta-analysis and the recently completed FDA-commissioned epidemiology study.
- ORTHO EVRA safety and efficacy information is provided in consumer-friendly language in the Detailed Patient Labeling that is in each box of ORTHO EVRA patches, and on the ORTHO EVRA website (www.orthoevra.com).

The Company appreciates the opportunity to participate in this Advisory Committee and is interested in the input of the Advisory Committee and the FDA. We are committed to continue to work with the FDA to enable appropriate product usage and meet the needs of individual women.

# 1. INTRODUCTION

This document is intended to provide information and perspective to assist the Reproductive Health Drugs and Drug Safety and Risk Management Advisory Committees in evaluating the benefit-risk profile of ORTHO EVRA (norelgestromin/ethinyl estradiol Transdermal System) at their joint meeting on 9 December 2011. This information is being provided by Janssen Pharmaceuticals, Inc., the Sponsor of NDA 21-180 for ORTHO EVRA.

## 1.1. ORTHO EVRA

ORTHO EVRA is a member of the class of combination hormonal contraceptive products. The development of ORTHO EVRA occurred as a result of the Sponsor's determination 25 years ago that there was a need for a non-oral hormonal contraceptive delivery system for women who wanted the benefits provided by hormonal contraceptives but without the need for daily dosing. The product is unique in the contraceptive market, as it is the only birth control option that is delivered in a transdermal patch format and allows the convenience of once-weekly rather than once-daily dosing.

The 7-day ORTHO EVRA transdermal contraceptive system was approved in the United States by the Food and Drug Administration (FDA) for the prevention of pregnancy on 20 November 2001. The product was first made available in the United States in April 2002. The product marketed outside the United States is EVRA®, a different formulation. This briefing document will focus exclusively on the US formulation, ORTHO EVRA.

ORTHO EVRA is a square, flexible, matrix patch system with a contact surface area of 20 $cm^2$. Each patch contains 6.00 mg norelgestromin (NGMN) and 0.75 mg ethinyl estradiol (EE). NGMN is the primary active metabolite of norgestimate (NGM), a progestin found in many combination OCs. The pharmacological properties of NGMN are similar to those of NGM. EE is the estrogen most frequently used in combination OCs.

Each cycle of contraceptive treatment with the patch consists of 28 days. A new ORTHO EVRA patch is applied each week for 3 weeks (after removal of the prior week's patch at the beginning of weeks 2 and 3), resulting in 21 consecutive days with hormonal treatment followed by 7 days without treatment (no patch). The patch may be applied to one of 4 sites: buttock, abdomen, torso (excluding breasts) and upper arm.

Since approval, ORTHO EVRA has been used widely by women of multiple ethnic, age, and socioeconomic groups. There have been over 5.5 million woman-years of clinical experience with ORTHO EVRA since the product was introduced to the market.[70] Approximately one-third of women currently using ORTHO EVRA are 19 years of age and under, two-thirds are between 20 and 39 years, and a small proportion (<5%) are 40 years or older.[37]

## 1.2. Hormonal Contraceptives

<u>Hormonal contraceptive classification</u>

Hormonal contraceptives can be classified into 2 main types with respect to their active ingredients: those that contain estrogen and progestin (ie, combination hormonal contraceptives)

and those that contain only progestin (ie, progestin-only contraceptives). Both types of hormonal contraceptives are highly effective (ie, 99% effective) when used exactly as directed.

Hormonal contraceptive mechanism of action

All hormonal contraceptives induce their effects through a variety of mechanisms. The primary mechanism of action is ovulation suppression. Synthetic contraceptive hormones block the luteinizing hormone surge, the hormonal signal that triggers ovulation in a typical menstrual cycle. Combination hormonal contraceptives block ovulation in about 85-95% of cycles whereas progestin-only oral contraceptives block ovulation in approximately 40-50% of cycles. Secondary mechanisms of action include an increase in cervical mucus viscosity, making it impenetrable to sperm and forming a barrier to sperm ascent to the upper reproductive tract where fertilization normally occurs. This effect is due to the action of the progestin on cervical mucus production. A third mechanism of action is the progestin's effect on the endometrium, making it unreceptive to a fertilized egg.

Although estrogen is not needed for a highly effective hormonal contraceptive, its presence in combination hormonal contraceptives helps to stabilize the endometrium, allowing the user to have more regular and predictable withdrawal bleeds that mimic spontaneous menstrual cycles (ie, good "cycle control"). Progestin-only contraceptives are often associated with a higher rate of unscheduled bleeding, often referred to as "breakthrough bleeding and spotting", or the absence of withdrawal flow. While these altered bleeding patterns do not alter contraceptive efficacy, they are a major cause of user dissatisfaction and are frequently cited as a reason for discontinuation of the methods.

OC development

When OCs were first developed in the late 1950s and early 1960s, they had much higher doses of estrogen (150 µg mestranol or 100 µg EE) and progestin than do currently marketed combination OCs. Doses of contraceptive hormones were reduced over many years after early epidemiology studies that found an association between OC use and thromboembolic adverse events (ie, myocardial infarction [MI], ischemic stroke, venous thromboembolism [VTE]). Currently marketed combination OCs have EE doses ranging from 10-50 µg/tablet, providing many choices for women based on their individual needs. Lowering the doses of contraceptive hormones has resulted in lower risk of thromboembolic events among OC users, with the lowest rates being observed with OCs containing 20-35 µg EE (the 10 µg EE OC has been marketed recently and there are no epidemiology studies on VTE risk for this product). OCs with the lowest EE doses are highly effective yet are associated with the highest rates of unscheduled bleeding.

Along with the decrease in estrogen dose over time, new synthetic progestins were introduced as well. These newer progestins, and the combination OCs containing them, have been somewhat inconsistently classified into "generations" by various authors. For clarity, the classification scheme for progestins by generation that will be used in this document is shown in Table 1.

**Table 1 Classification of Progestins by Generation**

| Generation | Progestins |
|---|---|
| First | Norethynodrel |
| Second | Levonorgestrel (LNG)<br>Norethindrone (NET)<br>Norethindrone acetate<br>Norgestrel<br>Norgestimate (NGM)<br>Norelgestromin (NGMN) |
| Third | Desogestrel (DSG)<br>Etonogestrel (ETON)<br>Gestodene (GST) |
| Fourth | Drospirenone (DRSP) |

The progestins used in the original combination OCs have now become known as "first generation" progestins (and, correspondingly, the OCs containing these progestins are known as "first generation OCs"). OCs that use these progestins are used infrequently. In the 1970s, a second generation of progestins was introduced, and many of these progestins are used in currently available combination OCs. Some of these progestins include levonorgestrel (LNG), norethindrone, norethindrone acetate, NGM, NGMN, and norgestrel. These progestins have pharmacologic properties of natural progesterone but also demonstrate androgenic and estrogenic activity in vitro.

In the 1980s and 1990s, a third generation of progestins was introduced, the most notable of which were desogestrel (DSG) and gestodene (GST) (not marketed in the US). These progestins have pharmacologic properties of progesterone but minimal androgenic activity and it was hoped that, when combined with EE, they would produce an OC with minimal androgenic adverse events associated with combination OCs, such as acne and oily skin. However, third generation OCs were later found to be associated with a higher risk of VTE compared with second generation OCs.[34] After 2000, a fourth generation of progestins was introduced, the most popular being DRSP. This progestin was found to have anti-androgenic activity in vitro as well as anti-mineralocorticoid activity. Combination OCs that contain DRSP have been used to treat androgen-associated disorders (eg, moderate acne vulgaris) and decrease fluid retention due to their anti-mineralocorticoid effects. Some studies have suggested that fourth generation OCs are associated with higher rates of VTE than second generation OCs.[46,69] The currently marketed combination OCs, have EE doses ranging from 10-50 µg/tablet and either a second, third, or fourth generation progestin.

## 1.3. Venous Thrombosis in Reproductive Age Women

VTE

VTE events generally present as deep vein thrombosis (DVT; a blood clot in a deep vein, most commonly in one of the legs) or pulmonary embolism (PE; a blood clot in a pulmonary artery or one of its branches). Risk factors for VTE can be inherited (eg, deficiencies in antithrombin III,

protein S, protein C) or acquired (eg, age, obesity, smoking, pregnancy, trauma, prolonged immobilization following surgery or injury or during travel). In 25% to 50% of the cases of spontaneous venous thromboembolism, no identifiable risk factor can be found.[106] Virchow's triad refers to 3 mechanisms that increase thrombotic risk: endothelial disruption or injury, venous stasis, and hypercoagulability.

Effects of natural and synthetic estrogen and progestin on coagulation

The effects of natural and synthetic estrogen and progestin on coagulation are complex. These hormones modulate factors in the coagulation cascade that are associated with clot formation (eg, prothrombin) and clot lysis (eg, antithrombin). In general, all combination hormonal contraceptives (estrogen-progestin formulations) increase the risk of VTE. In any particular woman using combination hormonal contraception, there may be independent acquired risk factors for VTE such as age, obesity, smoking, malignancy, immobilization, trauma, pregnancy, and prolonged bed rest, as well as inherited risk factors such as prothrombin gene mutation, Factor V Leiden gene mutation (activated protein C resistance) and antithrombin III deficiency.

Annual incidence of VTE

The reported overall age- and sex- adjusted annual incidence of VTE is approximately 11.7 per 10,000 (4.8 per 10,000 for DVT and 6.9 per 10,000 for PE).[77] The incidence of DVT/PE increases markedly with age. With respect to all women of reproductive age not using hormonal contraception the incidence rate is reported to be approximately 1 to 5 per 10,000 woman-years; the incidence is much higher for women during pregnancy and in the postpartum period. A US population database study reviewed the cases of VTE in women during pregnancy and 3 months postpartum for the period 1966-1995.[32] The relative risk (standardized incidence ratio) for VTE among pregnant and postpartum women was 4.29 (95% CI 3.49-5.22; $p<0.001$) compared to non-pregnant women, and the overall incidence was 20 per 10,000 woman-years. The annual incidence was 5 times higher among postpartum women than pregnant women (51.1 vs. 9.6 per 10,000), and the incidence of DVT was 3 times higher than that of PE (15.2 vs. 4.8 per 10,000). A recent study reported the incidence of antepartum plus postpartum VTEs to be 17.2 per 10,000 deliveries.[41]

Clinical presentation of VTE

A person with a typical DVT may present with pain and swelling of the leg, but as many as half of the patients with a radiographically proven DVT do not have these symptoms. A person experiencing a PE may present with difficulty breathing, palpitations, inspiratory chest pain, and hemoptysis. Anticoagulant therapy is indicated for patients with symptomatic DVT, since PE can occur as a complication of untreated DVT. The same therapy is indicated for patients diagnosed with a PE. The duration of anticoagulation therapy varies depending on the clinical setting and risk factors, as well as the identification of any inherited thrombophilias. Roughly 30% of those who have a VTE in a given year will experience a recurrent episode in the next 10 years, with the risks being greatest in the first 6 to 12 months after the initial event.[33] Recurrence is less likely if the initial episode was provoked by a transient event such as contraceptive use.[33] While VTE, especially PE, causes morbidity, it is rarely fatal in otherwise healthy reproductive age women.

In a large study of women with VTEs over a 14-year period, the event was fatal in 0.6% of women aged 15-29 and 1.7% of women aged 30-44.[59]

Absolute risk of VTE

Many experts consider absolute risk of VTEs to be a more useful way to understand VTE risk for their patients using or considering combination hormonal contraception. For a healthy, non-obese, non-smoking woman of reproductive age not using a hormonal contraceptive, the risk of VTE is less than 1 per 10,000 woman-years; this rate increases to 3 to 4 per 10,000 woman-years in women who use OCs containing 30-40 µg EE.[102] The increase in VTE risk among women using combination OCs, or other combination hormonal contraceptives, compared to women not using this form of birth control has been known for over 40 years and is incorporated into the benefit/risk assessment made by clinicians in counseling women on their contraceptive choices.

## 2. MEDICAL NEED FOR CONTRACEPTIVE OPTIONS

Ideally, every pregnancy will be planned and prepared for in order to achieve the best outcomes for maternal and child health. Unfortunately, the United States has not achieved that standard. The statistics on pregnancy outcomes in the U.S., including morbidity and mortality, remain concerning:

- Almost half of the approximately 6.4 million pregnancies each year in this country are unintended.[27]
- In 2005, 19% of all pregnancies in the U.S. ended in elective abortion;[103] more than one-third of American women will have had an elective abortion by age 45.[35]
- Maternal mortality rates in the U.S. are the highest they have been in the last 20 years and a U.S. woman has a 1 in 2,100 lifetime risk of dying from pregnancy-related causes.[95] The most common causes of death are hemorrhage, pulmonary embolism, infection, hypertensive disorders of pregnancy, cardiomyopathy, cardiovascular conditions, and non-cardiovascular medical conditions, each contributing 10-13% of deaths.[6]
- Maternal morbidity in the U.S. is also high. In a recent study, rates of maternal morbidity were estimated for women enrolled in Kaiser Permanente Northwest, a large HMO. Overall, 50% of women had at least 1 complication. Among the more serious conditions were: antepartum hemorrhage (4.1%), postpartum hemorrhage (3.8%), diabetes in pregnancy (1.1%), pneumonia (0.6%), complications of anesthesia (0.6%), disseminated intravascular coagulation (0.2%), uterine rupture (0.1%), thrombophlebitis and embolism (0.1%).[9]

Contraceptive failures

Many women who conceive do so while using contraceptives. Contraceptive failure can be the result of method failure (ie, pregnancy occurs despite the product being used exactly as directed) or failure to use the method correctly and consistently.[53] Overall, contraceptives were used during the month of conception in 48% of all unintended pregnancies in the U.S., which resulted in 1.5 million unintended pregnancies despite contraceptive use.[27] Current estimates from the National Survey of Family Growth are that 8.7% of the more than 10 million women using OCs in the United States become pregnant each year,[66] resulting in almost one million unintended

pregnancies among OC users. The fact that the actual failure rate is more than 25-fold greater than the method failure rate (ie, failure rate with correct and consistent use) of OCs of 0.3%[96,98] suggests that many women do not use their OCs as directed.

Dosing simplification

Women acknowledge the difficulty of complying with a daily dosing regimen. In one study, the proportion of OC users who missed at least 3 birth control pills during a treatment cycle ranged from 30% to 51% over 3 cycles.[72] This difficulty with correct and consistent use of OCs highlights the need for a range of contraceptive options from which to choose. Finding the method best suited for a particular woman should increase the likelihood of correct usage which, in turn, has the potential to lower the risk of unintended pregnancy. As Trussell wrote in a 2004 review of contraceptive failure, "The most effective method for an individual woman or couple is a method that actually will be used correctly and consistently."[97]

Simplification of dosing should enhance compliance and successful use. With a daily method, there are 7 opportunities for error for every 1 opportunity for error with the weekly method. There is evidence to support this hypothesis in multiple therapeutic areas. Clinical trials have indicated higher compliance rates for the contraceptive patch and vaginal ring than for the pill. Clinical trial failure rates are many times lower than those seen in typical use. This differential is likely due to user failure rather than method failure. Methods that facilitate high compliance should have lower pregnancy rates. However, improved efficacy due to improved compliance may be difficult to demonstrate in clinical trials as typical contraceptive drug development programs generally expose between 1,500 and 3,500 women to the product in Phase 3 trials.

As described elsewhere in this document, there are no randomized clinical trials that demonstrate whether shifting ORTHO EVRA users to oral contraceptives would result in a loss of effectiveness. This reflects the fact that such a trial would face ethical issues, practical issues of blinding because the medications to be compared are administered by different routes, and difficulties in studying real-world effectiveness, as distinct from efficacy, in a randomized clinical trial. The observational trials that attempted to compare the effectiveness of ORTHO EVRA and oral contraceptives did not show higher effectiveness in the ORTHO EVRA group (see Section 3.3.4), but the interpretation of this finding is complicated by the fact that the populations using the contraceptive patch and OCs differ substantially in ways that are likely to affect compliance and hence effectiveness.

The mechanisms by which hormonal contraceptives act to produce their desired effect are reasonably well understood and it is clear from the comparison of Pearl indices between good compliers and poor compliers, or between clinical trials and actual use, that compliance is a major, but not the only, determinant of the effectiveness of currently marketed hormonal contraceptives. Therefore, in support of the potential for greater effectiveness of ORTHO EVRA in the population that uses it in preference to oral contraceptives, we provide a brief summary of several systematic reviews from other clinical areas, suggesting compliance is better with less frequent dosing schedules than with more frequent dosing schedules (eg, better with a once a day schedule than with twice a day schedule, and better with a once a week schedule than with a once a day schedule). These systematic reviews included medications for a wide range of

indications including cancer, hypertension, other cardiovascular diseases, diabetes, infectious diseases, psychiatric indications, respiratory diseases, and osteoporosis. The systematic reviews included prospective and retrospective studies, and focused on compliance rather than on the effect of compliance on therapeutic effectiveness. The studies used various measures of compliance (eg, the proportion of the prescribed pills taken each day, or the proportion taken within a specified time frame) and various methods to assess pill taking (eg, diaries, measurement of blood concentrations, electronic monitoring of times when the pill containers were opened). We recognize that neither the relationship between compliance and treatment effect, nor the measurement of compliance is a simple matter.[62,67]

A review of 76 studies that used electronic monitoring to assess pill taking compliance for a wide range of indications found the overall mean of dose taking compliance (taking the prescribed number of pills each day) was 71% and declined as the number of daily doses increased: 79% with 1 dose/day, 69% with 2 doses/day, 65%, with 3 doses/day, 51% with 4 doses/day.[11] The change in compliance with number of doses was statistically significant ($p<0.001$). A meta-analysis of the relationship of the number of daily doses to adherence to antihypertensive therapy identified 8 prospective or retrospective studies that met its inclusion criteria and found the average adherence rates were: 91.4% with 1 dose/day and 83.2% with multiple doses/day, a difference that was statistically significant ($p<0.001$).[40] Cramer reviewed 14 retrospective studies of compliance with (oral) bisphosphonates for osteoporosis and found that compliance, as measured by the mean medication possession ratio "was consistently higher for weekly versus daily therapy (0.58 to 0.76 versus 0.46 to 0.64 for women receiving weekly and daily bisphosphonate therapy, respectively). Persistence was also improved in women receiving weekly bisphosphonates, assessed by both length of persistence (194 to 269 days [weekly] and 134 to 208 days [daily]) and percentage of persistent women at the end of the follow-up period (35.7% to 69.7% [weekly] and 26.1% to 55.7% [daily])."[19] The authors observed that "All of the studies that examined compliance and persistence in patients receiving daily and weekly bisphosphonates found the same pattern – patients exhibited better medication-taking behavior with weekly therapy."

These systematic reviews indicate that, whether dosing frequency is measured in doses per day or doses per week, compliance is better with lower dosing frequency than with higher dosing frequency. This suggests that, at least among women who have elected to use ORTHO EVRA, compliance and therefore effectiveness will be better with once a week regimen of changing their ORTHO EVRA patch than with a 7 times per week regimen of taking an oral contraceptive.

Each OC has its own benefit-risk profile

There are more than 90 marketed branded and generic combination OCs as well as numerous other methods of contraception, each of which has its own benefit-risk profile. All combination OCs are approximately 99% effective when used as directed and are generally considered safe. However, all combination OCs are associated with a small (in absolute terms) increased risk of VTE. Women and their clinicians are familiar with and accept this well-known risk when selecting a combination hormonal contraceptive method.

Some attributes of available contraceptive methods that are considered when choosing a contraceptive are highlighted in Table 2.

**Table 2: Failure Rates and Attributes of Various Contraceptive Methods**

| Contraceptive Method | Failure Rate in First Year of Use | | Regulates/ Disrupts Cyclic Bleeding | Prompt Contraceptive Reversibility | Requires Vaginal Placement | Verifi-ability[a] | Dosing Frequency | Major Risks |
|---|---|---|---|---|---|---|---|---|
| | Typical Use | Perfect Use | | | | | | |
| No method | 85 | 85 | n/a | n/a | n/a | n/a | n/a | Pregnancy, Pregnancy-related risks |
| ORTHO EVRA® | 9[b] | 0.3[b] | R | Y | N | Y | Weekly | VTE |
| OC (combination and progestin only) | | | R | Y | N | N | Daily | |
| Vaginal ring | | | R | Y | Y | Y | Monthly | |
| Three-month injectable | 6 | 0.2 | D | N | N | N | 3 months | Bone loss, Weight gain, Abnormal bleeding |
| Implant | 0.05 | 0.05 | D | Y | N | Y | 3 years | Bleeding irregularities |
| IUC (levonorgestrel, copper) | 0.2-0.8 | 0.2-0.6 | D/ n/a | Y | Y | Y | 5 or 10 years | Ectopic pregnancy, Infection, Uterine perforation |
| Sterilization (male or female) | 0.15-0.5 | 0.1-0.5 | n/a | N | N | N | Once | Operative risks including bleeding, infection, and damage to nearby organs |
| Male condom | 18 | 2 | n/a | Y | N | Y | Each act | Pregnancy |
| Female barrier methods including spermicides, diaphragm, sponge, female condom | 12-28 | 5-20 | n/a | Y | Y | Y | Each act | Pregnancy |
| Withdrawal | 22 | 4 | n/a | Y | N | N | Each act | Pregnancy |
| Fertility awareness-based methods (“rhythm method”) | 24 | 0.4-5 | n/a | Y | N | N | Nearly daily evaluation for fertility timing | Pregnancy |
| Abstinence | | 0 | n/a | Y | N | n/a | n/a | n/a |

OC = oral contraceptive; IUC = intrauterine contraception
Note: Adapted from Tables 3-2 and 3-4 in reference 96 and includes updates from reference 98. (Table 4 of the USPI is Table 3-2 from the 1998 edition of reference 96.)
[a] The user can easily verify the presence of the method, providing reassurance about the continued protection.
[b] Reference 98.

Ensuring that women have comprehensive information about both benefits and risks is an important step toward improving contraceptive use and reducing the number of unintended pregnancies. Each individual woman has her own particular needs for her contraceptive method. These needs are based on her medical history and general health as well as lifestyle, social and cultural considerations. Choice of contraception is not static and women change methods throughout their reproductive years. Contraceptive choice tends to relate to specific life stages, events, or product attributes, such as: sexual debut, after childbirth, when relationship status changes, after difficulty with a particular contraceptive method, or method cost.[5]

Benefit-risk assessment varies with the woman

While some women are ambivalent about their choice of method and do not make conscious trade-offs, other women have priorities that lead them toward or away from certain methods. Some women want to maximize effectiveness, others prefer to minimize risk of adverse events, others place the highest value on convenience, and still others prioritize protection from sexually transmitted infections.[10] Some women are willing to accept the risks of general anesthesia and of bowel perforation with laparoscopic tubal sterilization; others accept the risks of bone loss and weight gain with depot medroxyprogesterone acetate; others accept the risks of uterine perforation and infection with intrauterine contraceptives; and others accept the risks of thromboembolic events with estrogen-containing contraceptives. The benefit-risk assessment varies with the woman. For instance, a woman with a history of migraine with aura may be willing to accept a method that leads to irregular bleeding or lower efficacy to avoid estrogen-containing OCs that have been shown to increase the risk of stroke in such women. A woman who puts a premium on predictable monthly withdrawal bleeding may find progestin-only methods less desirable. A woman who has trouble remembering to take a pill daily may seek the convenience of a method with less frequent dosing such as a weekly patch. These examples point to the importance in having a variety of contraceptive choices available.

All of the hormonal methods are safer for women than pregnancy. During contraceptive counseling sessions, like those occurring every day in clinics and offices around the country, the clinician has the opportunity to educate the woman and understand her preferences and perceptions concerning the risks and benefits of individual contraceptive options. The clinician provides the woman with appropriate information and medical advice, providing each individual woman the information required for her to weigh her choices and select the method best suited to her needs.

# 3. CLINICAL DEVELOPMENT

## 3.1. Pharmacokinetics of ORTHO EVRA

During development of a new drug formulation, the performance of the formulation must be characterized as fully as possible in order to understand how the formulation will behave under the conditions pertinent to its use (including both patient and non-patient factors). Clinical pharmacology studies are routinely conducted to generate drug concentration vs. time profiles (PK profiles) that are specific for a formulation and for the route of administration. These studies

provide critical information on the absorption, distribution, biotransformation and elimination of the drug in the body and how other factors impact the performance of the formulation.

When developing a new formulation of an existing drug or a formulation with a different route of administration, a typical approach for dose or exposure selection is to establish a range of serum or plasma drug concentrations (eg, average concentration or $C_{avg}$) based upon the PK of an existing formulation. This PK information provides some general reference information from which to start development of a new drug formulation.

In the case of ORTHO EVRA, exposure data from a 35 µg ethinyl estradiol (EE)-containing OC, ORTHO-CYCLEN® (35µg EE/250µg NGM), were used to provide some basic information for the new transdermal contraceptive system. As a starting point in this development process, reference serum drug concentration ranges for EE of 25 to 75 pg/mL and NGMN of 0.6 to 1.2 ng/mL were established based on a band of concentrations that captured 90% of the average steady-state serum drug concentration ($C_{avg}$) values for women taking ORTHO-CYCLEN.

Pilot test patches were manufactured, and 2 clinical studies were conducted to determine the amounts and proportion of EE and NGMN in the patch that would achieve concentrations within these reference ranges. Patches containing the same proportional amounts of EE and NGMN were then manufactured in 3 patch sizes: 10 $cm^2$, 15 $cm^2$, and 20 $cm^2$. The goal of the Phase 2 dose-ranging study was to test a range of patch sizes to determine the patch that would achieve predetermined levels of ovulation suppression coupled with good cycle control along with an acceptable risk/tolerability profile. Only the 20 $cm^2$ patch, which contained 6.0 mg NGMN and 0.75 mg EE, met both the ovulation suppression and cycle control criteria and was therefore selected for Phase 3 studies.

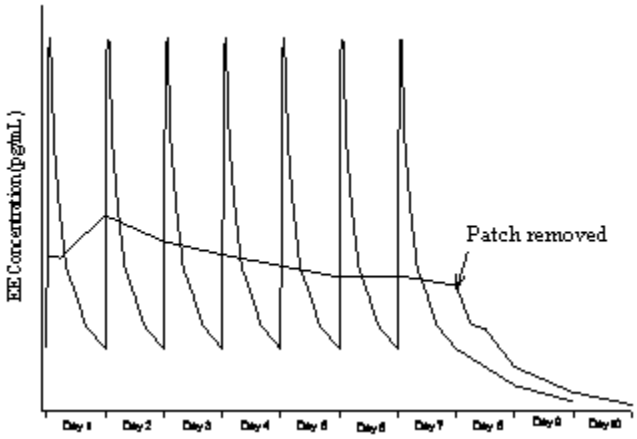
Additional pre-approval clinical pharmacology studies characterized the effects of physiologic and environmental factors that might potentially alter the transdermal delivery of hormones. The effects of age, body weight, and body surface area exhibited a trend toward slightly decreasing AUC and $C_{ss}$ values while multiple dosing, heat, and exercise exhibited a modest trend upward in AUC and $C_{ss}$ values. There were no effects on AUC and $C_{ss}$ to related to race. Subsequent Phase 3 studies were conducted to evaluate efficacy and safety of the patch. This information was included in the NDA submission.

In 2002, the Sponsor received an ex-US regulatory request to conduct a post approval study comparing the PK profiles of ORTHO EVRA and an OC with 35 µg EE and 250 µg NGM. In this 2-way crossover study (NED-1)[16] that was completed in 2003, healthy subjects (n=34) received two 28-day contraceptive cycles (2 cycles of three consecutive 7-day patch applications or 21 days of OC, followed by 7 days without treatment). ORTHO EVRA was shown to have a 60% higher $C_{ss}$ and AUC for EE relative to that from the OC. In contrast, the OC had a 25% higher $C_{max}$ for EE relative to that from ORTHO EVRA. Both products showed a high degree of inter-subject variability (based on coefficients of variation [CVs]) for all PK parameters, characteristic of the class of hormonal contraceptives; variability was slightly higher for ORTHO EVRA (CVs 32% to 33%) than for the OC (CVs 27% to 28%). It was also noted that the mean AUC and $C_{ss}$ values for EE in this study for the initial patch (Week 1) were somewhat higher

than those generally determined in the single application studies conducted during clinical development and for 12 of 13 lots of commercial product evaluated in another post-approval study evaluating the PK profiles across different commercial lots of the product.[15] The comparative PK data from the NED-1 study noting these differences between ORTHO EVRA and an OC in terms of AUC, $C_{ss}$, and $C_{max}$ of EE were incorporated into the US Prescribing Information (USPI) for ORTHO EVRA in 2005 as a bolded Warning that indicated that women taking ORTHO EVRA may be exposed to higher levels of estrogen. This labeling change was also communicated to prescribers in a Dear Healthcare Provider letter. In March 2011, the labeling was updated to add this information into a boxed Warning (see Appendix 1 for the current USPI).

Transdermal delivery provides contraceptive hormones at a slower, more constant rate compared with the peak and trough "sawtooth" profile characteristic of an immediate release oral product. This is illustrated schematically in Figure 1.

**Figure 1 Schematic Illustration Showing Different Profiles in the Serum EE Concentration-Versus-Time Profile Between ORTHO EVRA (Transdermal Application) and ORTHO-CYCLEN (Daily Oral Tablet Dosing)**




Because transdermal delivery of medicines is different from oral delivery (eg, steady serum concentrations vs peaks and troughs) and serious adverse events are rare, the clinical significance of the different PK profiles between oral and transdermal hormones was not known. No information was available in the literature correlating any specific PK parameter for EE from either oral or transdermal delivery and thromboembolic events (eg, VTE). Therefore, the safety and efficacy of the transdermal patch needed to be evaluated in large clinical studies.

## 3.2. Pharmacodynamic Study of Hemostatic Variables

Combination OCs induce numerous changes in hemostatic variables, and it is generally believed that both coagulation and fibrinolytic pathways are activated.[51] As part of the ORTHO EVRA clinical development program, a study was conducted in 1998 to compare the effects of the ORTHO EVRA transdermal contraceptive patch on hemostatic factors with those of a monophasic, EE/DSG-containing combination OC and a triphasic EE/LNG-containing combination OC. The study was undertaken with the understanding that changes in hemostatic

factors have not been prospectively validated as markers of thrombosis risk, and no single coagulation factor has been established as a valid surrogate marker for VTE.[18,29,30,63,82,107]

The clinical study was an open-label study of 104 women randomized to receive either ORTHO EVRA or 1 of 2 combination OCs, Mercilon® (20 µg EE/150 µg DSG) or Triphasil® (30/40/30 µg EE, 50/75/125 µg LNG), for 6 cycles. These combination OCs were the same ones used in the 2 comparative Phase 3 clinical studies. The percent increase from baseline that was observed at cycle 6 for each treatment group, along with the p-values for each combination OC versus ORTHO EVRA are shown in Table 3.[52]

**Table 3 Coagulation Parameters for ORTHO EVRA and 2 OCs**

| Variable (units) | Percent Change from Baseline for | | | P-value | |
|---|---|---|---|---|---|
| | ORTHO EVRA (n=32) | Mercilon (n=33) | Triphasil (n=31) | ORTHO EVRA vs Mercilon | ORTHO EVRA vs Triphasil |
| ***Clot forming variable*** | | | | | |
| F 1+2 (nmol/L) | 101 | 57.5 | 56.4 | 0.088 | 0.063 |
| ***Fibrinolysis variables*** | | | | | |
| D-dimer (mcg/L) | 83.3 | 96.1 | 56.3 | 0.134 | 0.405 |
| PAP (mcg/L) | 38.6 | 70.6 | 53.3 | 0.029 | 0.54 |
| ***Other Variables*** | | | | | |
| AT (U/mL) | -8.4 | -3.0 | -6.5 | 0.093 | 0.532 |
| APCr (normalized) | 238 | 163 | 113 | 0.071 | 0.002 |
| Protein S (%) | -19.5 | -10.4 | -6.0 | 0.027 | 0.001 |
| Fibrinogen (g/L) | 12.4 | 11.2 | 9.6 | 0.979 | 0.937 |
| aPTT (s) | -6.4 | -6.8 | -9.2 | 0.928 | 0.504 |
| PT (s) | -4.6 | -4.3 | -7.3 | 0.319 | 0.32 |
| Glucose (mmol/L) | 1.6 | 3.6 | -1.2 | 0.546 | 0.495 |
| SHBG (nmol/L) | 276 | 209 | 114 | 0.005 | <0.0005 |
| CRP (mg/L) | 429 | 345 | 228 | 0.607 | 0.0885 |

Abbreviations: APCr = activated protein C resistance; aPPT = activated partial thromboplastin time; AT = antithrombin; CRP = C-reactive protein; F 1+2 = Prothrombin fragment 1+2; PAP = plasmin–plasmin inhibitor complex; PT = prothrombin time; SHBG = sex hormone-binding globulin

Source: Reference 52

The results showed that there were changes in hemostatic variables with all 3 contraceptives. There were increases in F 1+2 in all 3 groups, with the percent increases from baseline greater for ORTHO EVRA than for Mercilon or Triphasil. For D-Dimer and PAP (both reflecting fibrinolytic activity), ORTHO EVRA increases were less than with Mercilon and similar to Triphasil for PAP, and less than Mercilon and greater than Triphasil for D-Dimer.

A more recently conducted study compared hemostatic variables of women taking a 250 µg NGM/35 µg EE -containing combination OC (ORTHO-CYCLEN) with ORTHO EVRA.[50] The "major finding of the study" was that transdermal and oral contraceptives containing EE and NGM/norelgestromin have "similar effects on biomarkers of vascular disease after 2 months of treatment."

## 3.3. Clinical Efficacy

Three principal Phase 3 studies (CONT-002, CONT-003, and CONT-004) provided direct evidence of the contraceptive efficacy and safety of ORTHO EVRA.[2,12,13,14,76,79]

Studies CONT-003 (ex-US study) and CONT-004 (North American study) were multicenter, randomized, open-label, controlled comparative studies, conducted in Europe/South Africa and North America, respectively. Study CONT-002 (global noncomparative study) was a multicenter, open-label, noncomparative study, conducted in the United States, Europe, Australia, and Israel. These studies were designed to evaluate ORTHO EVRA with respect to contraceptive efficacy, cycle control, safety, compliance, and subject satisfaction, and, in the case of the ex-US and North American studies, to compare these characteristics of ORTHO EVRA with those of an OC comparator. The comparators in the ex-US and North American studies were Mercilon (20 µg EE/150 µg desogestrel) and Triphasil (30/40/30 µg EE, 50/75/125 µg LNG), respectively, which were widely used OCs in the regions where each study was conducted. Approximately the first third of subjects enrolled in each study were to receive the study medication for 13 cycles, while the remaining subjects were to receive 6 cycles of treatment. The study designs for the 3 studies are summarized in Table 4.

**Table 4 Phase 3 Safety and Efficacy Studies for ORTHO EVRA**

| Protocol No. | Study Description/Design | Treatment Regimen/Duration | No. Female Subjects: Enrolled Evaluated[a] | Age (years): Mean Range |
|---|---|---|---|---|
| NRGEEP-CONT-002 (Global noncomparative study) | Multicenter, nonrandomized, open-label, international study in healthy female subjects. Contraceptive efficacy evaluated from pregnancy rates; presence of pregnancy was determined by radioimmunoassay for urinary β-HCG. Cycle control efficacy evaluated by analysis of bleeding patterns (breakthrough bleeding and/or spotting, early withdrawal flow, intermenstrual bleeding, duration of menses, and duration of latent period). | ORTHO EVRA:<br>Patch content: NGMN: 6.0 mg; EE: 0.75 mg; patch worn for three 7-day intervals (Days 1-21, with first application on Day 1 of menses) followed by a 7-day patch-free interval (Days 22-28).<br><br>Total duration of treatment for each regimen was 6 or 13 cycles, depending on stage of recruitment. | 1,754 enrolled<br>1,672 evaluated for safety<br>1,664 evaluated for efficacy | 28.7<br>18-45 |
| NRGEEP-CONT-003 (ex-US study) | Multicenter, randomized, open-label, international, parallel-group study in healthy female subjects. Contraceptive efficacy evaluated from pregnancy rates; presence of pregnancy was determined by radioimmunoassay for urinary β-hCG. Cycle control efficacy evaluated by analysis of bleeding patterns (breakthrough bleeding and/or spotting, early withdrawal flow, intermenstrual bleeding, duration of menses, and duration of latent period). | ORTHO EVRA:<br>Patch content: NGMN: 6.0 mg; EE: 0.75 mg; patch worn for three 7-day intervals (Days 1-21, with first application on Day 1 of menses) followed by a 7-day patch-free interval (Days 22-28).<br><br>Mercilon:<br>150 μg desogestrel, 20 μg EE pill taken starting on Day 1 of cycle (first day of menses) and continuing through Day 21 (Weeks 1-3 inclusive); drug-free interval, Week 4.<br><br>Total duration of treatment for each regimen: was 6 or 13 cycles, depending on stage of recruitment | ORTHO EVRA:<br>861 enrolled (including 1 subject randomized to receive Mercilon but treated with ORTHO EVRA)<br>846 evaluated for safety<br>844 evaluated for efficacy<br><br>Mercilon:<br>656 enrolled (including 2 subjects randomized to receive ORTHO EVRA but treated with Mercilon)<br>643 evaluated for safety<br>640 evaluated for efficacy | 28.8<br>18-45<br><br>28.3<br>17-45 |

[a] No. subjects evaluated=number of subjects who were enrolled in the study, received study medication, and provided any on-treatment data
Abbreviations: β-hCG= beta human chorionic gonadotrophin, μg=microgram, NGMN=norelgestromin, EE=ethinyl estradiol

**Table 4 Phase 3 Safety and Efficacy Studies for ORTHO EVRA**

| Protocol No. | Study Description/Design | Treatment Regimen/Duration | No. Female Subjects: Enrolled Evaluated[a] | Age (years): Mean Range |
|---|---|---|---|---|
| NRGEEP-CONT-004 (North American study) | Multicenter, randomized, open-label, parallel-group study in healthy female subjects. Contraceptive efficacy evaluated from pregnancy rates; presence of pregnancy determined by radioimmunoassay for urinary β-hCG. Cycle control efficacy evaluated by analysis of bleeding patterns (breakthrough bleeding and/or spotting, early withdrawal flow, intermenstrual bleeding, duration of menses, and duration of latent period). | ORTHO EVRA:<br>Patch content: NGMN: 6.0 mg; EE: 0.75 mg; patch worn for three 7-day intervals (Days 1-21, with first application on Day 1 of menses) followed by a 7-day patch-free interval (Days 22-28). | 856 enrolled;<br>812 evaluated for safety;<br>811 evaluated for efficacy | 28.0<br>18-45 |
| | | Triphasil:<br>50 µg levonorgestrel/30 µg EE, Days 1-6<br>75 µg levonorgestrel/40 µg EE, Days 7-11<br>125 µg levonorgestrel/30 µg EE, Days 12-21<br>Placebo, Days 22-28.<br><br>Total duration of treatment for each regimen: 6 cycles or 13 cycles, depending on stage of recruitment. | 639 enrolled;<br>605 evaluated for safety and efficacy | 27.8<br>18-45 |

Abbreviations: $cm^2$=square centimeter, i.v.=intravenous, mg=milligram, µg=microgram, EE=ethinyl estradiol, NG=norgestrel, NGM=norgestimate; NGMN=norelgestromin.

[a] No. subjects evaluated=number of subjects who were enrolled in the study, received study medication, and provided any on-treatment data.

### 3.3.1. Subject Disposition

A total of 3,471 subjects were assigned to treatment with ORTHO EVRA in the three Phase 3 studies. Of these, 3,330 were treated with ORTHO EVRA and were evaluable for safety; 3,319 were evaluable for efficacy.

Study completion status and reasons for withdrawal are summarized in Table 5 for ORTHO EVRA subjects in the three Phase 3 studies. Seventy-four percent of all subjects completed the studies. Overall and within each study, the most common reasons for withdrawal from treatment with ORTHO EVRA were adverse events (12% overall) and subject choice (7% overall).

**Table 5 Study Completion and Reasons for Withdrawal for All Subjects Who Received ORTHO EVRA (Studies CONT-004, CONT-003, and CONT-002)**

| | Study CONT-004 N=812 | | Study CONT-003 N = 846 | | Study CONT-002 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[a] | 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 |

Note: CONT-002 = global noncomparative study, CONT-003 = ex-US study, and CONT-004 = North American study.

[a] The subject's death was a suicide.

Source: Reference 38

Study completion status and the reasons for premature discontinuation from the ex-US study are shown by treatment group in Table 6. Twenty percent of subjects in the ORTHO EVRA group and 14% of subjects in the Mercilon group withdrew from the study prematurely. The rate of withdrawal from the study due to adverse events was 10% in the ORTHO EVRA group and 5% in the Mercilon group.

**Table 6 Study Completion Information and Reasons for Withdrawal (All Subjects Evaluable for Safety; Study CONT-003)**

| | ORTHO EVRA N=846 | | Mercilon N=643 | |
|---|---|---|---|---|
| **Status** | N | % | N | % |
| **Completed** | 678 | 80.1 | 550 | 85.5 |
| **Withdrawal** | 168 | 19.9 | 93 | 14.5 |
| Lost to Follow-up | 14 | 1.7 | 14 | 2.2 |
| Adverse Event | 81 | 9.6 | 29 | 4.5 |
| Subject Choice | 49 | 5.8 | 29 | 4.5 |
| Protocol Violation | 6 | 0.7 | 3 | 0.5 |
| Pregnancy[a] | 3 | 0.4 | 4 | 0.6 |
| Other | 15 | 1.8 | 13 | 2.0 |
| Unknown | 0 | | 1 | 0.2 |

Note: CONT-003 = ex-US study.

[a] Reason for withdrawal on termination Case Report Form was noted as pregnancy.

Source: Reference 13

Study completion status and the reasons for premature discontinuation from the North American study are shown by treatment group in Table 7. Thirty percent of subjects in the ORTHO EVRA group and 24% of subjects in the Triphasil group withdrew from the study prematurely. The rate of withdrawal due to adverse events was 13% in the ORTHO EVRA group and 5% in the Triphasil group.

**Table 7 Study Completion Information and Reasons for Withdrawal (All Subjects Evaluable for Safety; Study CONT–004)**

| | ORTHO EVRA N=812 | | Triphasil N=605 | |
|---|---|---|---|---|
| **Status** | n | % | n | % |
| **Completed** | 571 | 70.3 | 458 | 75.7 |
| **Withdrawal** | 240 | 29.6 | 147 | 24.3 |
| Lost to Follow-up | 32 | 3.9 | 48 | 7.9 |
| Adverse Event | 102 | 12.6 | 33 | 5.5 |
| Subject Choice | 77 | 9.5 | 40 | 6.6 |
| Protocol Violation | 6 | 0.7 | 5 | 0.8 |
| Pregnancy[a] | 4 | 0.5 | 7 | 1.2 |
| Death | 0 | 0.0 | 1[b] | 0.2 |
| Other | 19 | 2.3 | 13 | 2.1 |
| **Unknown** | 1 | 0.1 | 0 | 0.0 |

Note: CONT-004 = North American study.

[a] Reason for withdrawal on termination Case Report Form was noted as pregnancy.

[b] The subject's death was a suicide.

Source: Reference 14

The higher rate of withdrawals due to adverse events in the ORTHO EVRA groups versus the comparator groups in the 2 comparative studies is partially attributable to withdrawals in the

ORTHO EVRA groups due to application site reactions (2.6% in the North American study and 1.2% in the ex-US study), an adverse event that is not relevant in the OC groups.[39] In addition, withdrawals due to other individual adverse events were somewhat more common among ORTHO EVRA subjects versus OC subjects, but no individual adverse event other than application site reactions in the North American study (2.6%) and breast symptoms in the ex-US study (3.0%) led to discontinuation of more than 2% of ORTHO EVRA subjects in the 2 comparative studies.

### 3.3.2. Efficacy

Of the 3,330 women who received ORTHO EVRA across the three Phase 3 studies, 3,319 were evaluable for efficacy and provided data on 22,160 cycles, with 643 subjects completing 13 cycles (1 year) of ORTHO EVRA use.

The Pearl Index was used to evaluate contraceptive efficacy in the Phase 3 studies. The Pearl Index, an estimate of the number of pregnancies per 100 woman-years of use, is calculated as:

(# on-therapy pregnancies x 1300) / # on-therapy cycles.

The Pearl Indices for the 3,319 efficacy-evaluable subjects who received ORTHO EVRA are summarized in Table 8. The Pearl Index for ORTHO EVRA subjects in all three Phase 3 studies combined was 0.88.

**Table 8 Pearl Indices (with 95% Confidence Intervals)for All Subjects Who Received ORTHO 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 | Total N=3319 |
|---|---|---|---|---|
| Overall Failure (95% CI) | 1.24 (0.15, 2.33) | 0.88 (0.02, 1.74) | 0.71 (0.14, 1.28) | 0.88 (0.44, 1.33) |

Note: CONT-002 = global noncomparative study, CONT-003 = ex-US study, and CONT-004 = North American study.

Source: Reference 38

In the ex-US study, the Pearl Indices were 0.88 for ORTHO EVRA and 0.56 for Mercilon (Table 9). In the North American study, the Pearl Indices were 1.24 for ORTHO EVRA and 2.18 for Triphasil (Table 10).

**Table 9 Pearl Indices by Treatment Group (All Subjects Evaluable for Efficacy; Protocol NRGEEP-CONT-003)**

| Pearl Index | ORTHO EVRA | Mercilon |
|---|---|---|
| Overall (95% CI) | 0.88 (0.02, 1.74) | 0.56 (0.00, 1.33) |

Note: CONT-003 = ex-US study.

Source: Reference 13

**Table 10 Pearl Indices by Treatment Group (All Subjects Evaluable for Efficacy; Protocol NRGEEP-CONT-004)**

| Pearl Index | ORTHO EVRA | Triphasil |
|---|---|---|
| Overall | 1.24 | 2.18 |
| (95% CI) | (0.15, 2.33) | (0.57, 3.80) |

Note: CONT-004 = North American study.

Source: Reference 14

### 3.3.3. Compliance

Compliance in Phase 3 studies

Compliance was assessed for subjects who received ORTHO EVRA and the comparator OCs in the Phase 3 studies. In a post hoc analysis, compliance was defined as 21 days of consecutive patch wear or pill taking, followed by a 7-day drug-free interval during a 28-day cycle, with no single patch worn for more than 7 days. These definitions evaluated the ability of the subject to take the contraceptives as directed in a controlled clinical trial setting.

In this analysis, the overall percentage of cycles with compliance in the pooled Phase 3 studies was 90% for ORTHO EVRA.[38] By study, the overall percentages of compliant cycles were:

- Non-comparative study: 90% for ORTHO EVRA.
- Ex-US study: 90% for ORTHO EVRA and 88% for Mercilon.
- North American study: 89% for ORTHO EVRA and 79% for Triphasil (statistically significantly different; $p<0.001$).[1]

The association between compliance and the outcome of pregnancy is important to evaluate. The Pearl Indices for each hormonal contraceptive in the three Phase 3 studies for ORTHO EVRA were computed in a post hoc analysis. As shown in Table 11, for each hormonal contraceptive in all 3 studies, the Pearl Index is lower in compliant cycles than in non-compliant cycles.

**Table 11 Pearl Indices by Compliance Status**

| | | Compliant Cycles | | | Non-Compliant Cycles | | |
|---|---|---|---|---|---|---|---|
| Study | Hormonal Contraceptive | **Pearl Index** | No. of Pregnancies | No. of Woman-Years | **Pearl Index** | No. of Pregnancies | No. of Woman -Years |
| CONT-004 | ORTHO EVRA | **0.86** | 4 | 350.8 | **2.24** | 1 | 44.7 |
| | Triphasil | **0.79** | 2 | 251.9 | **7.55** | 5 | 66.2 |
| CONT-003 | ORTHO EVRA | **0.50** | 2 | 401.6 | **4.33** | 2 | 46.2 |
| | Mercilon | **0.32** | 1 | 315.6 | **2.36** | 1 | 42.2 |
| CONT-002 | ORTHO EVRA | **0.53** | 4 | 753.6 | **2.47** | 2 | 80.9 |

Note: CONT-002 = global noncomparative ORTHO EVRA study, CONT-003 = ex-US ORTHO EVRA study, and CONT-004 = North American ORTHO EVRA study.

Although these results need cautious interpretation given the small number of pregnancies, it is notable that for all 5 comparisons in Table 11 the Pearl Index is lower in compliant cycles than in non-compliant cycles. The 3- to 10-fold increase in Pearl Indices for non-compliant cycles versus compliant cycles underscores the need for high compliance with contraceptive methods.

Additional post hoc analyses were conducted to evaluate whether the rates of compliance were associated with age (Table 12). In the North American ORTHO EVRA study (CONT-004), the rate of compliance decreases with decreasing age for Triphasil users ($p<0.001$), whereas there is no trend by age for ORTHO EVRA users ($p>0.20$).[1] The test of interaction was highly statistically significant ($p<0.0001$ for 1 degree of freedom comparison of slopes; $p=0.0016$ for 5 degrees of freedom categorical comparison), indicating that the association between age and compliance differs between ORTHO EVRA and Triphasil users. The observation of no trend by age with ORTHO EVRA was also observed in both of the other Phase 3 ORTHO EVRA studies. Notably, in the ex-U.S. ORTHO EVRA study, there was no trend in the OC comparator group toward decreasing compliance with decreasing age. The reason for the different patterns in OC users in the 2 studies is unclear, but might be explained by regional or national differences. To the extent that this is true, the North American results may be most relevant for the US population.

**Table 12 Percentage of Cycles With Compliance by Age**

| | CONT-004 | | CONT-003 | | CONT-002 |
|---|---|---|---|---|---|
| **Age** | **ORTHO EVRA** | **Triphasil** | **ORTHO EVRA** | **Mercilon** | **ORTHO EVRA** |
| < 20 | 87.7 | 67.7 | 92.3 | 87.3 | 89.8 |
| 20-24 | 88.2 | 74.4 | 87.8 | 87.2 | 90.0 |
| 25-29 | 88.3 | 79.8 | 89.3 | 88.2 | 89.6 |
| 30-34 | 89.3 | 85.2 | 90.3 | 88.3 | 90.9 |
| 35-39 | 88.3 | 82.6 | 90.8 | 87.7 | 90.3 |
| ≥ 40 | 91.6 | 84.8 | 91.8 | 94.0 | 91.9 |

Note: CONT-002 = global noncomparative ORTHO EVRA study, CONT-003 = ex-US ORTHO EVRA study, and CONT-004 = North American ORTHO EVRA study.

In summary, subjects in the Phase 3 studies used ORTHO EVRA correctly in 90% of cycles, which was similar to or better than what was observed with OCs. This high compliance with ORTHO EVRA was consistent across all age groups. In addition, for ORTHO EVRA and OCs, Pearl Indices were lower for compliant cycles versus non-compliant cycles.

Compliance in "real world"

Clinical trials use a very narrow definition of compliance to evaluate the ability of the subject to take the contraceptives as directed in a controlled clinical trial setting. These results provide information about what can happen under controlled conditions, although they may not reflect patterns in "real world" clinical use. In practice, not all forms of non-compliance will place a woman at the same degree of increased probability of becoming pregnant.

### 3.3.4. Published Post-Marketing Effectiveness Studies

The medical literature includes reports of 3 effectiveness studies, not sponsored by the Sponsor, in which ORTHO EVRA was one of the evaluated contraceptive treatments.[4,74,93] All 3 studies were conducted in the United States among women at high risk for unintended pregnancy and subsequent abortion. None of the 3 studies was randomized. Two of the studies were conducted at Planned Parenthood clinics and the third was conducted at a tertiary care medical center. All 3 studies were observational with women, together with their clinician, selecting their method of contraception. As a result, particularly in the 2 studies conducted at Planned Parenthood clinics, the women who chose ORTHO EVRA as their method of contraception appear to be at a higher inherent risk for a subsequent unintended pregnancy than women who chose the other methods of hormonal contraception. For example, one study evaluated discontinuation and pregnancy rates in first-time users of hormonal contraception who were prescribed OCs or ORTHO EVRA at Planned Parenthood clinics in the Rochester and Syracuse regions.[4] In this study, the women prescribed ORTHO EVRA were significantly more likely than the women prescribed OCs to have had 1 or more prior abortions (59% vs 10%), to have had 1 or more prior births (49% vs 7%), or to have been pregnant prior to starting contraception (25% vs 4%). Such powerful selection bias, in addition to other methodologic limitations, makes it difficult to make

meaningful comparisons between ORTHO EVRA and comparator hormonal contraceptive products in these studies. A summary of the study designs, treatments, results and limitations are shown in Table 13.

**Table 13 Published Effectiveness Studies of ORTHO EVRA**

| Investigator | Study Description / Design | Treatments / Patient Population | Results | Limitations |
|---|---|---|---|---|
| Bakhru[a] | Planned Parenthood Clinics (3) in Rochester – Syracuse region; Women of any age seen for contraceptive counseling and prescribed ORTHO EVRA or an OC between November 2003 and March 2005 and were contraceptive naïve or first-time users of hormonal contraception; Prospective assessment; Total of 1,230 women with 3,206 cycles | ORTHO EVRA (n=651):<br>Age (mean): 21.9<br>Race(W/B/O): 53%/35%/12%<br>Pregnant prior to starting contraception: 25%<br>Abortion History:<br>0:41%; 1: 33%; >1: 26%<br>Birth History (%):<br>0:61%; 1: 23%; >1: 16%<br><br>OC (n=579):<br>Age (mean): 20.4<br>Race(W/B/O): 83%/11%/6%<br>Pregnant prior to starting contraception: 4%<br>Abortion History:<br>0:90%; 1: 9%; >1: 1%<br>Birth History:<br>0:93%; 1: 4%; >1: 3% | Loss to follow-up:<br>ORTHO EVRA: 45%<br>OC: 30%<br><br>Use beyond 3 cycles:<br>ORTHO EVRA: 67%<br>OC: 89%<br><br>Pearl Index:<br>ORTHO EVRA: 14.84<br>OC: 3.62 | Observational study (ie, not randomized);<br>Selection bias: High-risk population for pregnancy and abortion;<br>Women treated with ORTHO EVRA had history of significantly more abortions;<br>Women treated with ORTHO EVRA had significantly more pregnancies at treatment initiation;<br>Pregnancy at initiation of treatment was not an exclusion criterion (and, therefore, may contribute, in part, to the increased Pearl Index) |
| Raine[b] | Planned Parenthood Clinics (4) in Northern California; Women of ages 15-24, not married, not pregnant, seen for contraceptive counseling and prescribed the ORTHO EVRA, an OC, contraceptive ring ("ring") or Depot medroxyprogesterone (DMPA); Study conducted from September 2005 to July 2008; Women may have previously used hormonal contraception but not the one used in this study; Prospective assessment; Total of 1,387 women | OC (n=~433):<br>Age (mean): 18.6<br>Race(W/B/O): 12%/29%/59%<br>Prior pregnancy: 33%<br><br>ORTHO EVRA (n=~401):<br>Age (mean): 19.2<br>Race(W/B/O): 7%/41%/52%<br>Prior pregnancy: 52%<br><br>Ring (n=~259):<br>Age (mean): 20.4<br>Race(W/B/O): 11%/35%/54%<br>Prior pregnancy: 60%<br><br>DMPA (n=~295):<br>Age (mean): 18.9<br>Race(W/B/O): 15%/37%/48%<br>Prior pregnancy: 59% | Continuing at 12 months (per 100 woman- years):<br>OC: 32.7<br>ORTHO EVRA: 10.9<br>Ring: 29.4<br>DMPA: 12.1<br><br>Pearl Index:<br>OC: 16.5<br>ORTHO EVRA: 30.1<br>Ring: 30.5<br>DMPA: 16.1 | Observational study (ie, not randomized);<br>Selection bias: At high-risk for unintended pregnancy;<br>Women treated with ORTHO EVRA and the ring had higher rates of prior pregnancies than the OC group |

**Table 13 Published Effectiveness Studies of ORTHO EVRA**

| Investigator | Study Description / Design | Treatments / Patient Population | Results | Limitations |
|---|---|---|---|---|
| Thurman[c] | Tertiary medical center in South Carolina; Postpartum women of ages 13-19 who self-select ORTHO EVRA, an OC or DMPA; Women recruited from December 2003 to March 2005; Prospective assessment every 3 months by structured telephone interview; Total of 252 women | OC (n=55):<br>Race(W/B): 36%/64%<br>Antepartum contraceptive counseling: 80%<br><br>ORTHO EVRA (n=55):<br>Race(W/B): 27%/73%<br>Antepartum contraceptive counseling : 71%<br><br>DMPA (n=142):<br>Race(W/B): 14%/86%<br>Antepartum contraceptive counseling: 77% | Pregnancy rate at 12 months:<br>OC: 29.7%<br>ORTHO EVRA: 31.8%<br>DMPA: 14.2%<br><br>Use of hormonal contraception at 12 months:<br>OC: 76.0%<br>ORTHO EVRA: 55.2%<br>DMPA: 78.9% | Selection bias: At high-risk for unintended pregnancy; Observational study (ie, not randomized); Telephone interview for study outcomes |

a Reference 4
b Reference 74
c Reference 93

Abbreviation: Race(W/B/O), W=White, B-=Black, O=Other.

## 3.4. Clinical Safety and Tolerability

Safety information was collected for 6,217 women who participated in the ORTHO EVRA clinical investigations, including 3,330 women who wore the ORTHO EVRA patch in the three Phase 3 contraceptive efficacy and safety studies and who collectively received 22,176 treatment cycles.

A total of 2,665 (80.0%) of the 3,330 ORTHO EVRA subjects in the three Phase 3 studies reported at least 1 treatment emergent adverse event. Treatment-emergent adverse events with an incidence >5% are shown in Table 14. Individual adverse events with the highest incidence were breast symptoms (22%), headache (21%), application site reaction (17%), and nausea (17%). Most events, including those commonly reported, were mild or moderate in severity and were not treatment limiting; most resolved either spontaneously or after appropriate treatment.

**Table 14 Treatment-Emergent Adverse Events Reported with an Incidence >5% Summarized by WHOART Preferred Term for Subjects Who Received ORTHO EVRA (Studies CONT-002, CONT-003, and CONT-004)**

| | ORTHO EVRA (N=3,330) | |
|---|---|---|
| Adverse Event (Preferred Term) | n | (%) |
| Breast Symptoms[a] | 734 | (22.0) |
| Headache | 704 | (21.1) |
| Application Site Reaction | 581 | (17.4) |
| Nausea | 559 | (16.8) |
| Upper Respiratory Tract Infection | 336 | (10.1) |
| Dysmenorrhea | 335 | (10.1) |
| Abdominal Pain | 302 | ( 9.1) |
| Influenza-like Symptoms | 238 | ( 7.1) |
| Vaginitis | 180 | ( 5.4) |
| Sinusitis | 180 | ( 5.4) |
| Pharyngitis | 173 | ( 5.2) |
| Vomiting | 171 | ( 5.1) |
| **Any Adverse Event** | **2,665** | **(80.0)** |

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

Note: The rates for treatment-emergent adverse events in this table differ slightly from those in Table 7 of the USPI, which reports adverse drug reaction rates.

Note: CONT-002 = global noncomparative study, CONT-003 = ex-US study, and CONT-004 = North American study.

Source: Reference 39

The types and rates of treatment-emergent adverse events experienced by ORTHO EVRA subjects were consistent with expected events and event rates reported in association with the use of combination OCs (Table 15 and Table 16). Exceptions were breast symptoms (breast discomfort, engorgement, or pain) and application site reactions. Application site reactions, were generally mild or moderate in severity, not serious, and did not result in treatment

discontinuation. Breast symptoms were reported by 25% of ORTHO EVRA subjects versus 9% of Mercilon users in the ex-US study and 19% of ORTHO EVRA subjects versus 6% of Triphasil subjects in the North American study. Application site reactions were only reported by ORTHO EVRA subjects (14% in Study CONT-003 and 20% in the North American study) due to the route of administration. Breast symptoms associated with the use of ORTHO EVRA occurred primarily during Cycle 1 (17% incidence in Cycle 1 declining to <3% in Cycle 4 and later), were generally mild to moderate in severity (86%), and generally did not result in treatment discontinuation (2% of subjects discontinued due to breast symptoms). Nausea occurred more frequently in patch patients than in OC patients in the ex-US comparative study, but not in the North American comparative study.

**Table 15 Treatment-Emergent Adverse Events Reported with an Incidence >5% Summarized by WHOART Preferred Term and Treatment Regimen (Study CONT-003)**

| | ORTHO EVRA (N=846) | | Mercilon (N=643) | |
|---|---|---|---|---|
| Adverse Event (Preferred Term) | n | (%) | n | (%) |
| Breast Symptoms[a] | 212 | (25.1) | 57 | (8.9) |
| Headache | 171 | (20.2) | 152 | (23.6) |
| Application Site Reaction | 117 | (13.8) | 0 | |
| Nausea | 103 | (12.2) | 38 | (5.9) |
| Abdominal Pain | 93 | (11.0) | 72 | (11.2) |
| Influenza-Like Symptoms | 63 | (7.4) | 61 | (9.5) |
| Pruritus | 51 | (6.0) | 11 | (1.7) |
| Vaginitis | 50 | (5.9) | 40 | (6.2) |
| Dysmenorrhea | 45 | (5.3) | 30 | (4.7) |
| Vomiting | 43 | (5.1) | 17 | (2.6) |
| Back Pain | 26 | (3.1) | 38 | (5.9) |
| **Any Adverse Event** | **612** | **(72.3)** | **424** | **(65.9)** |

Note: CONT-003 = ex-US study.

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

WHOART = World Health Organization Adverse Reactions Terminology

Source: Reference 39

**Table 16 Treatment-Emergent Adverse Events Reported with an Incidence >5% Summarized by WHOART Preferred Term and Treatment Regimen (Study CONT-004)**

| | ORTHO EVRA (N=812) | | Triphasil (N=605) | |
|---|---|---|---|---|
| Adverse Event (Preferred Term) | n | (%) | n | (%) |
| Headache | 178 | (21.9) | 134 | (22.1) |
| Nausea | 166 | (20.4) | 111 | (18.3) |
| Application Site Reaction | 164 | (20.2) | 0 | |
| Breast Symptoms[a] | 153 | (18.8) | 37 | ( 6.1) |
| Upper Respiratory Tract Infections | 108 | (13.3) | 108 | (17.9) |
| Dysmenorrhea | 108 | (13.3) | 58 | ( 9.6) |
| Abdominal Pain | 66 | ( 8.1) | 51 | ( 8.4) |
| Sinusitis | 62 | ( 7.6) | 47 | ( 7.8) |
| Influenza-like Symptoms | 62 | ( 7.6) | 45 | ( 7.4) |
| Pharyngitis | 61 | ( 7.5) | 52 | ( 8.6) |
| Back Pain | 55 | ( 6.8) | 40 | ( 6.6) |
| Vomiting | 51 | ( 6.3) | 27 | ( 4.5) |
| Vaginitis | 50 | ( 6.2) | 41 | ( 6.8) |
| Dizziness | 43 | ( 5.3) | 29 | ( 4.8) |
| **Any Adverse Event** | **698** | **(86.0)** | **477** | **(78.8)** |

Note: CONT-004 = North American study.

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

WHOART = World Health Organization Adverse Reactions Terminology

Source: Reference 39

Among the 3,330 subjects treated with ORTHO EVRA in the Phase 3 clinical studies, 1 death occurred (a suicide), in the global noncomparative study. In the opinion of the investigator, attribution of the suicide to the study drug was doubtful. In the North American study, 1 subject who received Triphasil experienced depression and died of a drug overdose. The investigator assessed this event as possibly related to the study drug. No deaths were reported in any of the Phase 1 or 2 studies.

Fifty (1.5%) of the 3,330 subjects who received ORTHO EVRA in the pooled Phase 3 studies experienced 1 or more serious adverse events (Table 17). Of these 50 subjects, 7 subjects experienced a total of 10 serious adverse events that the investigators judged to be possibly, probably, or very likely related to study drug treatment. These events included 2 events of pulmonary embolus and 1 event each of thrombosis (reported in 1 of the 2 subjects who reported a pulmonary embolus), menorrhagia, pain, hypoesthesia, paresthesia, migraine, cholecystitis, and carcinoma in situ of the cervix. All of the serious adverse events that were at least possibly related to ORTHO EVRA treatment resolved either spontaneously or with appropriate treatment.

**Table 17 Summary of Serious Treatment-Emergent Adverse Events Reported for More Than 1 Subject Who Received ORTHO EVRA (Studies CONT-002, CONT-003, and CONT-004)**

| Adverse Event (Preferred Term) | ORTHO EVRA (N=3,330) No. of Subjects |
|---|---|
| **Total Subject Incidence, n (%)** | 50 (1.5%) |
| **Serious Adverse Events Reported for More Than 1 Subject** | |
| Abdominal Pain | 8 |
| Injury | 6 |
| Cervical Smear Test Positive | 3 |
| Cholecystitis | 2 |
| Embolism Pulmonary | 2 |
| Meningitis | 2 |
| Pneumonia | 2 |
| Pyelonephritis | 2 |
| **Serious Adverse Events (Preferred Terms) Each Reported for 1 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, Tuberculosis | Thrombosis |
| Leg Pain | Tooth Disorder |
| Melanoma Malignant | Uterine Disorder NOS |
| Menorrhagia | Vomiting |

Abbreviation: NOS, not otherwise specified.
Note: Subjects may have experienced more than 1 serious adverse event.
Note: CONT-002 = global noncomparative study, CONT-003 = ex-US study, and CONT-004 = North American study.

Source: Reference 39

In the 2 comparative Phase 3 studies, the overall incidence of serious adverse events was similar in the ORTHO EVRA and OC comparator groups (approximately 2% for all groups in both studies) (Table 18 and Table 19).[39]

**Table 18 Summary of Treatment-Emergent Serious Adverse Events by Regimen (Study CONT-003)**

| | ORTHO EVRA (N=846) | Mercilon (N=643) |
|---|---|---|
| **Subject Incidence, n (%)** | 15 (1.8%) | 13 (2.0%) |
| **Serious Adverse Events Reported for More Than One Subject in Either Treatment Group** | | |
| Adverse Event (Preferred Term) | No. of Subjects | No. of Subjects |
| Abdominal pain | 5 | 2 |
| Cervical Smear Test Positive | 2 | 0 |
| Pneumonia | 2 | 2 |
| **Serious Adverse Events Reported for One Subject Per Treatment Group** | | |
| | Cholelithiasis | Back Pain |
| | Embolism Pulmonary | Breast Neoplasm, Female |
| | Gastritis | Convulsions |
| | Infection TBC | Encephalopathy |
| | Injury | Headache |
| | Meningitis | Mastitis |
| | Ovarian Disorder | Ovarian Cyst |
| | Uterine Disorder NOS | Pleurisy |
| | | Pyelonephritis |
| | | Sialoadenitis |
| | | Vomiting |

Abbreviations: NOS, not otherwise specified; TBC, tuberculosis.
Note: Subjects may have experienced more than 1 serious adverse event.
Note: CONT-003 = ex-US study

Source: Reference 39.

**Table 19 Summary of Treatment-Emergent Serious Adverse Events by Regimen (Study CONT-004)**

| | ORTHO EVRA (N=812) | Triphasil (N=605) |
|---|---|---|
| **Subject Incidence, n (%)** | 16 (2.0%) | 11 (1.8%) |
| **Serious Adverse Events Reported for More Than One Subject in Either Treatment Group** | | |
| Adverse Event (Preferred Term) | No. of Subjects | No. of Subjects |
| Injury | 3 | 3 |
| Abdominal Pain | 3 | 1 |
| Cholecystitis | 2 | 1 |
| Pyelonephritis | 1 | 2 |
| **Serious Adverse Events Reported for One Subject Per Treatment Group** | | |
| | Dehydration | Back Pain |
| | Diabetes Mellitus | Depression |
| | Hypoesthesia | Hematuria |
| | Leg Pain | Hypertension Intercranial |
| | Migraine | Melena |
| | Nausea | Pelvic inflammation |
| | Pain | Pharyngitis |
| | Paresthesia | |
| | Pharyngitis | |
| | Psychosis Manic-Depressive | |
| | Sleep Disorder | |
| | Vomiting | |

Note: Subjects may have experienced more than 1 serious adverse event.
Note: CONT-004 = North American study.

Source: Reference 39.

Two ORTHO EVRA subjects experienced non-fatal pulmonary emboli in the Phase 3 studies. In 1 case, the woman had no known risk factors other than use of a hormonal contraceptive; in the second case, the woman had several risk factors, including obesity (body mass index of 32.6 kg/m$^2$) and wearing the ORTHO EVRA patch until the day before undergoing multiple extensive surgical procedures. The first case was assessed by the investigator as possibly related to the study drug, and the other was assessed as probably related to the study drug. Additional details on these 2 cases are provided below.

Subject 1181 (Study CONT-003), a 30-year-old white South African non-smoking female G2P2 (ie, 2 previous pregnancies both resulting in viable births), was randomized to ORTHO EVRA for 13 cycles as a direct switch from Mercilon. Her entry weight was 158.7 lbs and her height was 65 inches. 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 to anticoagulate the subject. She recovered without sequela.

Subject 21022 (Study CONT-002), a 34-year-old white American non-smoking female G2P2, was randomized to ORTHO EVRA for 6 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

(b) (6). 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.

There were 22,176 cycles of experience with ORTHO EVRA in the Phase 3 studies, equating to 1,706 woman-years of experience. With 1,706 woman-years of observation and 2 cases of clotting associated with use of ORTHO EVRA, the estimated rate of deep vein thrombosis/pulmonary embolus, based on the Phase 3 studies, was 11.8 (95% CI 0-28.0) cases per 10,000 woman-years.

## 4. POST-MARKETING SURVEILLANCE

### Background

Post-marketing surveillance of drug adverse events is essential because not all adverse events associated with a drug can be anticipated based on preapproval studies involving only several hundred to several thousand women.[71] Safety surveillance after a product has been approved and marketed provides insight into "real world use," in which a broader population of women is exposed to the product and in which the conditions of use are not as tightly controlled as in clinical trials. As exposure increases, monitoring provides potentially relevant information as the safety profile of a product evolves over time.

Surveillance approaches include collecting adverse events from spontaneous reports from women, health care providers, the medical literature, regulatory authorities, and ongoing clinical trials in a single database, so that adverse events can be tracked and analyzed. The amount of medical detail provided in post-marketing adverse event reports varies. These details may include co-morbid conditions, concurrent medications, age, weight, and smoking, all of which modify treatment-associated risks.

The incidence (or true rate of new events that occur during a specified time period in a specified population at risk) of a particular adverse event in the population under study can be estimated from clinical trial data. Post-marketing surveillance data have neither a precise numerator (the number of women with the adverse event) nor an accurate denominator (the number of women who used the product). Adverse event reporting is voluntary and under-reporting is the norm, so the total number of events is not known. Similarly, the number of women exposed to the product is not known but can be estimated using the amount of product sold as a proxy for true product use. For a hormonal contraceptive or any other medication that has fixed dosing, the person-years of exposure to the medication can be reasonably approximated from the number of doses sold.

A reporting rate for a given adverse event can be calculated from post-marketing surveillance data. The reporting rate is the number of adverse event reports for a product for a given event divided by the estimated number of women exposed to the product in a specified time period. Although reporting rates are not equivalent to incidence rates, they can be used to detect signals of potential new safety concerns. The reporting rate is almost always lower than the true incidence because of under-reporting, but the extent of under-reporting is variable and difficult to quantify. A 2006 publication reviewed studies from 12 countries regarding under-reporting. Under-reporting ranged from 36% to 99% with a median of 95% (ie 5% of adverse events were reported). Not surprisingly, reporting for "severe" adverse events was more common than for all adverse events.[31] In a publication describing reporting practices for serious adverse events, under-reporting was found to be 86%.[3]

Reporting of adverse events can be increased or "stimulated" by factors unrelated to their frequency of occurrence. Factors known to stimulate reporting include recent entry of a product into the market (known as the Weber effect[104]), media coverage, litigation, and direct-to-consumer marketing, all of which increase product awareness and lead to increased reporting of adverse events.[105] For instance, it was estimated that 15% of the cases of a particular serious adverse event were being reported for a lipid-lowering product until a "Dear Health Care Provider Letter" was sent alerting prescribers, after which 35% of the cases of the serious adverse event were reported.[65] Even when stimulated, reporting of events is not equivalent to incidence; rather it represents a fraction of the true incidence of an adverse event. Conclusions about the incidence of adverse events or relative risks of events as compared with other products cannot be made from reporting rates. Post-marketing surveillance can only generate hypotheses about drug-associated safety issues.

**Post-marketing Surveillance for ORTHO EVRA**

The Sponsor systematically collects adverse event reports from women, clinicians, the medical literature, and regulatory authorities. Using adverse event reports collected from women, clinicians, and other sources, safety professionals conduct real-time and periodic medical assessments of single and aggregate cases to identify potential changes to the product's safety profile ("safety signals"). This surveillance has been conducted for ORTHO EVRA since its launch in April 2002.

All combination hormonal contraceptives, regardless of delivery system, increase the risk of thromboembolic events in users compared with women not using these products; nevertheless the number of reports received by the Sponsor was greater for ORTHO EVRA than for the Sponsor's NGM-EE OCs (ORTHO TRI-CYLCLEN [35 µg EE/180-215-250 µg NGM];and ORTHO TRI-CYLCEN LO [25 µg EE/180-215-250 µg NGM]). In fact, reporting of all types of adverse events for ORTHO EVRA (serious and non-serious, not just thromboembolic events) was greater than expected. Many non-serious adverse events that had similar incidences in the ORTHO EVRA and the comparator OC groups in Phase 3 studies, such as abdominal pain, also were reported at higher than expected rates during post-marketing surveillance.

In 2003, the Sponsor's post-marketing surveillance program identified a greater than expected number of reports of multiple adverse events including VTE and 2 rare types of thromboembolic

events: ischemic stroke in women ≤30 years of age and MI. Because of these findings, additional postmarketing safety surveillance activities were initiated. These began in 2003 with implementation of activities to collect more complete medical information about ischemic stroke and MI events and to better characterize the increased frequency of reported thromboembolic events with the use of ORTHO EVRA. These heightened surveillance efforts were extended to all thromboembolic events in 2004. They included:

- telephone contact with reporting clinicians (instead of or in addition to written contact)
- systematic use of specialized thromboembolic adverse event questionnaires for incoming reports to collect additional details about risk factors, diagnostic evaluation, and treatment
- identification of factors that could impact the number of reports received, such as direct-to-consumer advertising
- cumulative reviews of thromboembolic events reported with ORTHO EVRA; the Sponsor's leading OC, ORTHO TRI-CYCLEN® and the Sponsor's newest OC, ORTHO TRI-CYCLEN LO® in the Sponsor's safety data base

Events occurring between April 2002 and February 2004 were included in an analysis presented to the FDA. Two types of calculations were performed, reporting rate and fractional reporting ratio (Table 20). Reporting rates for thromboembolic events were higher for the contraceptive patch than for the comparator OCs in the Sponsor's data base, therefore an analysis of fractional reporting ratio was performed to examine the issue further. The fractional reporting ratio calculates the cumulative number of reports of an adverse event of interest divided by the cumulative number of all adverse event or serious adverse event reports received for the product overall. This assessment provides the relative reporting frequency of a certain adverse event to determine whether reporting overall has increased for all types of adverse events or whether there is a disproportionate increase in the reporting of a particular adverse event.

Fractional reporting ratios were similar for the patch and the comparator OC. The analysis of reporting rates suggested that thromboembolic events were reported more frequently in patch users than in users of the comparator products, but the analysis of fractional reporting ratios suggested that adverse event reporting overall was elevated for the patch; and in this context the greater-than-expected number of patch reports overall might be attributed to stimulated reporting of all types of adverse events rather than a true increase in the number of specific adverse events (increased occurrence).

**Table 20 Thrombotic Adverse Events: Spontaneous US Reports April 2002 through February 2004**

| Event | Product | Reporting Rate[a] | Fractional Reporting Ratio: Spontaneous Events per Number of All Serious Spontaneous Events[b] |
|---|---|---|---|
| Cerebrovascular accident | ORTHO EVRA | 1.3 | 0.1 |
| | ORTHO TRI-CYCLEN | 0.1 | 0.1 |
| | ORTHO TRI-CYCLEN LO | 0 | 0 |
| Pulmonary embolism | ORTHO EVRA | 1.8 | 0.1 |
| | ORTHO TRI-CYCLEN | 0.1 | 0.1 |
| | ORTHO TRI-CYCLEN LO | 0.1 | 0.1 |
| Arterial thrombotic events | ORTHO EVRA | 0.1 | 0.01 |
| | ORTHO TRI-CYCLEN | 0 | 0 |
| | ORTHO TRI-CYCLEN LO | 0 | 0 |
| Venous thromboembolism | ORTHO EVRA | 3.1 | 0.2 |
| | ORTHO TRI-CYCLEN | 0.2 | 0.2 |
| | ORTHO TRI-CYCLEN LO | 0.3 | 0.3 |

[a] Spontaneous events from Apr 2002 to Feb 2004 per April 2002 to Feb 2004 exposure (per 100,000 woman-years)
[b] Events from April 2002 to Feb 2004

The increased reporting rates for both serious and non-serious adverse events for the contraceptive patch compared to reporting rates for similar events with NGM-containing OCs during the same time period raised the question: is there a true increase in VTE with ORTHO EVRA or is the high reporting rate secondary to stimulated reporting that had increased reporting of VTE along with all other events?

Because of the higher adverse event reporting rate but similar fractional reporting ratios for adverse events of interest compared to the sponsor's OCs, the pattern of adverse event reporting with ORTHO EVRA could not clearly be attributed to either an increased incidence of thromboembolic events or to stimulated reporting. To further investigate thromboembolic events, pharmacoepidemiologic studies were initiated. These studies are described in the next section.

# 5. EPIDEMIOLOGIC STUDIES

## 5.1. Epidemiologic Studies of ORTHO EVRA

### 5.1.1. Background

Higher than expected rates of postmarketing reports of thrombotic events were observed during the first 2 years after product launch. In addition to VTE, these reports included MI and ischemic stroke, which are unusual among hormonal contraceptive users of reproductive age. Postmarketing reports cannot shed light on whether the events being reported reflect a genuine

association (causal or not) between the exposure and the events being reported, or simply reflect chance associations, or biased ascertainment of events due to, eg, increased interest or improved channels of communication. Therefore, the sponsor initiated epidemiologic studies of the relative risk of MI and ischemic stroke, as well as VTE among women who used ORTHO EVRA compared with those who used OCs containing EE and either NGM or LNG, the progestins found in many widely used OCs. Because MI and ischemic stroke are relatively unusual and serious, these studies took MI + ischemic stroke, as a composite, as their primary endpoint, and VTE as a key secondary endpoint.

### 5.1.2. Overview of Studies

Post-marketing epidemiologic studies of ORTHO EVRA users and users of selected OCs were conducted by 2 independent research groups, Boston Collaborative Drug Surveillance Program (BCDSP) and i3 Drug Safety, beginning when data became available on a sufficiently large number of ORTHO EVRA-exposed women to make such studies feasible.

Four studies were conducted. The initial 2 studies used OCs containing EE and NGM as the comparator. This comparator was chosen because of the chemical similarity between NGM and NGMN (90-95% of NGM is metabolized to NGMN), which allowed the evaluation of the effect of a different delivery system without any potential confounding by type of progestin. Two subsequent studies using OCs containing EE and LNG as the comparator were conducted at the request of the European Medicines Agency because LNG-containing OCs were thought to have the lowest rate of thrombotic events among all combination OCs. In addition, a study comparing the risk of VTEs among women using NGM-containing OCs and those using LNG-containing OCs was done and showed an odds ratio of 1.1 (95% confidence interval [CI]: 0.8-1.6),[49] which suggests that NGM- and LNG-containing OCs are associated with similar rates of VTEs, so it is reasonable to compare results from studies that assessed risks with ORTHO EVRA relative to risks with these different OCs.

All of the studies were retrospective case-control studies using US health insurance claims databases. The main advantage of using retrospective data from these relatively large databases was the ability to obtain results years sooner than would have been possible from a prospective study, which was estimated to require approximately 10 years to complete. Although claims databases provide large sample sizes, and allow more rapid conduct of a study than with primary data collection, they lack information on potentially important confounding variables. A more detailed discussion of limitations of claims databases is provided following the presentation of all 4 studies.

The studies were as follows:

- i3 Drug Safety used the Ingenix Research Data Mart, a US medical claims database to study MI, ischemic stroke, and VTE among women using ORTHO EVRA compared with women using NGM-containing OCs with 35 µg EE. The work was reported in 2 publications[17,22] that covered, respectively 2002-2004 and 2005-2006, and 2 reports[89,90] that covered the same time periods.

- BCDSP used the PharMetrics database, a US medical claims database, to study MI, ischemic stroke, and VTE among women using ORTHO EVRA compared with women using NGM-containing OCs with 35 µg EE. The work was reported in 3 publications[43,45,48] and 4 reports[83,86,87,88] that covered the period from 2002 through 2007.
- BCDSP used the PharMetrics database, a US medical claims database, to study VTE, ischemic stroke, and MI among women using ORTHO EVRA compared with women using LNG-containing OCs with 30 µg EE.[84] The results on VTE from this study and the one below were reported in a single publication.[44]
- BCDSP used the MedStat database, a US medical claims database, to study VTE among women using ORTHO EVRA compared with women using LNG-containing OCs with 30 µg EE.[85] The results from this study and the results on VTE from the one above were reported in a single publication.[44]

### 5.1.3. Epidemiologic Studies of Thrombotic Events with ORTHO EVRA Compared With NGM-Containing OCs

A comparison of the design of the first 2 studies, both using NGM-containing OCs as the comparator, is provided in Table 21. This comparison is particularly relevant because the results from these studies emerged first, and yielded estimates of relative risk that differed in magnitude from each other.

**Table 21: Description of the 2 Studies From US Health Insurance Databases That Compared ORTHO EVRA to NGM-containing OCs With 35 µg EE**

| ♦ | ♦ **BCDSP study** | ♦ **i3 study** |
|---|---|---|
| ♦ **Purpose** | ♦ Assess the risk of thrombotic events with ORTHO EVRA as compared with OCs with 35 µg of ethinyl estradiol (EE) and norgestimate (NGM). | |
| ♦ **Endpoints** | ♦ Primary: MI and ischemic stroke (combined)<br>♦ Secondary:<br>• VTE<br>• Ischemic Stroke (IS)<br>• Myocardial Infarction (MI) | |
| ♦ **Design** | ♦ Case-control studies nested in the cohort of women age 15-44 who used the study drugs<br>♦ Protocols developed jointly by J&JPRD, i3, and BCDSP with a view to making them as similar as possible within the limitations imposed by the differences between the databases. The FDA played a very important role as well, by defining the primary endpoint and providing input to the analysis plan. Subjects with malignancy, coagulation defects, long-term anticoagulant use, chronic inflammatory disease, chronic renal failure, or prior history of the study endpoints were excluded. | |
| ♦ **Data Sources** | ♦ PharMetrics database - charts not available for review | ♦ United HealthCare database - selected charts available for review |
| ♦ **Case Definitions for VTE** | • Criteria applied with exposure (ORTHO EVRA or OC) masked<br>• Medical claim for a VTE diagnosis with hospital admission, ER visit or positive indication of VTE from diagnostic test results<br>• Subsequent anticoagulation and discontinuation of hormonal contraceptives<br>• Tabulation was limited to idiopathic cases (ie, those without short term risk factors for VTE: significant lower limb injury, major trauma, surgery or pregnancy in the past 90 days. | • Criteria applied with exposure (ORTHO EVRA or OC) masked<br>• Medical claim for VTE diagnosis, inpatient or outpatient<br>• Review of medical and pharmacy claims data was consistent with a VTE<br>• Medical record abstract was reviewed by a physician otherwise not associated with the study to adjudicate case status<br>• Separate tabulations were provided for all cases and idiopathic cases |
| ♦ **Eligibility** | • No prior history of the study endpoints<br>• Required all subjects to be new users of the hormonal contraceptive to which they were exposed in the study<br>• Matched up to 4 controls to each case on birth year and index date (date of the case's event) | • No prior history of the study endpoints<br>• Did not require all subjects to be new users of the hormonal contraceptive to which they were exposed in the study, but stratified subjects according to their hormonal contraceptive usage pattern for the study drug (Initiator, switcher, unknown, interrupted)<br>• Matched up to 4 controls to each case on birth year and index date and usage pattern for study drug |

The initial results of the BCDSP and i3 studies were published in 2006 and 2007, respectively.[48,17] Subsequently, the studies were extended, to improve statistical precision, and additional results from the BCDSP study were published in 2007 and 2010,[43,45] and from the i3 study in 2010.[21] The estimates in the BCDSP study were limited to idiopathic cases. The i3 study included estimates for idiopathic cases as well as estimates for all cases.

**Definitions related to history of hormonal contraceptive use**

Because of the concern that long-term users of a particular hormonal contraceptive might differ systematically from new users of that same contraceptive, both the i3 and BCDSP investigators took specific steps to address this potential source of confounding. In particular, the concern relates to the concept of "depletion of susceptibles." Briefly, the issue is that new users of a particular compound may be at relatively high risk of VTE, compared to experienced users. There is some evidence that VTE risk might be higher soon after hormonal contraceptives are begun.[36,56] Women who are particularly susceptible to VTE risk during this new use would thus experience early events, and be removed from the exposed population (usually because clinicians would typically no longer prescribe hormonal contraception for such women). This would mean that experienced users represent those women who have essentially demonstrated that they can safely use that compound, and therefore, as a group, have lower risk. Of note, Hennessy et al.,[34] in a meta-analysis of 12 studies comparing VTE risk between users of third generation OCs with that among users of second generation OCs, showed that the increased risk for third generation vs. second generation OCs is also apparent when restricting analyses to new users of third generation pills during their first year of use. Similarly, a recent study by van Hylckama Vlieg and colleagues also showed an increased risk for combination OCs containing certain progestins, regardless of duration of OC use.[101]

Thus it is important to understand the definitions of new use that were applied by the investigators in the studies of ORTHO EVRA. (The "index date" is the date of onset of the thrombotic event.) Quoting directly from their final report[89]:

> For the i3 study, the start date of the most recent course of therapy was identified according to the first interval in the chronological history of dispensing of the same drug, moving backward in time from the index date, which was greater than 28 days beyond the period covered by the days supply of the prior dispensing. Initiators and switchers of a study drug were classified as follows:
>
> **New Initiator**: no exposure to any HC [hormonal contraceptive] in the 122 days (4 months) before the start of the course of therapy
>
> **Switcher**: exposure to any other type of HC [hormonal contraceptive] in the 122 days (4 months) before the start of the course of therapy
>
> **Unknown**: no exposure to any HC [hormonal contraceptive] during a period of enrollment lasting less than 122 days (4 months) before the start of the course of therapy
>
> **Interrupted**: a break in the use of a drug of more than 28 days in the 122 days (4 months) before the start of the course of therapy followed by resumption of the same drug

In all 3 of the studies done by BCDSP, the following excerpts describe their definitions:

From their final report for the study with NGM-containing OCs as the comparator:

> For all sets of cases we required that there be at least 4 months of history in each subject's claims record before the first recorded study drug dispensing in order to determine when they started using the study contraceptive. The 4 month period is based on the knowledge that prescriptions for contraceptives in the PharMetrics database are written for no longer than 3 months at a time. Thus a window of at least 4 months provides assurance that the first identified prescription is a new prescription and not a refill of an existing prescription.[86]

And from their protocol for that same initial study:

> Current use of hormonal contraceptives will be defined as having a recorded claim for a study contraceptive prescription whose filled use extends to within 30 days of the index date or past the index date. The BCDSP will also consider time from first recorded claim for any estrogen-containing hormonal contraceptive in the current episode of use as a measure of the duration of hormonal contraceptive use....[73]

And later in the protocol:

> It is not possible to identify naïve users of hormonal contraceptives in this population because study subject records do not contain a complete historic record of past medical claims. As a result one cannot know what contraception was used prior to the patient's enrollment in their health plan and one cannot assume that a first prescription for a hormonal contraceptive on the computerized record is a first ever prescription for a hormonal contraceptive….

And,

> Women will be classified as having a history of switching hormonal contraceptives if they have any claim for a hormonal contraceptive prior to the one to which they are currently exposed on their index date that occurs within the 6 months prior to the index date.

The i3 database suffers from the same limitations as the PharMetrics database used by BCDSP. Thus, in essence, the BCDSP definition of a new user seems to incorporate the i3 definitions of "new initiator" and "switcher." When i3 performed analyses limited to new initiators, that group could have included women who had used another hormonal contraceptive, prior to the 4-month period with no recorded hormonal contraceptive use. When BCDSP performed analyses adjusted for past switching behavior, such adjustment did not change the estimated odds ratios for ORTHO EVRA vs. comparators by more than 10%.

**BCDSP study using NGM-containing OCs as comparators**

The risk of idiopathic thrombotic events in users of ORTHO EVRA compared with users of OCs containing NGM and 35 μg of EE was assessed in a study by the BCDSP with a nested case-control design conducted in the U.S. in women aged 15 to 44. This study was conducted using electronic health care claims data without chart review. It was conducted in 3 sequential portions as data accumulated. The first portion covered the period from the product launch on April 2002 through March 2005.[48] The second portion, which extended the first study portion

through August 2006, estimated an odds ratio* for the cases and controls new to this period and an odds ratio cumulatively for these study subjects together with the cases and controls from the first portion.[43] The third portion, which extended the observation period through October 2007, included new cases and controls, not identified in the first or second portions, and again estimated an odds ratio cumulatively for these study subjects together with the cases and controls from the first and second portions.[45,88]

Results from the 3 portions are tabulated in Appendix 2. In the first portion of the study, crude incidence rate ratios (rate of events per 10,000 woman-years in women exposed to ORTHO EVRA divided by the rate of events in women exposed to the comparator) were estimated for ischemic stroke together with MI (combined endpoint) [0.8 (95% CI 0.3-1.9)], the primary study endpoint; ischemic stroke alone [1.2 (95% CI 0.4-3.4)], and myocardial infarction alone [0.2 (95% CI 0.004-1.7)] in women exposed to ORTHO EVRA compared with those exposed to OCs containing NGM and 35 µg of EE.[47,87] The later portions of the study were unable to estimate incidence rate ratios because of an artifact of the PharMetrics database.† The estimated odds ratio for idiopathic VTE, for all 3 portions combined, was 1.2 (95% CI 0.9-1.8).[45]

**i3 study using NGM-containing OCs as comparators**

Another retrospective study from medical claims data was done by i3 and included chart review. Its first portion examined data from April 2002, when ORTHO EVRA was launched, through December 2004 and found an increased VTE risk for current users of ORTHO EVRA compared with current users of the OCs containing NGM and 35 µg of EE (see Appendix 2).[17,90] An extension was added to this study to include the period from 1 January 2005 through 31 December 2006 (see Appendix 2).[21,89] As did the BCDSP study just described, this study reported separately on the new cases and controls identified in this 2-year extension period among current ORTHO EVRA users, as well as providing a cumulative result for the entire study.[89] At the time of the extension of the study, separate mortality endpoints (deaths due to MI, ischemic stroke, or VTE; sudden or unknown causes; and all causes) were added. No deaths due to acute MI, ischemic stroke, VTE, or sudden or unknown causes were observed among the women currently exposed to ORTHO EVRA during this second study period.[89] Cumulatively, for the idiopathic cases and controls from both portions of the study combined (ie, those from April 2002 through December 2006) the odds ratio for the combined endpoint myocardial infarction or ischemic stroke was 1.2 (95% CI 0.4-3.4). The odds ratio for idiopathic VTE among

* The odds ratio estimates the risk of VTE in women exposed to ORTHO EVRA, relative to the risk in women exposed to the comparator. A value of 1.0 indicates equal risk in exposed and unexposed women. Values above 1.0 indicate increased risk with ORTHO EVRA relative to the comparator. When the 95% confidence interval excludes 1.0, this corresponds to a value of the odds ratio that is statistically significantly different from 1.0.

† The issue was as follows: The insurance plans represented in the PharMetrics database varied over time, and case identification numbers were not necessarily retained from one edition of the database to the next. It was possible to ascertain which cases were new to each edition by manually comparing, for example, the birth dates and event dates, so it was possible to accumulate data for the case-control analysis used for VTEs. Similarly, the previously reported cases of arterial events could be distinguished from the new ones, but there was no practical way to do likewise for the tens of thousands of women exposed to the medications. Thus, for the second and third editions of the database, it was not possible to calculate the incidence rate for the new portion of the data. If each new edition of the database were analyzed by including all the cases and all the exposure it described, then the analyses would share some cases and some exposure and therefore not be independent.

current ORTHO EVRA users was 2.2 (95% CI 1.2-4.0), for myocardial infarction alone was 1.6 (95% CI 0.4-6.5), and for ischemic stroke alone was 0.8 (95% CI 0.2-4.5). The odds ratio for deaths from all causes was 0.2 (95% CI 0.1-0.5). Cumulatively, no deaths due to MI, ischemic stroke, VTE, or sudden or unknown causes were observed among the women with current exposure to ORTHO EVRA.[89,22]

### 5.1.4. Epidemiologic Studies of Thrombotic Events with ORTHO EVRA Compared With LNG-Containing OCs

The BCDSP and i3 studies described above both involved comparisons of ORTHO EVRA, which contains NGMN and EE, with OCs containing NGM and 35 µg EE. In addition to these studies, 2 studies comparing thrombosis rates in users of ORTHO EVRA with rates in users of OCs containing LNG and 30 µg of EE were also conducted. These studies were conducted by BCDSP and involved study designs similar to the previous BCDSP study. As noted above, LNG-containing OCs were considered by the European Medicine Agency to represent OCs with low risk for VTE, thereby providing a "gold standard" comparator. Both studies were reported in a single publication.[44]

**PharMetrics database: LNG-containing OCs as comparators**

The study population for this study was women aged 15-44 years who were cared for by practices included in the PharMetrics database and exposed to at least 1 of the study medications during the study period. The study period was April 1, 2002 through March 31, 2006. Subjects needed to be first-time users of their contraceptive as of entry into the cohort (ie, needed to have no recorded use of their study contraceptive prior to April 1, 2002). This study included ischemic stroke and MI as additional endpoints. VTE cases were current users of a study medication who had a first-time diagnosis of idiopathic VTE with hospitalization, a visit to the emergency room, or indication of VTE from diagnostic test results, subsequent multiple claims for anticoagulant treatment, and discontinuation of use of estrogen/progestin-containing contraceptives. Ischemic stroke cases and MI cases were current users of a study medication who were hospitalized with a first-time recorded diagnosis of ischemic stroke or MI, respectively. Potential cases with strong risk factors (eg, surgery or pregnancy within the past 90 days) were not included in the rate estimates. Controls, up to five per case, were matched to the VTE cases on year of birth and index date (date of the corresponding case's VTE diagnosis). As of the index date, the controls had to meet the same criteria as the cases (ie, had to be current new users of either of the study medications and free of prior claims for the thrombotic events being studied).

In the PharMetrics data, the unadjusted incidence rate ratio for ischemic stroke was 0.5 (95% CI 0.2-1.5) and for MI was 0.2 (95% CI 0.03-1.6) (Table 22).[84] No estimate for the composite endpoint was provided. Of note, there was overlap in the ORTHO EVRA-exposed cases in this analysis with the ORTHO EVRA-exposed cases in the BCDSP study using NGM-containing OCs as comparators, which was also performed in the PharMetrics database. The odds ratio for VTE among current users of ORTHO EVRA compared with current users of LNG-containing hormonal contraceptives with 30 µg of EE was 2.0 (95% CI 0.9-4.1) (Table 22).[44]

**Table 22 Summary of BCDSP Results From PharMetrics Study Comparing ORTHO EVRA to LNG-Containing OCs**

| | Point Estimate (95% CI) |
|---|---|
| VTE (age 15-44) – odds ratio | 2.0 ( 0.9 – 4.1) |
| VTE (age 15-39) – odds ratio | 1.4 ( 0.6 – 3.0) |
| Ischemic stroke – incidence rate ratio | 0.5 ( 0.2-1.5) |
| Myocardial infarction – incidence rate ratio | 0.2 ( 0.03-1.6) |

CI = confidence interval; LNG = levonorgestrel; OC = oral contraceptive; VTE = venous thromboembolism.

Source: References 44, 84

BCDSP routinely reports odds ratios stratified by age, and found that the odds ratio estimate from the PharMetrics data was substantially higher among women aged 40-44 years than in the other age groups. The age-stratified odds ratio estimates from the PharMetrics data were 1.7 (95% CI 0.6-5.2) for <30 years, 0.9 (95% CI 0.5-1.9) for 30-39 years, and 11.9 (95% CI 1.3-111.3) for 40-44 years. The odds ratio estimate among women aged 40 or older reflected only 2 cases exposed to LNG-containing OCs and 7 cases exposed to ORTHO EVRA. It was also noted by the authors that the incidence rate in the 40-44 age group taking LNG-containing OCs was lower than the incidence rate in the corresponding 30-39 age group, a finding that is inconsistent with previous studies of hormonal contraceptives and VTE in which the rate increased with age. The BCDSP investigators therefore viewed the odds ratio estimate from the ≥40 age group as unreliable. That led them to calculate an unplanned estimate of the odds ratio for study subjects aged less than 40 years, and also to repeat the study in another database (see the description of the MarketScan study that follows this paragraph.) Based on the PharMetrics data, the odds ratio for subjects aged less than 40 years was 1.4 (95% CI 0.6-3.0).

**MarketScan study using LNG-containing OCs as comparators**

The study population for this study was again women age 15-44 years who were cared for by practices described in the MarketScan database (another US medical claims database) and exposed to at least 1 of the study medications during the study period, April 1, 2002 through December 31, 2007. Subjects needed to be first-time users of their contraceptive as of entry into the cohort (ie, needed to have no recorded use of their study contraceptive prior to April 1, 2002). The study in the MarketScan database did not include MI or ischemic stroke as endpoints. VTE cases were current users of a study medication who had a first-time diagnosis of idiopathic VTE with hospitalization, a visit to the emergency room, or indication of VTE from diagnostic test results, subsequent multiple claims for anticoagulant treatment, and discontinuation of use of estrogen-containing contraceptives. Potential cases with strong risk factors were not included in the rate estimates. Controls, up to 4 per case, were matched to the VTE cases on year of birth and index date (date of the corresponding case's VTE diagnosis). As of the index date, the controls had to meet the same criteria as the cases (ie, they had to be current users of either of the study medications and free of prior claims for VTE).

The odds ratio for VTE among current users of ORTHO EVRA compared with current users of LNG-containing hormonal contraceptives with 30 µg of EE was 1.3 (95% CI 0.8-2.1) in the MarketScan database (Table 23).[44] Results are also reported separately for ages 15-39 in Table 23. This age-stratified analysis did not confirm the observation in the PharMetrics data of a substantially higher odds ratio in women 40 and older. Rather, the odds ratio in the older age group was consistent with the odds ratio in women <40 years old.

**Table 23 Summary of BCDSP results from MarketScan study comparing ORTHO EVRA to LNG-containing OCs**

| | Point Estimate (95% CI) |
|---|---|
| VTE (age 15-44) – odds ratio | 1.3 ( 0.8 – 2.1) |
| VTE (age 15-39) – odds ratio | 1.2 (0.7 – 2.0) |

CI = confidence interval; LNG = levonorgestrel; OC = oral contraceptive; VTE = venous thromboembolism.

Source: Reference 44

### 5.1.5. Discussion of Studies of Thrombotic Events with ORTHO EVRA Compared With NGM-containing or LNG-containing OCs

Results for all 4 studies are summarized in Table 24 for MI + ischemic stroke, and Table 25 for VTE. For MI + ischemic stroke, the results were variable across studies and all the studies individually had very wide confidence intervals, reflecting the small number of events. For VTE, the results of the epidemiologic studies of ORTHO EVRA were also variable across studies, with point estimates of the odds ratios ranging from 1.2 to 2.2, and with narrower confidence intervals than for the arterial events. Methodological differences among the studies could account for some of that variability, although the expected direction of the influence of these design factors is not clear.

**Table 24 Estimates of MI + Ischemic Stroke Risk in Current Users of ORTHO EVRA Compared with OC Users**

| Study | OC Comparator | OR or IRR (95% CI) |
|---|---|---|
| i3 Ingenix NGM Study in Ingenix Research Datamart[22,90] | NGM/35 µg EE | 1.2 (0.4 – 3.4)[a] |
| BCDSP NGM Study in PharMetrics database[88] | NGM/35 µg EE | 0.8 (0.3 – 1.9)[b,c] |
| BCDSP LNG Study in PharMetrics database[84] | LNG/30 µg EE | MI 0.22 (0.03 – 1.64)[b,d]<br>IS 0.47 (0.15 – 1.51)[b,d] |
| BCDSP LNG Study in MarketScan database[84] | LNG/30 µg EE | Not reported |

EE = ethinyl estradiol; IRR = incidence rate ratio; IS = ischemic stroke; LNG = levonorgestrel; MI = myocardial infarction; NGM = norgestimate; OC = oral

contraceptive; OR = odds ratio.
[a] Values given are odds ratios
[b] Values given are incidence rate ratios
[c] Value is for the initial 36 months of data. Value was not reported for subsequent installments.
[d] Estimate of the composite endpoint of MI + ischemic stroke were not reported. These estimates for MI and ischemic stroke share ORTHO EVRA-exposed cases with the estimate for MI + ischemic stroke in the BCDSP NGM study from the PharMetrics database (reference 88).

**Table 25 Estimates (Odds Ratios) of Venous Thromboembolism Risk in Current Users of ORTHO EVRA Compared with OC Users**

| Epidemiologic Study | OC Comparator | Odds Ratio (95% CI) |
|---|---|---|
| i3 Ingenix NGM Study in Ingenix Research Datamart[17,21,22] | NGM/35 µg EE | **2.2[a] (1.2-4.0)[b]** |
| BCDSP NGM Study in PharMetrics database[43,45,48] | NGM/35 µg EE | **1.2 (0.9-1.8)[c]** |
| BCDSP LNG Study in PharMetrics database[44] | LNG/30 µg EE | **2.0 (0.9-4.1)[d]** |
| BCDSP LNG Study in MarketScan database[44] | LNG/30 µg EE | **1.3 (0.8-2.0)[e]** |

CI = confidence interval; EE = ethinyl estradiol; LNG = levonorgestrel; NGM = norgestimate; OC = oral contraceptive.
[a] Increase in risk of VTE is statistically significant
[b] Pooled odds ratio from references 17 and 22. [Initial 33 months of data: Odds Ratio (95% CI) = 2.5[a] (1.1-5.5); Separate estimate from 24 months of data on new cases not included in the previous estimate: Odds Ratio (95% CI) = 1.4 (0.5-3.7)]
[c] Pooled odds ratio from references 43, 45, and 48. [Initial 36 months of data: Odds Ratio (95% CI) = 0.9 (0.5-1.6); Separate estimate from 17 months of data on new cases not included in the previous estimate: Odds Ratio (95% CI) = 1.1 (0.6-2.1); Separate estimate from 14 months of data on new cases not included in the previous estimates: Odds Ratio (95% CI) = 2.4[a] (1.2-5.0)]
[d] 48 months of data. This estimate shares ORTHO EVRA-exposed cases with the estimate in the BCDSP NGM study from the PharMetrics database (reference 88).
[e] 69 months of data.

An important point is that such variability is to be expected in most situations in which multiple epidemiologic studies address the same question. This has been the case for comparison studies of combination OCs, as well. As a relevant example, consider a meta-analysis comparing third generation with second generation OCs.[34] That publication summarized 12 observational studies comparing OCs containing third generation progestins to OCs containing a second generation progestin, and the estimated relative risk was 1.7 (95% CI 1.3-2.1). Study results in that situation were mostly, but not all, directionally consistent, with relative risk estimates ranging from 0.8 to 4.3.

A similar situation exists for comparisons of the fourth generation OCs, which contain the progestin DRSP, with combination OCs containing LNG. Two recent studies appeared in the literature. One study used the PharMetrics database, which was also used for one of the ORTHO EVRA studies, and the other used the UK General Practice Research Database (GPRD). In the

PharMetrics study,[46] the odds ratio from the case-control analysis was 2.3 (95% CI 1.6-3.2) for the comparison of DRSP with LNG. In the GPRD case-control study,[69] the corresponding odds ratio was 3.3 (95% CI 1.4-7.6). An earlier study by van Hylckama Vlieg found an odds ratio of VTE for DRSP-containing OCs vs. LNG-containing OCs of 1.7 (95% CI 0.7-3.9)[101], and a study by Lidegaard found a rate ratio of 1.6 (95% CI 1.3-2.1).[57] In contrast, the European Active Surveillance study was a primary data collection effort that did not rely on existing medical records, but instead was a study planned and conducted specifically to address adverse events in cohorts of women taking a variety of combination OCs, including DRSP-containing combination OCs. That study identified 118 VTEs and found a hazard ratio (relative risk) of 1.0 (95% CI 0.6-1.8) for the comparison of DRSP to LNG.[20] One other study, conducted in the United Healthcare database (used by i3 in one of the ORTHO EVRA studies), compared DRSP-containing combination OCs to combination OCs containing other progestins, and found a relative risk of 0.9 (95% CI 0.5-1.6).[75] A commentary accompanying the 2 most recent papers notes, "Faults can be found with any observational study, and those that use routinely collected data are more prone to error than those that use data collected specifically for the study."[23]

The question of whether there might be differential associations between ORTHO EVRA and VTE risk for older women was raised by the BCDSP study in the PharMetrics database, with LNG-containing OCs as the comparator group. To address this point, results are summarized in Table 26 for all 4 studies, separated by age groups (<30, 30-39, and 40-44). The table shows no consistent differences in the estimated odds ratios (or incidence rate ratios) across age groups. Specifically, there is no clear pattern of a higher relative risk among women aged 40-44 than in the other age groups.

**Table 26 Estimates (Odds Ratios) of Venous Thromboembolism Risk in Current Users of ORTHO EVRA Compared with OC Users by Age**

| Study | <30 years | 30-39 years | >39 years |
|---|---|---|---|
| i3 Ingenix NGM Study in Ingenix Research Datamart[90,92] | 3.1 (1.2 - 8.3)[a,b] | 1.6 (0.7 - 3.9)[a,b] | 2.2 (0.5 – 9.8)[a,b] |
| BCDSP NGM Study in PharMetrics database[88] | 1.3 (0.75- 2.1) | 1.5 (0.8-2.7) | 0.8 (0.3-1.9) |
| BCDSP LNG Study in PharMetrics database[84] | 1.7 (0.6-5.2) | 1.1 (0.4-3.4) | 11.9 (1.3-111.3) |
| BCDSP LNG Study in MarketScan database[85] | 1.4 (0.7 - 2.8) | 1.0 (0.5 - 1.9) | 3.1 (0.8 - 12) |

LNG = levonorgestrel; NGM = norgestimate; OC = oral contraceptive.
[a] Values given are for incidence rate ratios, not odds ratios.
[b] Excludes those who used NGM OCs during the period Oct 2001 – March 2002.

*Limitations of the Epidemiologic Studies*

The primary data sources for these studies were medical claims databases. Exposure to ORTHO EVRA or OC was identified by an entry in the database indicating the medication had been

dispensed (ie, notation of an economic transaction). This does not necessarily mean that the woman who filled the prescription actually used the medication as directed, or at all.

In the i3 study, cases were confirmed by review of abstracts of medical records. Of 400 medical records sought for review to establish the diagnosis of a study endpoint, 290 (73%) were successfully abstracted. It is unknown to what extent the records that were successfully abstracted may have differed from the records that were not.

BCDSP did not have access to charts, and identified VTE by the presence of a diagnostic code for VTE followed by anticoagulation and discontinuation of estrogen-containing hormonal contraceptives. The diagnostic code could come from a hospital, an emergency department, or from an outpatient source of service if accompanied by a diagnostic test within +2 days. To assess the accuracy of the BCDSP's algorithm for VTE, i3 applied it to the data from the i3 database. This was a way of identifying cases that mimicked what i3 would have seen had they not had access to medical charts. The investigators were then able to compare, specifically, cases identified using the claims-based algorithm against subjects in the i3 study whose charts they had reviewed as possible VTE cases. Based on this review, the sensitivity of the BCDSP's algorithm was 51/61 = 84% and the predictive positive value was 51/56 = 91% (Table 27).[91]

**Table 27: Assessment of the BCDSP Algorithm by i3**

| | | Claims-containing VTE Cases | | |
|---|---|---|---|---|
| | | Yes | No | Total |
| Chart-Confirmed VTE Cases | Yes | 51 | 10 | 61 |
| | No | 5 | - | |
| | Unknown[a] | 16 | | |
| | Total | 72 | | |

VTE = venous thromboembolism.

[a] Chart was not abstracted (15 cases) or subject was not study-eligible (1 subject aged <15 years).

i3 also explored the difference between the studies by re-calculating the odds ratio from their potential cases if one identified VTE cases by means of the BCDSP's claims-based algorithm or by chart confirmation. That is, they estimated the odds ratio using cases identified by the claims-based algorithm and a set of matched controls, estimating the odds ratio they would have obtained had they done a study using only the claims-based algorithm. The odds ratio for idiopathic cases, after excluding cases and controls with exposure to NGM-containing OCs before April 2003 was 1.58 (95% CI 0.72--3.47) based on the cases identified by the claims-based algorithm, and was 2.72 (95% CI 1.09-6.79) based on the cases identified by chart-confirmation.[91] (Note: these estimates differ from the results in the tables above, because they are drawn from the versions of the respective study reports that were available at that point in time.) There are 2 implications of this comparison. First, the claims-based analysis of the i3 data, including women during the same time period as the original BCDSP study, had a higher estimated odds ratio (point estimate of 1.58) than the BCDSP study (odds ratio point estimate of 0.9 in an early report from BCDSP, when this comparison was made). This highlights potential differences between databases when using the exact same methodology. Second, when the same i3 data set is used to produce both a claims-based estimate of the odds ratio and an estimate

based on chart-confirmed cases, the chart-based estimate was higher. Whether this pattern of a higher odds ratio using chart review compared with a claims-based case definition would apply to other databases is not known.

As noted above, several potentially important confounders were not captured, or not adequately captured, in the databases and therefore could not be adequately addressed. Among these are socioeconomic status, health behaviors, smoking, and obesity. In one portion of the i3 study,[90] the investigators did a sub-study based on cases and matched controls whose medical records they were able to review for risk factors. (This was done in addition to the review of potential cases to confirm their case status.) Of the 420 subjects (both cases and controls) whose charts they sought to review for risk factors, abstracted medical records were obtained for 269 (64%) including 53 (65%) of 85 cases whose charts were sought. After setting aside controls matched to cases whose records were not abstracted, there remained 138 controls with abstracted risk factor data who were matched to cases with abstracted risk factor data. The most common reason for non-completion of the abstract was provider refusal. Blood pressure was recorded in the majority of charts reviewed. Mean value of body mass index was similar for cases and controls, but a body mass index ≥30 was recorded for 18% of VTE cases and 11% of VTE controls. Current smoking was documented in no VTE cases, but 5% of VTE controls. (Because smoking is a known risk factor for VTE, the expectation would be that a higher proportion of cases would be identified as smokers, not a lower proportion). Physical activity was documented in 11% of VTE cases and 13% of VTE controls. For the cases and controls whose charts were abstracted for risk factors, the odds ratio's for acute MI, ischemic stroke, and the combined endpoint acute MI or ischemic stroke were similar whether or not they were adjusted for the risk factors ascertained from the charts. For VTE, the odds ratio adjusted for the risk factors ascertained from the charts, 3.1 (95% CI 1.1-8.72), was higher than the odds ratio estimated without such adjustment, 2.3 (95% CI 0.9-5.9). The authors commented that they suspect there may have been preferential documentation of smoking in the records of the ORTHO EVRA users, noting that ORTHO EVRA was a novel form of hormonal contraception delivery and the doctors may have been more careful in documenting risk factors for the various complications of hormonal contraception. They described the finding of smoking being negatively associated with VTE as contradicting established science, for the reason noted above.

Dispensing of professional samples is not recorded in the database and it was not possible to include exposure due to professional samples in the studies. Among the women whose charts were abstracted for risk factor data, 2 VTE cases (5%) and 4 matched controls (4%) had documented professional sample use of ORTHO EVRA.[90]

Cerebral venous thrombosis was captured as a separate endpoint in these studies. The number of cerebral venous thromboses was small relative to the number of VTEs and including them in the tabulations of VTE does not appear likely to substantially change the results.

The studies required study subjects to have been enrolled in the database for a period of 4 to 6 months prior to starting the study contraceptive so subjects could be classified as new users, switchers, etc. The studies captured information about recent users as well as current users, and about non-idiopathic cases as well as idiopathic cases. The descriptions above were limited to

results pertaining to the current use and idiopathic cases. In the protocols, it was stated that the estimates of the odds ratios would be adjusted for any covariates whose inclusion produced a change in the estimate of more than 10%. In none of the studies were any such confounders identified. Age and calendar time were addressed through matching.

The medical claims databases also did not identify deaths that occurred outside the context of the medical care system. Thus, they would not have identified, for example, the death of a woman who sustained a pulmonary embolism while alone and received no medical services, if such a death had occurred in the study population. The i3 investigators had access to personal identifiers and were therefore able to use the National Death Index (NDI) to identify such deaths. Their inclusion did not substantially affect the study results. BCDSP, working with an anonymized database was not able to make similar use of the NDI. This is why the BCDSP studies are limited to non-fatal VTE.

### 5.1.6. Meta-Analysis of the 4 ORTHO EVRA Epidemiologic Studies

Described above are the 4 epidemiologic studies conducted in US populations that compared VTE rates with ORTHO EVRA to VTE rates with OCs with NGM and 35 µg EE or with LNG and 30 µg EE. These same studies also compared rates of MI and ischemic stroke between the same exposure groups. The results from these studies are summarized above in Table 24 and Table 25. The results summarized for VTE are the odds ratios cited in the USPI.

As noted above, the odds ratios vary across studies, and with one exception, the confidence intervals include the null value of 1.0. In situations such as this, it may be reasonable to consider performing a meta-analytic summary of the data. For such a summary to produce interpretable results, one must assume that the methodologic approaches of the studies are similar, and that the variability (heterogeneity) of results across studies is not excessive. In the presence of too much heterogeneity, the overall summary would arguably not meaningfully apply to any single population or methodologic approach. For the studies of ORTHO EVRA, the methods used were quite similar. Although only one study[22] included chart review, and several different medical claims databases were used, all used the case-control design with essentially the same definitions of cases and substantively similar approaches to the control of potential confounding. In principle, then, these studies might be combined, although an empirical assessment of the assumptions is still needed.

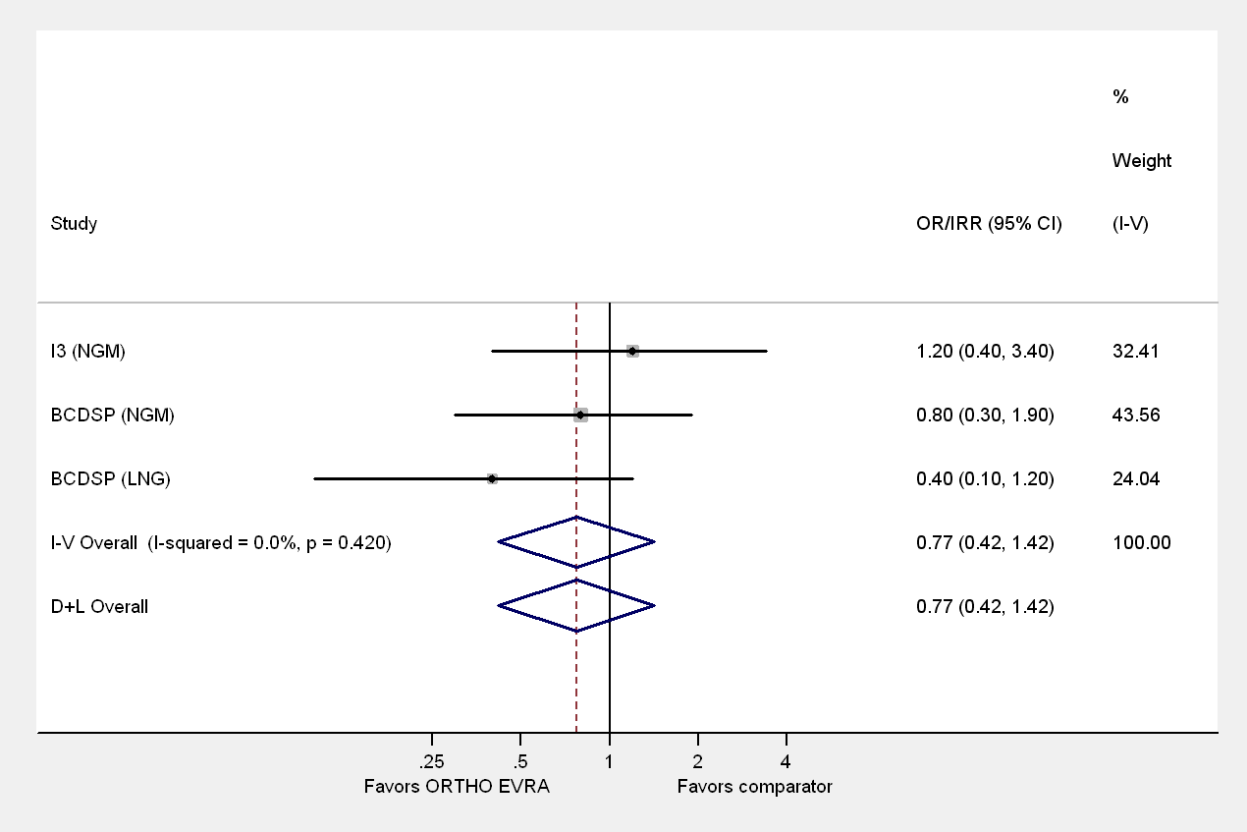
The Sponsor undertook a meta-analysis in preparation for this advisory committee meeting. The primary analysis was a meta-analytic combination of the 4 studies using the DerSimonian and Laird random-effects model as the primary method to estimate a summary odds ratio for VTE, and a summary rate ratio (unadjusted) for MI and ischemic stroke. This involves calculating an inverse-variance weighted average of the study-specific effects. Larger studies, with smaller variance estimates, contribute more to the average than smaller studies. As a sensitivity analysis, a fixed-effect summary, which assumes the studies are estimating a single, common odds ratio or incidence rate ratio, was also calculated. In the presence of heterogeneity, random-effects models tend to produce wider confidence intervals than fixed-effects models, but they do not make the assumption of a single, common odds ratio (or incidence rate ratio).

As described above, because of the small number of events, and the consequent inability to do a proper adjustment for confounders in 2 of the studies done by BCDSP, only unadjusted incidence rate ratios were generated for MI and ischemic stroke. The BCDSP study done in the MarketScan database did not report results for MI and ischemic stroke. The i3 study, presented an adjusted odds ratio. The DerSimonian and Laird method was also used to summarize these results.

We evaluated the degree of variability of results among studies, ie, statistical heterogeneity, using the $I^2$ and chi squared values. The $I^2$ statistic measures the relative amount of among-study variability, as a proportion of total variability (within-study + among-study) of the effect estimates (odds ratio or incidence rate ratio). Values of $I^2 \geq 50\%$ or chi squared test p-values less than 0.1 were defined a priori to indicate among-study heterogeneity. Performing the calculations involves converting the ratios to the natural logarithmic scale (ln). Standard errors for the ln (odds ratio) were also calculated from the 95% CI on the ln scale. The results of these calculations are reported after being converted back to more usual units (by exponentiation). As in the above tables, odds ratios greater than one indicate an increased risk of VTE or MI/ischemic stroke with ORTHO EVRA. A forest plot is presented as well for each of the outcomes. The analyses were conducted using STATA version 10.0.

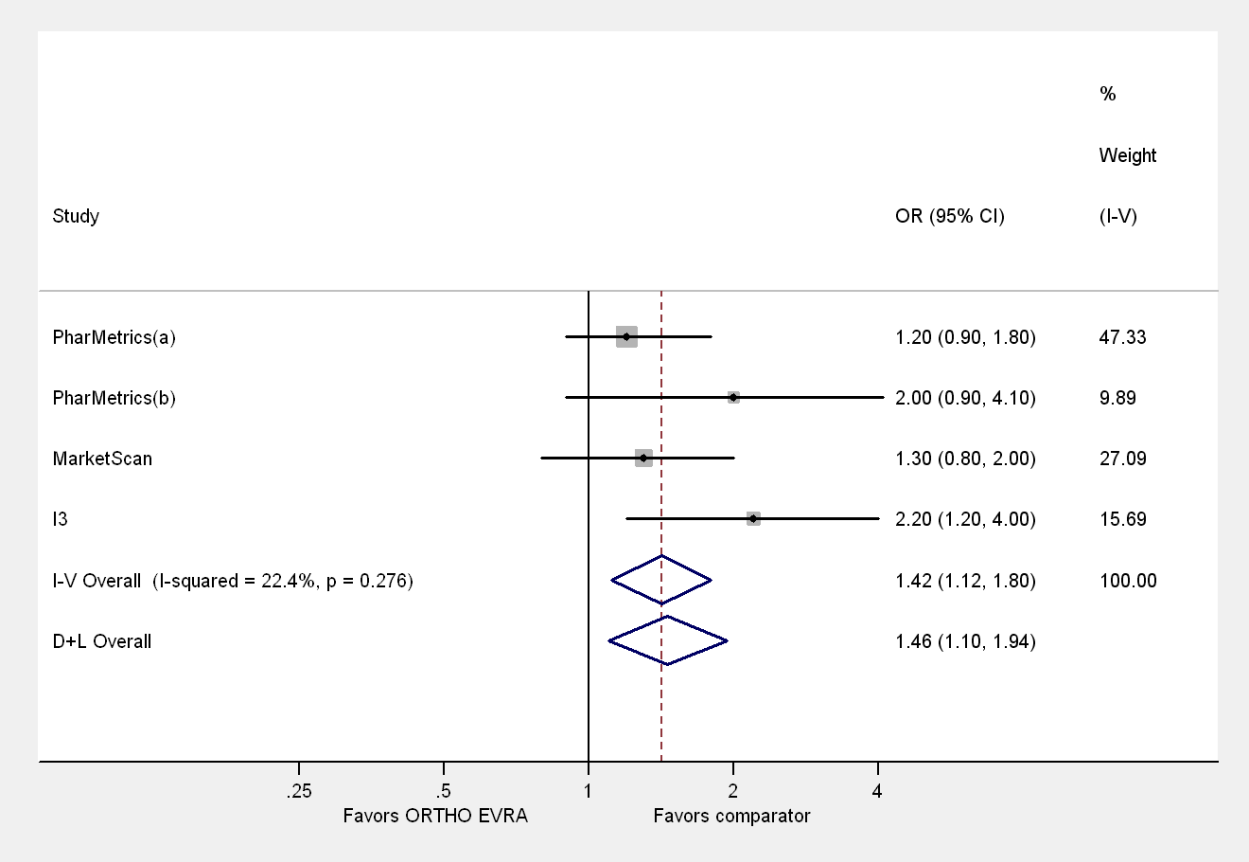
The results of the meta-analyses are presented in Figure 2 and Figure 3. For stroke and MI (Figure 2), the random-effects and fixed-effect summary estimates were identical; ie, the summary relative risk was 0.8 (95% CI 0.4-1.4). The $I^2$ value was 0.0%, and the p-value for the test of heterogeneity was 0.42. For VTE (Figure 3), the summary odds ratio using the DerSimonian and Laird method was 1.5 (95% CI 1.1-1.9). The fixed-effect model yielded a very similar result (odds ratio = 1.4; 95% CI 1.1-1.8). For VTE (Figure 3), the $I^2$ value was 22.4% with a p-value of 0.28. These values suggest modest heterogeneity, but well within the pre-specified threshold of 50%. Both analytic methods for VTE exclude the null value of 1.0, consistent with a statistically significant increase in risk of VTE of approximately 50% on average.

**Figure 2 Meta-Analysis Results for Stroke + MI**




Note: I-V = fixed effects model; D+L = DerSimonian and Laird method
Note: The % weight column presents the relative (percent) contribution of each study, based on the variability within that study, relative to other studies.

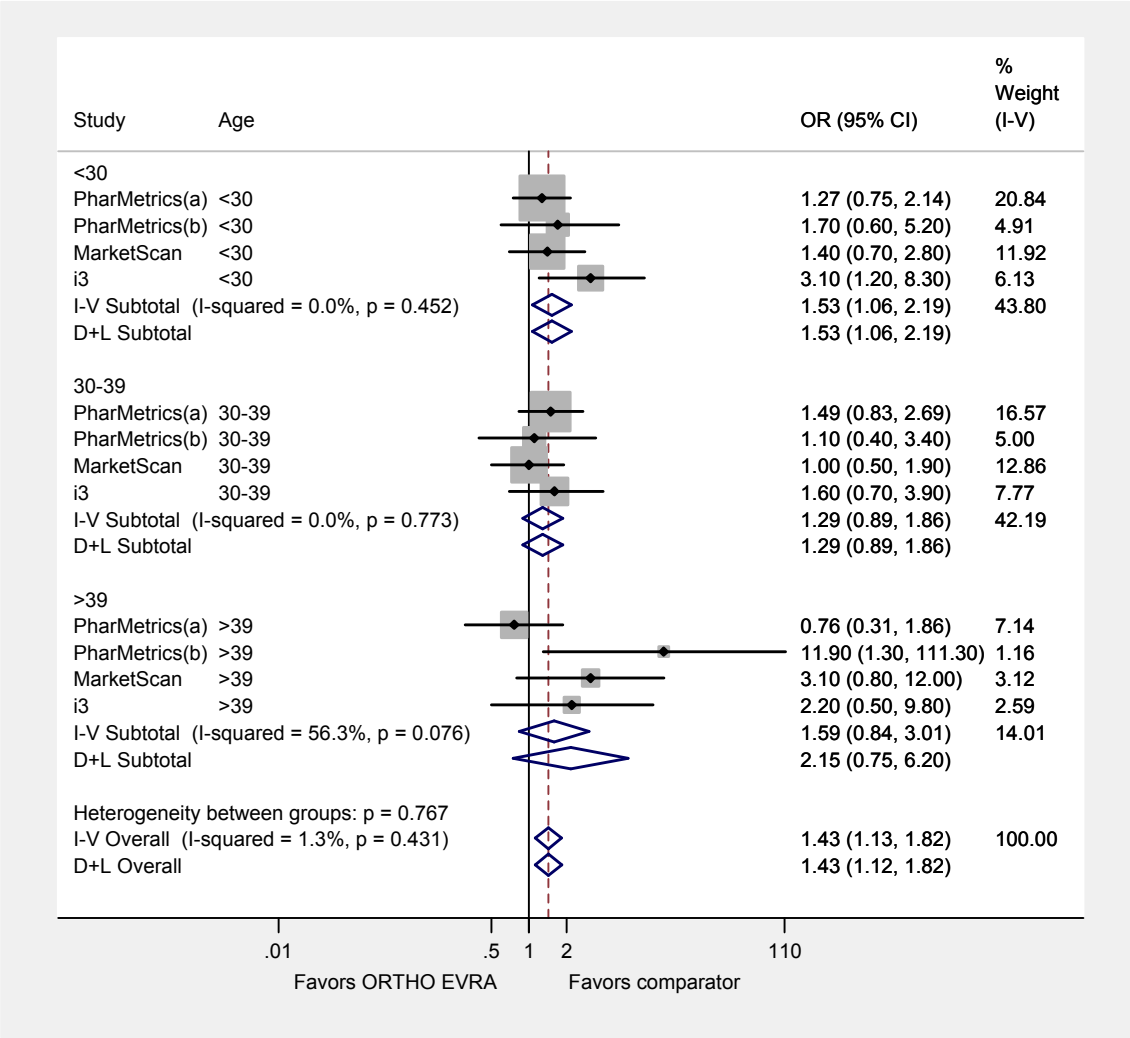
**Figure 3 Meta-Analysis Results for VTE**




Note: I-V = fixed effects model; D+L = DerSimonian and Laird method
Note: The % weight column presents the relative (percent) contribution of each study, based on the variability within that study, relative to other studies.

Meta analysis results for VTE by age are shown in Figure 4. For women aged <30, the random-effects and fixed-effect summary estimates were identical: the summary relative risk was 1.5 (95% CI 1.1-1.2). For women aged 30 through 39, the random-effects and fixed-effect summary estimates were also identical: the summary relative risk was 1.3 (95% CI 0.9-1.9). For women aged >39, the summary odds ratio using the DerSimonian and Laird method was 2.15 (95% CI 0.75-6.2). The fixed-effect model yielded a somewhat different result with an odds ratio of 1.6 (95% CI 0.8-3.0). The p-value for the test of heterogeneity between groups (ie, comparing the odds ratios across age groups) was 0.77, suggesting that the differences in point estimates across age groups were consistent with random variability.

**Figure 4 Meta-Analysis Results for VTE by Age**




Note: I-V = fixed effects model; D+L = DerSimonian and Laird method
Note: The % weight column presents the relative (percent) contribution of each study, based on the variability within that study, relative to other studies.

These results need to be interpreted with caution. There are differences in design and populations across studies that need to be considered, although the formal statistical tests do not suggest excessive heterogeneity of results. As noted above, epidemiologic studies can always be subject to bias and confounding introduced by unmeasured subject characteristics (eg, smoking and obesity). Thus, any summary of biased studies may simply propagate those biases and lend a possibly spurious degree of precision and credibility. Nonetheless, to the extent that the results of the studies are internally valid and vary primarily due to sampling error, a weighted average provides a summary of the evidence that adds precision not provided by the individual studies.

### 5.1.7. Recent FDA-commissioned Epidemiologic Study

The FDA Office of Surveillance and Epidemiology recently released results of a study that it commissioned, entitled "Combined Hormonal Contraceptives (CHCs) and the Risk of Cardiovascular Disease Endpoints."[68] The FDA office was the lead site for a study that utilized

computerized data files from 2 integrated medical care programs (Kaiser Permanente Northern California and Kaiser Permanente Southern California) and 2 state Medicaid programs [Tennessee State Medicaid (Vanderbilt) and Washington State Medicaid (University of Washington)]. Outpatient cases from one of the 4 sites were validated by medical chart review. Most inpatient cases were also subjected to adjudication.

In adjusted analyses, DRSP-containing OCs, ORTHO EVRA patch (abbreviated as NGMN in the FDA report), and etonogestrel/estradiol vaginal ring (ETON) were associated with a significantly higher risk of VTE relative to a combined comparator group of combination OCs containing LNG, NGM, or norethindrone acetate. Estimates of relative risk were 1.74 (95% CI 1.42-2.14) for DRSP, 1.55 (95% CI 1.17-2.07) for ORTHO EVRA (NGMN), and 1.56 (95% CI 1.02-2.37) for ETON. For the analysis restricted to new users, only DRSP was associated with a significantly higher risk of both arterial thrombotic events [2.01 (95% CI 1.06-3.81)] and VTE [1.77 (95% CI 1.33-2.35)]. The results for ORTHO EVRA were based on a total of 33 events in users of ORTHO EVRA.

The results for ORTHO EVRA from this study (relative risk of VTE of 1.55 [95% CI 1.17-2.07]) were not available for inclusion in the meta-analysis of the 4 ORTHO EVRA studies described in Section 5.1.6, but are very consistent with those results (which found a summary relative risk of 1.5 [95% CI 1.1-1.9]).

The one new finding in the FDA-commissioned study is of an increased hazard ratio (relative risk) in new users of ORTHO EVRA with >12 months duration of use. That hazard ratio of 3.05 (95% CI 1.23-7.53) is based on 6 events in users of ORTHO EVRA and was not seen in the 4 earlier studies. VTE rates appeared to increase in this longer duration group, in both ORTHO EVRA users and users of comparators.

### 5.1.8. Summary of ORTHO EVRA Epidemiology Studies

In summary, results for the 4 epidemiologic studies, for MI + ischemic stroke, varied among studies on both sides of the null value of 1.0 for the measure relative risk, and all the studies individually had very wide confidence intervals, reflecting the small number of events. For VTE, the results of the epidemiologic studies of ORTHO EVRA were also variable among the studies, with point estimates of the odds ratios ranging from 1.2 to 2.2. Methodological differences among the studies could account for some of the variability in odds ratios, although the expected direction of the influence of these design factors is not clear.

A meta-analysis of the 4 studies showed that for MI + ischemic stroke, the summary relative risk was 0.8 (95% CI 0.4-1.4), consistent with no difference between ORTHO EVRA and second generation OCs. For VTE, the summary odds ratio was 1.5 (95% CI 1.1-1.9), suggesting a 50% increase in risk. However, based on the ends of the 95% confidence intervals, the results of the meta-analyses are consistent with a 60% decrease to a 40% increase in risk for MI + ischemic stroke, and with a 10% increase to a 90% increase in risk for VTE. The results of a recently released study commissioned by the FDA are consistent with the meta analysis results for VTE.

## 5.2. Epidemiologic Studies Comparing VTE Rates of Other Combination Hormonal Contraceptives to VTE Rates with LNG-containing OCs

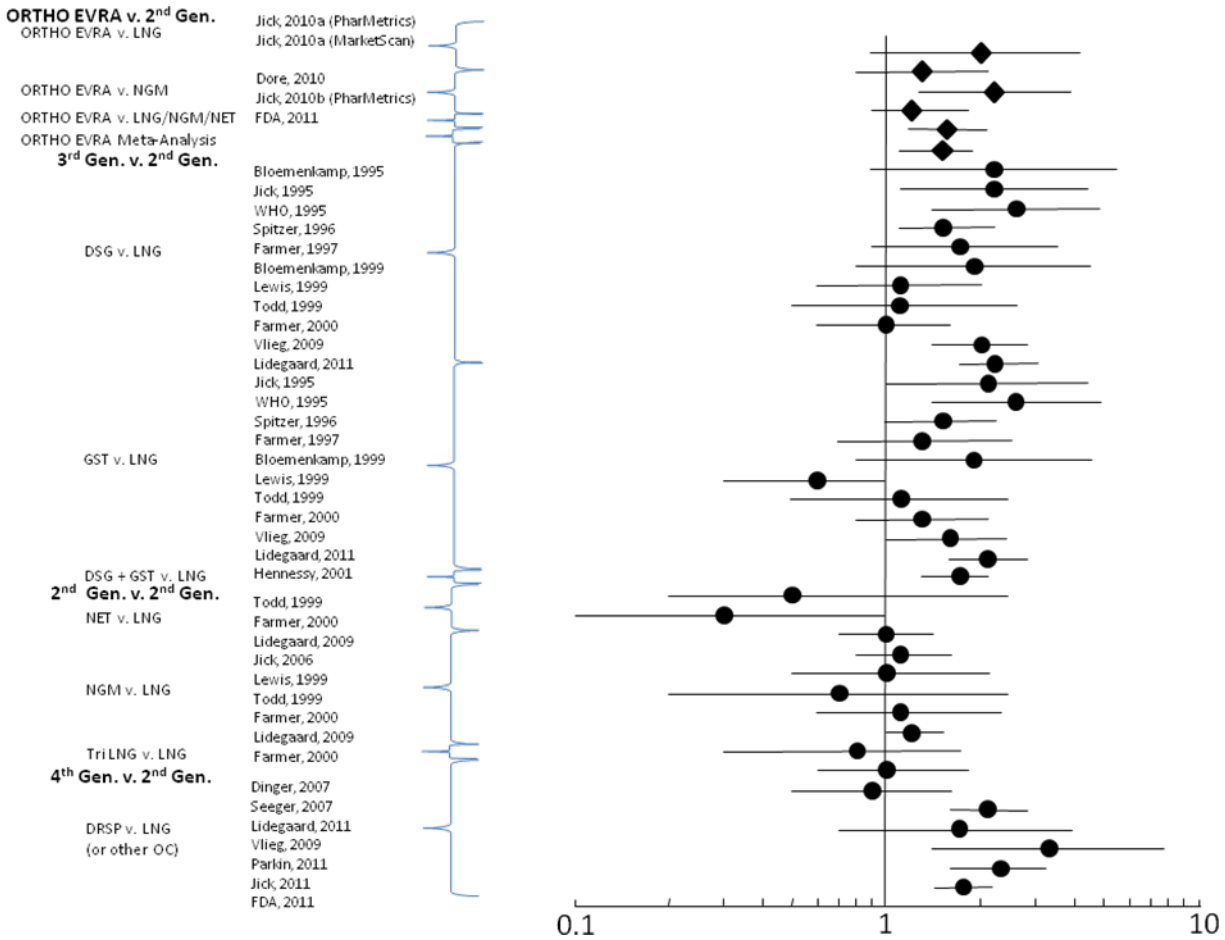
Relative risks for VTE associated with combination hormonal contraception

The VTE risk associated with ORTHO EVRA should be considered in the context of the VTE risks of other hormonal contraceptives, both as a context for the material in Section 5.1 and because these are the contraceptives to which current users of ORTHO EVRA are likely to transition if women using ORTHO EVRA were to switch to another form of contraception. A comprehensive review of the literature identified 22 relevant population-based studies.[7,8,20,22,24,25,26,34,42,44,45,46,48,55,57,58,68,69,75,81,94,101] These include case-control and cohort studies, and describe VTE rates among users of hormonal contraceptives with second generation progestins (LNG, NGM, NGMN, and norethindrone), third generation (DSG, ETON, and GST) and fourth generation (DRSP). All these progestins, except for NGMN, which is the progestin in the ORTHO EVRA patch, are administered orally. We caution that the review of the literature may not be exhaustive, but believe it includes all major relevant studies.

Four of the 22 studies included in this review were the ORTHO EVRA studies described in Section 5.1. The other 18 studies compare combination OCs having a second generation progestin with other combination OCs and allow a qualitative comparison with the findings for ORTHO EVRA, as the comparators were the same. For 16 of these studies, the progestin was LNG, with the dose of EE restricted to 30 µg in 6 of these studies. The comparator in the other 2 studies[68,75] was a combination OC with either LNG or NGM as the progestin. Some of these studies reported results from both a cohort analysis and a nested case-control analysis. For these studies, the nested case-control results were typically adjusted or matched for more factors than the cohort results. Thus, in studies with both types of results, the case-control results were considered.

The comparative results from the 22 studies, either odds ratios or relative risks, and the associated 95% confidence intervals, are presented graphically in Figure 5 and in tabular format in Appendix 3. From this presentation, it is clear that the magnitude of the relative risks for ORTHO EVRA compared with second generation OCs is similar to the magnitude of the relative risks for third and fourth generation OCs compared with second generation OCs. This highlights the fact that many other combination hormonal contraceptive options appear to have increased VTE risks relative to second generation products that need to be discussed with the woman and weighed against the possible benefits.

**Figure 5 Comparison of VTE Odds Ratios or Relative Risks and Associated 95% Confidence Intervals From Literature Studies**




Abbreviations:, LNG = Levonorgestrel, DSG = Desogestrel, NGM = Norgestimate, GST = Gestodene, NET = Norethisterone / Norethindrone, DRSP = Drospirenone
Cross-reference: Appendix 3

Figure 5 compares relative risk estimates for VTE rather than absolute risk estimates for VTE across studies because studies may use various definitions of VTE. For example one study may be limited to idiopathic VTEs while another may include all VTEs, or one study may include clinically diagnosed cases, while another requires confirmatory tests. However, within each study the same definition of VTE is applied, regardless of exposure. Thus, the relative risk estimates are more comparable across studies than are the absolute risk estimates and form the basis for the above figure. However, despite this advantage in comparability, relative risks do not convey how common or rare an adverse event is. Therefore, absolute risk estimates are also a critical part of public health decision-making.

Absolute Risk for VTE associated with hormonal contraception

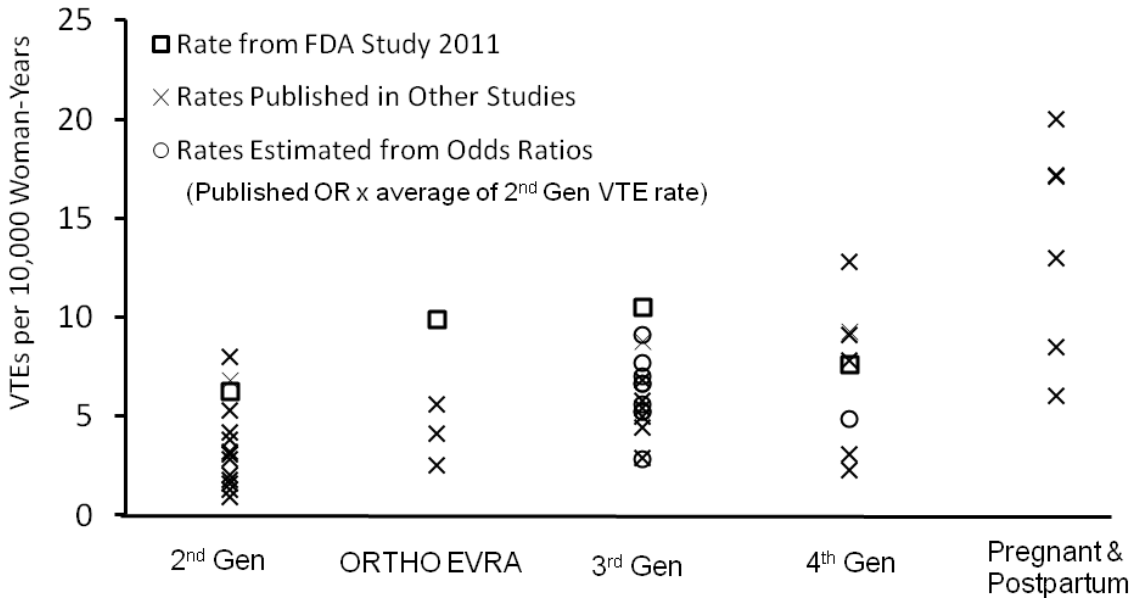
To explore the absolute rates of VTEs associated with various contraceptive options, we began with the 22 population-based studies described above. We noted that, because most of these studies used the same comparator (LNG-containing combination OCs). To avoid including such

information redundantly, we excluded studies that had substantial overlap (ie, used the same dataset during substantially overlapping time periods). This left 19 studies.[7,8,20,22,24,25,26,42,44,46,48,55,58,68,69,75,81,94,101] Absolute VTE rates were available from 14 of these studies. Results were categorized by contraceptive class (second generation, third generation, fourth generation, or ORTHO EVRA) and are shown in Figure 6. Included among these is the FDA's recent study (see Section 5.1.7),[68] which has not yet been published or peer-reviewed, but is presented here for completeness. For studies that reported on multiple contraceptives of the same class, a point estimate of absolute VTE rates in that class was estimated by weighting each contraceptive option in proportion to the woman-years of use observed in that study. Rates were not available from an extension[22] of an earlier ORTHO EVRA study.[17] Therefore, the value shown in Figure 6 was taken from the earlier publication.[17]

For the remaining 5 studies, only odds ratios were available.[7,8,55,81,101] To obtain an estimate of absolute risks, odds ratios published in these studies were multiplied by a weighted average of absolute VTE rates observed for second generation oral contraceptives, 3.5 per 10,000 woman-years. Weighting was in proportion to the woman-years of second generation oral contraceptive use in each study, except for that conducted by the WHO,[24] which was excluded from the average because woman-years of exposure were not available in the associated publications.

Figure 6 additionally includes reported VTE rates for pregnancy and the postpartum period, considered together.[28,32,41,60,61,78] The result of Heit et al,[32] which is the highest value displayed, is in units of events per woman-year. All other results are in units of events per pregnancy, delivery, or maternity, but a pregnancy, delivery, and a three month postpartum period represent approximately one woman year, though the duration of the postpartum period included in the 6 studies above varies somewhat. Many other studies also report VTE risks among pregnant and/or postpartum women. Though the sample of pregnancy-related VTE rate estimates used for this figure is by no means complete, it agrees with ranges noted in the literature, including 7.6-17.2 per 10,000 pregnancies as reported by Marik et al.[64] and 5-30 per 10,000 pregnancies, as referenced by the American College of Physicians and the American Academy of Family Practice.[80]

**Figure 6 Expected VTEs per 10,000 woman-years for various contraceptive options.**




**Note:** VTEs per 10,000 woman-years of use for various contraceptive options, and for pregnancy and the postpartum period. Excluding the greatest value shown, all reported rates for pregnancy and postpartum are in units of VTEs per 10,000 pregnancies, deliveries, or maternities. Because the postpartum is approximately three months, a pregnancy together with postpartum represents approximately one woman-year.

While definitive conclusions cannot be drawn from the results of such a simple analysis as that presented here, the published incidence rates shown in Figure 6 suggest the general scale of VTE risks and the degree of uncertainty in our present understanding of those risks. ORTHO EVRA and third generation oral contraceptives present similar VTE rates. Rates for fourth generation contraceptives appear to be higher but more variable across studies. The combination of pregnancy and the postpartum period has the highest associated VTE rate.

This basic analysis of absolute risks is limited in that we gave no consideration to variation in study methodology. We simply reported all published VTE rates. Additionally, absolute rates used here were not adjusted for confounders, such as age. Due to this limitation, in Figure 6 the VTE rate from the recent FDA study[68] for users of ORTHO EVRA is slightly higher than the VTE rate for users of fourth generation oral contraceptives containing DRSP even though the adjusted relative risks reported by this same study (relative to second generation OCs) were slightly lower for ORTHO EVRA than for third generation OCs, 1.55 (95% CI 1.17-2.07) and 1.74 (95% CI 1.42-2.14) respectively.[68]

## 6. PRODUCT LABELING AND COMMUNICATION

Since the approval of ORTHO EVRA in November 2001, several revisions to the USPI have been implemented based on clinical PK or epidemiologic data obtained from studies conducted post-approval. In some instances, information was also conveyed to health care professionals or the public via Dear Healthcare Provider letters or press releases. For example, in November 2005, language was added to the WARNINGS section of the labeling stating that exposure

(ie, AUC and $C_{ss}$) to EE is 60% higher in users of ORTHO EVRA than in users of a 35 µg-EE OC but maximum blood concentration (ie, $C_{max}$) is 25% lower for ORTHO EVRA. To ensure that clinicians were aware of this important labeling change, the Sponsor disseminated a Dear Healthcare Provider letter as soon as this change was made. When initial data became available for the first 2 epidemiology studies in February 2006, this information was communicated first in a press release and then again in a Dear Healthcare Provider letter when the labeling was updated in September 2006. For all these labeling revisions, discussions were held with the FDA regarding proposed language and all changes were submitted as prior approval supplements. Table 28 summarizes some of the major changes in product labeling since product approval related to PK and epidemiology data derived from post-approval studies.

**Table 28: Summary of PK and Epidemiology Study-Related Changes to the USPI and Corresponding Communications**

| Data | Labeling Change | Sections Revised | Approval Date | Communication |
|---|---|---|---|---|
| Results of NED-1 PK study | Systemic exposures for EE are higher than in women using a 35 µg EE OC; $C_{max}$ is lower | Description, Clinical Pharmacology, Indications and Usage, Warnings, Dosage and Administration, Detailed Patient Labeling | Labeling supplement approved May 2005; second supplement approved November 2005 | Dear HCP letter disseminated November 2005 |
| Initial results of BCDSP and i3 epidemiology studies available | BCDSP study showed similar (OR 0.9) VTE risk as 35 µg EE OC and i3 study showed approximate 2-fold (OR 2.4) increase in ORTHO EVRA users compared with OC | Indications and Usage, Warnings, Detailed Patient Labeling | Labeling supplement approved September 2006 | Press release sent February 2006; Dear HCP letter disseminated September 2006 |
| Results of BCDSP LNG study and update to BCDSP NGM study | OR 2.0 for ORTHO EVRA vs 30 µg EE LNG product and OR 1.1 for 35 µg EE NGM product | Warnings | Labeling supplement approved January 2008 | Dear HCP letter disseminated February 2008 |
| Results of third dataset of BCDSP NGM study | OR 2.4 for third data set and cumulative OR 1.2 for all data sets | Warnings | Labeling supplement approved October 2008 | No communication[a] |
| Reanalysis of i3 study | Change of OR from 2.4 to 2.5 for i3 study | Warnings | Labeling supplement approved September 2009 | No communication[a] |
| Additional 24 months of data for i3 study and new BCDSP LNG study | OR for additional data from i3 study 1.4, cumulative OR 2.2 and BCDSP LNG study OR 1.3 | Warnings | Labeling supplement approved April 2010 | No communication[a] |
| Request from the FDA February 2011 for label change | Information from WARNINGS section was added into Boxed Warning | Boxed Warning | Labeling supplement approved March 2011 | Dear HCP letter disseminated June 2011 |

HCP = healthcare professional

[a] Dear HCP letters are not routinely disseminated for every change to the USPI

In March 2011, information on the PK profile, VTE risks, and CV risks associated with smoking and use of any hormonal contraception, which was already described in the Warnings, was included in a revised Boxed Warning to better inform health care providers of this information. The full text of the Boxed Warning is shown below.

**WARNINGS: CARDIOVASCULAR RISK ASSOCIATED WITH SMOKING, RISK OF VENOUS THROMBOEMBOLISM, AND PHARMACOKINETIC PROFILE OF ETHINYL ESTRADIOL**

**Cigarette Smoking and Serious Cardiovascular Risks**
Cigarette smoking increases the risk of serious cardiovascular events from hormonal contraceptive use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, hormonal contraceptives, including ORTHO EVRA®, should not be used by women who are over 35 years of age and smoke.

**Risk of Venous Thromboembolism**
The risk of venous thromboembolism (VTE) among women aged 15-44 who used the ORTHO EVRA® patch compared to women who used oral contraceptives containing 30-35 mcg of ethinyl estradiol (EE) and either levonorgestrel or norgestimate was assessed in four U.S. case-control studies using electronic healthcare claims data. The odds ratios ranged from 1.2 to 2.2; one of the studies found a statistically significant increased risk of VTE for current users of ORTHO EVRA® (*see **WARNINGS - Table 5***).

**Pharmacokinetic Profile of Ethinyl Estradiol**
The pharmacokinetic (PK) profile for the ORTHO EVRA® patch is different from the PK profile for oral contraceptives in that it has higher steady state concentrations and lower peak concentrations. Area under the time-concentration curve (AUC) and average concentration at steady state for ethinyl estradiol (EE) are approximately 60% higher in women using ORTHO EVRA® compared with women using an oral contraceptive containing 35 mcg of EE. In contrast, peak concentrations for EE are approximately 25% lower in women using ORTHO EVRA®. It is not known whether there are changes in the risk of serious adverse events based on the differences in PK profiles of EE in women using ORTHO EVRA® compared with women using oral contraceptives containing 30-35 mcg of EE. Increased estrogen exposure may increase the risk of adverse events, including venous thromboembolism. (*See **WARNINGS** and **CLINICAL PHARMACOLOGY**, Transdermal versus Oral Contraceptives.*)

In addition to being prominently displayed in the Boxed Warning, information on the PK profile and the risk of VTEs is provided in several other sections of the USPI, including the Warnings, Clinical Pharmacology, and Indications and Usage sections (see Appendix 1). The inclusion of this PK information in the Indications and Usage section of the USPI is unique to ORTHO EVRA among hormonal contraceptives as it places PK and epidemiology information directly following the indication itself:

> ORTHO EVRA® is indicated for the prevention of pregnancy in women who elect to use a transdermal patch as a method of contraception.
>
> The pharmacokinetic profile for the ORTHO EVRA® transdermal patch is different from that of an oral contraceptive. Healthcare professionals should balance the higher estrogen exposure and the possible increased risk of venous thromboembolism with ORTHO EVRA® against the chance of pregnancy if a contraceptive pill is not taken daily. (See BOLDED WARNING; WARNINGS; CLINICAL PHARMACOLOGY, Transdermal versus Oral Contraceptives).
>
> Like oral contraceptives, ORTHO EVRA® is highly effective if used as recommended in this label.

The Detailed Patient Labeling also includes information on estrogen exposure as well as the risk of VTEs. In particular, it contains the following:

> Hormones from ORTHO EVRA® get into the blood stream and are processed by the body differently than hormones from birth control pills. **You will be exposed to about 60% more estrogen if you use ORTHO EVRA® than if you use a typical birth control pill containing 35 micrograms of estrogen.** In general, increased estrogen may increase the risk of side effects.
>
> The risk of venous thromboembolic events (blood clots in the legs and/or the lungs) may be increased with ORTHO EVRA® use compared with use of birth control pills. Studies examined the risk of these serious blood clots in women who used either ORTHO EVRA® or birth control pills containing one of two progestins (levonorgestrel or norgestimate) and 30-35 micrograms of estrogen. Results of these studies ranged from an approximate doubling of risk of serious blood clots to no increase in risk in women using ORTHO EVRA® compared to women using birth control pills.
>
> You should discuss this possible increased risk with your healthcare professional before using ORTHO EVRA®.

In addition to the product-specific language cited above, the USPI for ORTHO EVRA contains language in the Warnings section that is also contained in the USPIs for all combination hormonal contraceptives. This "class labeling" contains information related to the risks of VTE, MI, and ischemic stroke as exemplified by the following excerpt from the ORTHO EVRA USPI:

> The use of combination hormonal contraceptives is associated with increased risks of several serious conditions including myocardial infarction, thromboembolism, stroke, hepatic neoplasia, and gallbladder disease, although the risk of serious morbidity or mortality is very small in healthy women without underlying risk factors. The risk of morbidity and mortality increases significantly in the presence of other underlying risk factors such as hypertension, hyperlipidemias, obesity and diabetes.
>
> The information that follows in this section of the package insert is principally based on studies carried out in women who used combination oral contraceptives with higher formulations of estrogens and progestins than those in common use today. The effect of long-term use of combination hormonal contraceptives with lower doses of both estrogen and progestin administered by any route remains to be determined….
>
> **1. Thromboembolic Disorders and Other Vascular Problems**
> a. Thromboembolism
> An increased risk of thromboembolic and thrombotic disease associated with the use of hormonal contraceptives is well established. Case control studies have found the relative risk of users compared to nonusers to be 3 for the first episode of superficial venous thrombosis, 4 to 11 for deep vein thrombosis or pulmonary embolism, and 1.5 to 6 for women with predisposing conditions for venous thromboembolic disease. Cohort studies have shown the relative risk to be somewhat lower, about 3 for new cases and about 4.5 for new cases requiring hospitalization. The risk of thromboembolic disease associated with hormonal contraceptives is not related to length of use and disappears after hormonal contraceptive use is stopped. A two- to four-fold increase in relative risk of post-operative thromboembolic complications has been reported with the use of hormonal contraceptives. The relative risk of venous thrombosis in women who have predisposing conditions is twice that of women without such medical conditions. If feasible, hormonal contraceptives should be discontinued at least four weeks prior to and for two weeks after elective surgery of a type associated with an increase in risk of thromboembolism and

during and following prolonged immobilization. Since the immediate postpartum period is also associated with an increased risk of thromboembolism, hormonal contraceptives should be started no earlier than four weeks after delivery in women who elect not to breastfeed.

b. Myocardial Infarction
An increased risk of myocardial infarction has been attributed to hormonal contraceptive use. This risk is primarily in smokers or women with other underlying risk factors for coronary artery disease such as hypertension, hypercholesterolemia, morbid obesity, and diabetes. The relative risk of heart attack for current hormonal contraceptive users has been estimated to be two to six compared to non-users. The risk is very low under the age of 30.

Smoking in combination with oral contraceptive use has been shown to contribute substantially to the incidence of myocardial infarctions in women in their mid-thirties or older with smoking accounting for the majority of excess cases. Mortality rates associated with circulatory disease have been shown to increase substantially in smokers, especially in those 35 years of age and older among women who use oral contraceptives….

c. Cerebrovascular Diseases
Hormonal contraceptives have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes), although, in general, the risk is greatest among older (>35 years), hypertensive women who also smoke. Hypertension was found to be a risk factor for both users and nonusers, for both types of strokes, and smoking interacted to increase the risk of stroke. In a large study, the relative risk of thrombotic strokes has been shown to range from 3 for normotensive users to 14 for users with severe hypertension. The relative risk of hemorrhagic stroke is reported to be 1.2 for non-smokers who used hormonal contraceptives, 2.6 for smokers who did not use hormonal contraceptives, 7.6 for smokers who used hormonal contraceptives, 1.8 for normotensive users and 25.7 for users with severe hypertension. The attributable risk is also greater in older women.

In summary, the sequence of events following the marketing of ORTHO EVRA, including updates to the USPI and communication of these updates to clinicians, highlights the dynamic nature of learning about newly marketed products, the importance of working closely with the FDA to make sure a product is labeled appropriately, and ensuring timely communication of new information to women and their clinicians. Information about the risk of VTEs, along with information on the different PK profiles of ORTHO EVRA compared with OCs, is presented in several sections of the current USPI, including a Boxed Warning; in the Warnings, Product Description, and Clinical Pharmacology sections; and in Detailed Patient Labeling.

## 7. BENEFIT-RISK ASSESSMENT

ORTHO EVRA has been marketed for almost a decade and has been safely and effectively used by millions of women to ensure their pregnancies are planned and prepared for. Many of these women have found it to be the “best option” for them based on its unique delivery system and dosing regimen. The substantial post-marketing experience confirms the findings of the clinical development program, which demonstrated ORTHO EVRA is highly efficacious, with a pooled Pearl Index from all Phase 3 studies of 0.88. This, coupled with its ability to reduce dosing frequency to once-per-week, is of benefit to some women, including those with difficulty complying with a daily pill-taking regimen.

The clinical trial and post-marketing experience also confirm the safety and tolerability of ORTHO EVRA. The frequency and types of adverse events have been found to be similar to those of other hormonal contraceptive options available to women. Nonetheless, all combination hormonal contraceptives carry a small, but real, increased risk of VTE. Multiple pharmacoepidemiologic studies, including the one recently conducted by the FDA, have demonstrated this risk and provided reasonably consistent estimates of the relative risks associated with other combination hormonal contraceptives relative to second generation combination OCs. Many of these studies have also estimated the absolute VTE rates for these products. The information on the VTE risk associated with ORTHO EVRA relative to that of second generation combination OCs is prominently displayed in ORTHO EVRA labeling and all professional and patient materials.

Although ORTHO EVRA is associated with an incremental increase in VTE risk versus the second generation combination OCs, the difference in absolute terms is small and amounts to approximately 1.5 to 4.5 events per 10,000 woman-years of use, depending on the assumed baseline risk, which varies among the studies. When compared to the widely used third and fourth generation combination oral contraceptives, the risks of VTE associated with ORTHO EVRA are essentially the same. All of these risks are substantially lower than the VTE risk associated with planned or unplanned pregnancies and during the post partum period. Thus, an unintended consequence of reducing contraceptive choice, by eliminating or limiting access to ORTHO EVRA among women for whom it is the option that works best, could be an increase in VTE risks and the other consequences of unintended or unplanned pregnancies. The health of the public will be best served by ensuring that clinicians are well informed and by encouraging clinicians to have meaningful dialogues with their patients to ensure the benefits and risks of the various contraceptive options are understood and decisions among these options are well informed.

## 8. CONCLUDING REMARKS

- It is important for clinicians and women to have a wide array of safe and effective contraceptive options and to be able to choose a method that is best suited for the individual woman, based on her medical history, non-medical needs, and product attributes.
- For those women who are candidates for hormonal contraception and who elect to use a transdermal patch, ORTHO EVRA is a unique contraceptive option with a favorable benefit-risk profile. ORTHO EVRA should remain available as a contraceptive option for those women and their clinicians.
- All combination hormonal contraceptives carry a risk of VTE, which is less than the risk of VTE during pregnancy and the post-partum period. Results from the recently conducted meta-analysis and FDA-commissioned epidemiology study indicated that VTE risk associated with ORTHO EVRA:
  - is higher than that of norgestimate-containing oral contraceptives (meta-analysis data) and levonorgestrel-containing oral contraceptives (meta-analysis data and FDA-commissioned epidemiology study)
  - is in the range of other combination hormonal contraceptives.

- Since the launch of ORTHO EVRA, the Company has been diligent in generating and communicating comprehensive product information to clinicians and patients. The ORTHO EVRA labeling prominently communicates information on risk of VTE in multiple sections: Boxed Warning, Warnings, Indications and Usage and in other sections.
  - ORTHO EVRA has a unique Indication and Usage section that advises clinicians to balance the higher estrogen exposure and "the possible increased risk of VTE with ORTHO EVRA against the chance of pregnancy if a contraceptive pill is not taken daily." It is the only combination hormonal contraceptive that is indicated "for the prevention of pregnancy in women who elect to use a transdermal patch as a method of contraception."
  - The labeling will continue to be updated appropriately as new information becomes available, including the Company's recently completed meta-analysis and the recently completed FDA-commissioned epidemiology study.
- ORTHO EVRA safety and efficacy information is provided in consumer-friendly language in the Detailed Patient Labeling that is in each box of ORTHO EVRA patches, and on the ORTHO EVRA website (www.orthoevra.com).

The Company appreciates the opportunity to participate in this Advisory Committee and is interested in the input of the Advisory Committee and the FDA. We are committed to continue to work with the FDA to enable appropriate product usage and meet the needs of individual women.

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# APPENDICES

# APPENDIX 1
# US PRESCRIBING INFORMATION FOR ORTHO EVRA

**ORTHO EVRA®**
**(norelgestromin / ethinyl estradiol TRANSDERMAL SYSTEM)**

**Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.**

**WARNINGS: CARDIOVASCULAR RISK ASSOCIATED WITH SMOKING, RISK OF VENOUS THROMBOEMBOLISM, AND PHARMACOKINETIC PROFILE OF ETHINYL ESTRADIOL**

**Cigarette Smoking and Serious Cardiovascular Risks**
Cigarette smoking increases the risk of serious cardiovascular events from hormonal contraceptive use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, hormonal contraceptives, including ORTHO EVRA®, should not be used by women who are over 35 years of age and smoke.

**Risk of Venous Thromboembolism**
The risk of venous thromboembolism (VTE) among women aged 15-44 who used the ORTHO EVRA® patch compared to women who used oral contraceptives containing 30-35 mcg of ethinyl estradiol (EE) and either levonorgestrel or norgestimate was assessed in four U.S. case-control studies using electronic healthcare claims data. The odds ratios ranged from 1.2 to 2.2; one of the studies found a statistically significant increased risk of VTE for current users of ORTHO EVRA® *(see **WARNINGS - Table 5**).*

**Pharmacokinetic Profile of Ethinyl Estradiol**
The pharmacokinetic (PK) profile for the ORTHO EVRA® patch is different from the PK profile for oral contraceptives in that it has higher steady state concentrations and lower peak concentrations. Area under the time-concentration curve (AUC) and average concentration at steady state for ethinyl estradiol (EE) are approximately 60% higher in women using ORTHO EVRA® compared with women using an oral contraceptive containing 35 mcg of EE. In contrast, peak concentrations for EE are approximately 25% lower in women using ORTHO EVRA®. It is not known whether there are changes in the risk of serious adverse events based on the differences in PK profiles of EE in women using ORTHO EVRA® compared with women using oral contraceptives containing 30-35 mcg of EE. Increased estrogen exposure may increase the risk of adverse events, including venous thromboembolism. *(See **WARNINGS** and **CLINICAL PHARMACOLOGY**, Transdermal versus Oral Contraceptives.)*

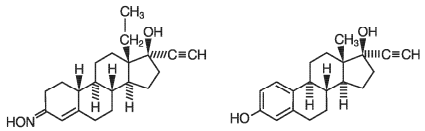
**DESCRIPTION**

ORTHO EVRA® is a combination transdermal contraceptive patch with a contact surface area of 20 $cm^2$. It contains 6.00 mg norelgestromin (NGMN) and 0.75 mg ethinyl estradiol (EE). Systemic exposures (as measured by area under the curve [AUC] and steady state concentration [$C_{ss}$]) of NGMN and EE during use of ORTHO EVRA® are higher and peak concentrations ($C_{max}$) are lower than those produced by an oral contraceptive containing norgestimate 250 mcg / EE 35 mcg. (See BOLDED WARNING; CLINICAL PHARMACOLOGY, Transdermal versus Oral Contraceptives).

ORTHO EVRA® is a thin, matrix-type transdermal contraceptive patch consisting of three layers. The backing layer is composed of a beige flexible film consisting of a low-density pigmented polyethylene outer layer and a polyester inner layer. It provides structural support and protects the middle adhesive layer from the environment. The middle layer contains polyisobutylene/polybutene adhesive, crospovidone, non-woven polyester fabric and lauryl lactate as inactive components. The active components in this layer are the hormones, norelgestromin and ethinyl estradiol. The third layer is the release liner, which protects the adhesive layer during storage and is removed just prior to application. It is a transparent polyethylene terephthalate (PET) film with a polydimethylsiloxane coating on the side that is in contact with the middle adhesive layer.

The outside of the backing layer is heat-stamped "ORTHO EVRA®."

The structural formulas of the components are:




norelgestromin ethinyl estradiol

**Molecular weight, norelgestromin: 327.47**

**Molecular weight, ethinyl estradiol: 296.41**

**Chemical name for norelgestromin: 18,19-Dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-,3-oxime,(17α)**

**Chemical name for ethinyl estradiol: 19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol,(17α)**

**CLINICAL PHARMACOLOGY**

**Pharmacodynamics**

Norelgestromin is the active progestin largely responsible for the progestational activity that occurs in women following application of ORTHO EVRA®. Norelgestromin is also the primary active metabolite produced following oral administration of norgestimate (NGM), the progestin component of the oral contraceptive products ORTHO-CYCLEN® and ORTHO TRI-CYCLEN®.

Combination oral contraceptives act by suppression of gonadotropins. Although the primary mechanism of this action is inhibition of ovulation, other alterations include changes in the cervical mucus (which increase the difficulty of sperm entry into the uterus) and the endometrium (which reduce the likelihood of implantation).

Receptor and human sex hormone-binding globulin (SHBG) binding studies, as well as studies in animals and humans, have shown that both NGM and NGMN exhibit high progestational activity with minimal intrinsic androgenicity.[90-93] Transdermally-administered norelgestromin, in combination with ethinyl estradiol, does not counteract the estrogen-induced increases in SHBG, resulting in lower levels of free testosterone in serum compared to baseline.

One clinical trial assessed the return of hypothalamic-pituitary-ovarian axis function post-therapy and found that FSH, LH, and estradiol mean values, though suppressed during therapy, returned to near baseline values during the 6 weeks post therapy.

**Pharmacokinetics**

Absorption

Following a single application of ORTHO EVRA®, both NGMN and EE reach a plateau by approximately 48 hours. Pooled data from the 3 clinical studies have demonstrated that steady state is reached within 2 weeks of application. The mean steady state $C_{ss}$ concentrations ranged from 0.305–1.53 ng/mL for NGMN and from 11.2–137 pg/mL for EE.

Absorption of NGMN and EE following application of ORTHO EVRA® to the buttock, upper outer arm, abdomen and upper torso (excluding breast) was examined. While absorption from the abdomen was slightly lower than from other sites, absorption from these anatomic sites was considered to be therapeutically equivalent.

The mean (%CV) pharmacokinetic parameters $C_{ss}$ and $AUC_{0-168}$ for NGMN and EE following a single buttock application of ORTHO EVRA® are summarized in Table 1.

In multiple dose studies, $AUC_{0-168}$ for NGMN and EE was found to increase over time (Table 1). In a three-cycle study, these pharmacokinetic parameters reached steady state conditions during Cycle 3 (Figures 1 and 2). Upon removal of the patch, serum levels of EE and NGMN reach very low or non-measurable levels within 3 days.

**Table 1: Mean (%CV*) Pharmacokinetic Parameters of Norelgestromin (NGMN) and Ethinyl Estradiol (EE) Following 3 Consecutive Cycles of ORTHO EVRA® Wear on the Buttock**

| Analyte | Parameter | Cycle 1 Week 1 | Cycle 3 Week 1 | Cycle 3 Week 2 | Cycle 3 Week 3 |
|---|---|---|---|---|---|
| NGMN | $C_{ss}$ (ng/mL) | 0.70 (39.4) | 0.70 (41.8) | 0.80 (28.7) | 0.70 (45.3) |
| | $AUC_{0-168}$ (ng·h/mL) | 107 (44.2) | 105 (43.2) | 132 (43.4) | 120 (43.9) |
| | $t_{1/2}$(h) | nc | nc | nc | 32.1 (40.3) |
| EE | $C_{ss}$ (pg/mL) | 46.4 (38.5) | 47.6 (36.4) | 59.0 (42.5) | 49.6 (54.4) |
| | $AUC_{0-168}$ (pg·h/mL) | 6796 (39.3) | 7160 (40.4) | 10054 (41.8) | 8840 (58.6) |
| | $t_{1/2}$(h) | nc | nc | nc | 21.0 (43.2) |

nc = not calculated,*%CV is % of Coefficient of variation = 100 (standard deviation/mean)

Figure 1: Mean Serum NGMN Concentrations (ng/mL) in Healthy Female Volunteers Following Application of ORTHO EVRA® on the Buttock for Three Consecutive Cycles (Vertical arrow indicates time of patch removal)

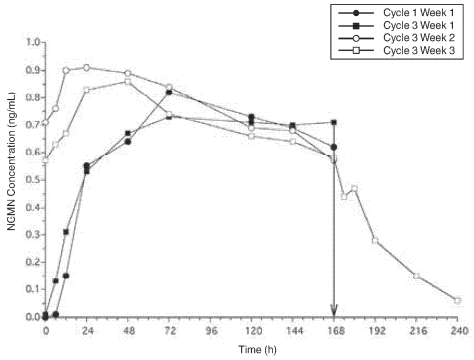
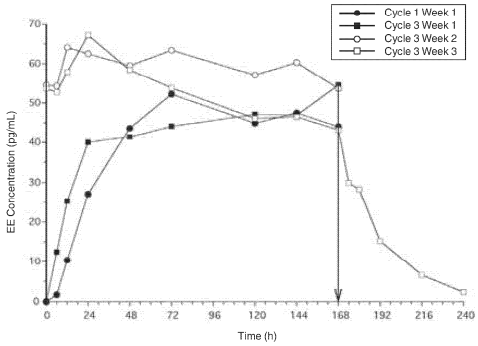



Figure 2: Mean Serum EE Concentrations (pg/mL) in Healthy Female Volunteers Following Application of ORTHO EVRA® on the Buttock for Three Consecutive Cycles (Vertical arrow indicates time of patch removal.)




The absorption of NGMN and EE following application of ORTHO EVRA® was studied under conditions encountered in a health club (sauna, whirlpool and treadmill) and in a cold water bath. The results indicated that for NGMN there were no significant treatment effects on $C_{ss}$ or AUC when compared to normal wear. For EE, increased exposures were observed due to sauna, whirlpool and treadmill. There was no significant effect of cold water on these parameters.

Results from a study of consecutive ORTHO EVRA® wear for 7 days and 10 days indicated that serum concentrations of NGMN and EE dropped slightly during the first 6 hours after the patch replacement, and recovered within 12 hours. By Day 10 of patch administration, both NGMN and EE concentrations had decreased by approximately 25% when compared to Day 7 concentrations.

Metabolism

Since ORTHO EVRA® is applied transdermally, first-pass metabolism (via the gastrointestinal tract and/or liver) of NGMN and EE that would be expected with oral administration is avoided. Hepatic metabolism of NGMN occurs and metabolites include norgestrel, which is highly bound to SHBG, and various hydroxylated and conjugated metabolites. Ethinyl estradiol is also metabolized to various hydroxylated products and their glucuronide and sulfate conjugates.

Distribution

NGMN and norgestrel (a serum metabolite of NGMN) are highly bound (>97%) to serum proteins. NGMN is bound to albumin and not to SHBG, while norgestrel is bound primarily to SHBG, which limits its biological activity. Ethinyl estradiol is extensively bound to serum albumin and induces an increase in the serum concentrations of SHBG (see CLINICAL PHARMACOLOGY, Transdermal versus Oral Contraceptives, Table 3).

Elimination

Following removal of patches, the elimination kinetics of NGMN and EE were consistent for all studies with half-life values of approximately 28 hours and 17 hours, respectively. The metabolites of NGMN and EE are eliminated by renal and fecal pathways.

**Transdermal versus Oral Contraceptives**

The ORTHO EVRA® transdermal patch was designed to deliver EE and NGMN over a seven-day period while oral contraceptives (containing NGM 250 mcg / EE 35 mcg) are administered on a daily basis. Figures 3 and 4 present mean pharmacokinetic (PK) profiles for EE and NGMN following administration of an oral contraceptive (containing NGM 250 mcg / EE 35 mcg) compared to the 7-day transdermal ORTHO EVRA® patch (containing NGMN 6.0 mg / EE 0.75 mg) during cycle 2 in 32 healthy female volunteers.

Figure 3: Mean Serum Concentration-Time Profiles of NGMN Following Once-Daily Administration of an Oral Contraceptive for 2 Cycles or Application of ORTHO EVRA® for 2 Cycles to the Buttock in Healthy Female Volunteers. [Oral contraceptive: Cycle 2, Days 15-21, ORTHO EVRA®: Cycle 2, Week 3]

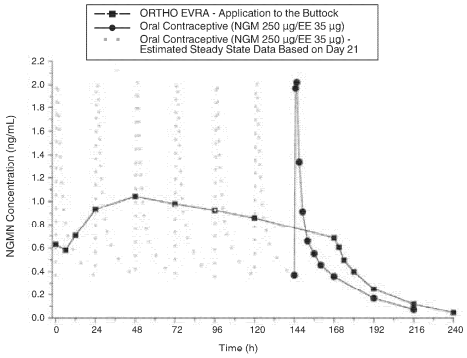



Figure 4: Mean Serum Concentration-Time Profiles of EE Following Once-Daily Administration of an Oral Contraceptive for 2 Cycles or Application of ORTHO EVRA® for 2 Cycles to the Buttock in Healthy Female Volunteers. [Oral contraceptive: Cycle 2, Days 15-21, ORTHO EVRA®: Cycle 2, Week 3]

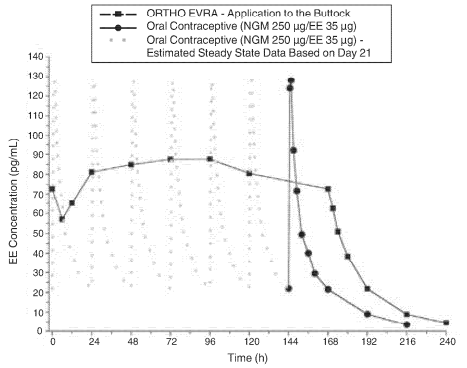



Table 2 provides the mean (%CV) for NGMN and EE pharmacokinetic (PK) parameters.

**Table 2: Mean (%CV) NGMN and EE Steady State Pharmacokinetic Parameters Following Application of ORTHO EVRA® and Once-Daily Administration of an Oral Contraceptive (containing NGM 250 mcg / EE 35 mcg) in Healthy Female Volunteers**

| Parameter | ORTHO EVRA®* | ORAL CONTRACEPTIVE† |
|---|---|---|
| NGMN‡ | | |
| $C_{max}$ (ng/mL) | 1.12 (33.6) | 2.16 (25.2) |
| $AUC_{0-168}$ (ng·h/mL) | 145 (36.8) | 123 (30.2)§ |
| $C_{ss}$ (ng/mL) | 0.888 (36.6) | 0.732 (30.2)¶ |
| EE | | |
| $C_{max}$ (pg/mL) | 97.4 (31.6) | 133 (27.7) |
| $AUC_{0-168}$ (pg·h/mL) | 12971 (33.1) | 8281(26.9)§ |
| $C_{ss}$ (pg/mL) | 80.0 (33.5) | 49.3 (26.9)¶ |

* Cycle 2, Week 3
† Cycle 2, Day 21
‡ NGM is rapidly metabolized to NGMN following oral administration
§ Average weekly exposure, calculated as $AUC_{24}$ x 7
¶ $C_{avg}$

In general, overall exposure for NGMN and EE (AUC and $C_{ss}$) was higher in subjects treated with ORTHO EVRA® for both Cycle 1 and Cycle 2, compared to that for the oral contraceptive, while $C_{max}$ values were higher in subjects administered the oral contraceptive. Under steady state conditions, $AUC_{0-168}$ and $C_{ss}$ for EE were approximately 55% and 60% higher, respectively, for the transdermal patch, and the $C_{max}$ was about 35% higher for the oral contraceptive, respectively. Inter-subject variability (%CV) for the PK parameters following delivery from ORTHO EVRA® was higher relative to the variability determined from the oral contraceptive. The mean pharmacokinetic profiles are different between the two products and caution should be exercised when making a direct comparison of these PK parameters.

In Table 3, percent change in concentrations (%CV) of markers of systemic estrogenic activity (Sex Hormone Binding Globulin [SHBG] and Corticosteroid Binding Globulin [CBG]) from Cycle 1 Day 1 to Cycle 1 Day 22 is presented. Percent change in SHBG concentrations was higher for ORTHO EVRA® users compared to women taking the oral contraceptive; percent change in CBG concentrations was similar for ORTHO EVRA® and oral contraceptive users. Within each group, the absolute values for SHBG were similar for Cycle 1, Day 22 and Cycle 2, Day 22.

**Table 3: Mean Percent Change (%CV) in SHBG and CBG Concentrations Following Once-Daily Administration of an Oral Contraceptive (containing NGM 250 mcg / EE 35 mcg) for One Cycle and Application of ORTHO EVRA® for One Cycle in Healthy Female Volunteers**

| Parameter | ORTHO EVRA® (% change from Day 1 to Day 22) | ORAL CONTRACEPTIVE (% change from Day 1 to Day 22) |
|---|---|---|
| SHBG | 334 (39.3) | 200 (43.2) |
| CBG | 153 (40.2) | 157 (33.4) |

**Special Populations**

Effects of Age, Body Weight, Body Surface Area and Race

The effects of age, body weight, body surface area and race on the pharmacokinetics of NGMN and EE were evaluated in 230 healthy women from nine pharmacokinetic studies of single 7-day applications of ORTHO EVRA®. For both NGMN and EE, increasing age, body weight and body surface area each were associated with slight decreases in $C_{ss}$ and AUC values. However, only a small fraction (10-25%) of the overall variability in the pharmacokinetics of NGMN and EE following application of ORTHO EVRA® may be associated with any or all of the above demographic parameters. There was no significant effect of race with respect to Caucasians, Hispanics and Blacks.

Renal and Hepatic Impairment

No formal studies were conducted with ORTHO EVRA® to evaluate the pharmacokinetics, safety, and efficacy in women with renal or hepatic impairment. Steroid hormones may be poorly metabolized in patients with impaired liver function (see PRECAUTIONS).

**Patch Adhesion**

In the clinical trials with ORTHO EVRA®, approximately 2% of the cumulative number of patches completely detached. The proportion of subjects with at least 1 patch that completely detached ranged from 2% to 6%, with a reduction from Cycle 1 (6%) to Cycle 13 (2%). For instructions on how to manage detachment of patches, refer to the DOSAGE AND ADMINISTRATION section.

**INDICATIONS AND USAGE**

ORTHO EVRA® is indicated for the prevention of pregnancy in women who elect to use a transdermal patch as a method of contraception.

The pharmacokinetic profile for the ORTHO EVRA® transdermal patch is different from that of an oral contraceptive. Healthcare professionals should balance the higher estrogen exposure and the possible increased risk of venous thromboembolism with ORTHO EVRA® against the chance of pregnancy if a contraceptive pill is not taken daily. (See BOLDED WARNING; WARNINGS; CLINICAL PHARMACOLOGY, Transdermal versus Oral Contraceptives).

Like oral contraceptives, ORTHO EVRA® is highly effective if used as recommended in this label.

In 3 large clinical trials in North America, Europe and South Africa, 3,330 women (ages 18-45) completed 22,155 cycles of ORTHO EVRA® use, pregnancy rates were approximately 1 per 100 women-years of ORTHO EVRA® use. The racial distribution was 91% Caucasian, 4.9% Black, 1.6% Asian, and 2.4% Other.

With respect to weight, 5 of the 15 pregnancies reported with ORTHO EVRA® use were among women with a baseline body weight ≥ 198 lbs. (90kg), which constituted <3% of the study population. The greater proportion of pregnancies among women at or above 198 lbs. was statistically significant and suggests that ORTHO EVRA® may be less effective in these women.

Healthcare professionals who consider ORTHO EVRA® for women at or above 198 lbs. should discuss the patient's individual needs in choosing the most appropriate contraceptive option.

Table 4 lists the accidental pregnancy rates for users of various methods of contraception. The efficacy of these contraceptive methods, except sterilization, IUD, and Norplant® depends upon the reliability with which they are used. Correct and consistent use of methods can result in lower failure rates.

**Table 4: Percentage of Women Experiencing an Unintended Pregnancy During the First Year of Typical Use and the First Year of Perfect Use of Contraception and the Percentage Continuing Use at the End of the First Year. United States.**

| Method (1) | % of Women Experiencing an Unintended Pregnancy within the First Year of Use: Typical Use† (2) | Perfect Use‡ (3) | % of Women Continuing Use at One Year* (4) |
|---|---|---|---|
| Chance# | 85 | 85 | |
| Spermicides[p] | 26 | 6 | 40 |
| Periodic abstinence | 25 | | 63 |
| Calendar | | 9 | |
| Ovulation Method | | 3 | |
| Sympto-Thermal[β] | | 2 | |
| Post-Ovulation | | 1 | |
| Cap[à] | | | |
| Parous Women | 40 | 26 | 42 |
| Nulliparous Women | 20 | 9 | 56 |
| Sponge | | | |
| Parous Women | 40 | 20 | 42 |
| Nulliparous Women | 20 | 9 | 56 |
| Diaphragm[à] | 20 | 6 | 56 |
| Withdrawal | 19 | 4 | |
| Condom[ò] | | | |
| Female (Reality®) | 21 | 5 | 56 |
| Male | 14 | 3 | 61 |
| Pill | 5 | | 71 |
| Progestin Only | | 0.5 | |
| Combined | | 0.1 | |
| IUD | | | |
| Progesterone T | 2.0 | 1.5 | 81 |
| Copper T380A | 0.8 | 0.6 | 78 |
| LNG 20 | 0.1 | 0.1 | 81 |
| Depo-Provera® | 0.3 | 0.3 | 70 |
| Norplant® and Norplant-2® | 0.05 | 0.05 | 88 |
| Female Sterilization | 0.5 | 0.5 | 100 |
| Male Sterilization | 0.15 | 0.10 | 100 |

Hatcher et al, 1998, Ref. # 1.

**Emergency Contraceptive Pills:**

Treatment initiated within 72 hours after unprotected intercourse reduces the risk of pregnancy by at least 75%.§

**Lactational Amenorrhea Method:**

LAM is a highly effective, *temporary* method of contraception.¶

Source: Trussell J, Contraceptive efficacy. In Hatcher RA, Trussell J, Stewart F, Cates W, Stewart GK, Kowal D, Guest F. Contraceptive Technology: Seventeenth Revised Edition. New York, NY: Irvington Publishers, 1998.

* Among couples attempting to avoid pregnancy, the percentage who continue to use a method for one year.

† Among *typical* couples who initiate use of a method (not necessarily for the first time), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.

‡ Among couples who initiate use of a method (not necessarily for the first time) and who use it *perfectly* (both consistently and correctly), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.

§ The treatment schedule is one dose within 72 hours after unprotected intercourse, and a second dose 12 hours after the first dose. The Food and Drug Administration has declared the following brands of oral contraceptives to be safe and effective for emergency contraception: Ovral® (1 dose is 2 white pills), Alesse® (1 dose is 5 pink pills), Nordette® or Levlen® (1 dose is 2 light-orange pills), Lo/Ovral® (1 dose is 4 white pills), Triphasil® or Tri-Levlen® (1 dose is 4 yellow pills).

¶ However, to maintain effective protection against pregnancy, another method of contraception must be used as soon as menstruation resumes, the frequency or duration of breastfeeds is reduced, bottle feeds are introduced, or the baby reaches six months of age.

\# The percents becoming pregnant in columns (2) and (3) are based on data from populations where contraception is not used and from women who cease using contraception in order to become pregnant. Among such populations, about 89% become pregnant within one year. This estimate was lowered slightly (to 85%) to represent the percent who would become pregnant within one year among women now relying on reversible methods of contraception if they abandoned contraception altogether.

[p] Foams, creams, gels, vaginal suppositories, and vaginal film.

[β] Cervical mucus (ovulation) method supplemented by calendar in the pre-ovulatory and basal body temperature in the post-ovulatory phases.

[à] With spermicidal cream or jelly.

[ò] Without spermicides.

***ORTHO EVRA® has not been studied for and is not indicated for use in emergency contraception.***

**CONTRAINDICATIONS**

ORTHO EVRA® should not be used in women who currently have the following conditions:

- Thrombophlebitis, thromboembolic disorders
- A past history of deep vein thrombophlebitis or thromboembolic disorders
- Known thrombophilic conditions
- Cerebrovascular or coronary artery disease (current or past history)
- Valvular heart disease with complications[103]
- Persistent blood pressure values of ≥ 160 mm Hg systolic or ≥ 100 mg Hg diastolic[103, 112]
- Diabetes with vascular involvement[100]
- Headaches with focal neurological symptoms
- Major surgery with prolonged immobilization
- Known or suspected carcinoma of the breast or personal history of breast cancer
- Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia
- Undiagnosed abnormal genital bleeding
- Cholestatic jaundice of pregnancy or jaundice with prior hormonal contraceptive use
- Acute or chronic hepatocellular disease with abnormal liver function[103]
- Hepatic adenomas or carcinomas
- Known or suspected pregnancy
- Hypersensitivity to any component of this product

**WARNINGS**

**Cigarette smoking increases the risk of serious cardiovascular events from hormonal contraceptive use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, hormonal contraceptives, including ORTHO EVRA®, should not be used by women who are over 35 years of age and smoke.**

**The pharmacokinetic (PK) profile for the ORTHO EVRA® patch is different from the PK profile for oral contraceptives in that it has higher steady state concentrations and lower peak concentrations. Area under the time-concentration curve (AUC) and average concentration at steady state for ethinyl estradiol (EE) are approximately 60% higher in women using ORTHO EVRA® compared with women using an oral contraceptive containing EE 35 mcg. In contrast, peak concentrations for EE are approximately 25% lower in women using ORTHO EVRA®. Inter-subject variability results in increased exposure to EE in some women using either ORTHO EVRA® or oral contraceptives. However, inter-subject variability in women using ORTHO EVRA® is higher. It is not known whether there are changes in the risk of serious adverse events based on the differences in pharmacokinetic profiles of EE in women using ORTHO EVRA® compared with women using oral contraceptives containing 30-35 mcg of EE. Increased estrogen exposure may increase the risk of adverse events, including venous thromboembolism. (See CLINICAL PHARMACOLOGY, Transdermal versus Oral Contraceptives).**

Four epidemiologic, case-control studies[107-111,113-115] were conducted in the U.S. using electronic healthcare claims data to evaluate the risk of venous thromboembolism (VTE) among women aged 15-44 who used ORTHO EVRA® compared to women who used oral contraceptives containing 30-35 mcg of ethinyl estradiol (EE) and either levonorgestrel (LNG) or norgestimate (NGM). NGM is the prodrug for norelgestromin, the progestin in ORTHO EVRA®.

These studies (see Table 5) used slightly different designs and reported odds ratios ranging from 1.2 to 2.2. The interpretations of these odds ratios range from no increase in risk to an approximate doubling of risk. One of the studies found a statistically significant increased risk of VTE for current users of ORTHO EVRA®.

The four studies are:

- The i3 Ingenix study with NGM-containing oral contraceptives as the comparator, including a 24-month extension, based on the Ingenix Research Datamart; only this study included patient chart review to confirm the VTE occurrence.
- The Boston Collaborative Drug Surveillance Program (BCDSP) with NGM-containing oral contraceptives as the comparator (BCDSP NGM), including two extensions of 17 and 14 months, respectively, based on the Pharmetrics database
- BCDSP with LNG-containing oral contraceptives as the comparator, based on the Pharmetrics database
- BCDSP with LNG-containing oral contraceptives as the comparator, based on the Marketscan database

The i3 Ingenix and BCDSP NGM studies have provided data on additional cases identified in study extensions; however, each study extension was not powered to provide independent estimates of risk. The pooled estimates provide the most reliable estimates of VTE risk. Odds ratios from the original and various extensions of the i3 Ingenix and BCDSP NGM studies are provided in the footnotes to Table 5.

**Table 5: Estimates (Odds Ratios) of Venous Thromboembolism Risk in Current Users of ORTHO EVRA® Compared to Oral Contraceptive Users**

| Epidemiologic Study | Comparator Product | Odds Ratio (95% CI) |
|---|---|---|
| i3 Ingenix NGM Study in Ingenix Research Datamart[107,113,114,115] | NGM/35 mcg EE* | **2.2† (1.2-4.0)‡** |
| BCDSP§ NGM Study in Pharmetrics database[108,109,111] | NGM/35 mcg EE | **1.2 (0.9-1.8)¶** |
| BCDSP LNG Study in Pharmetrics database[110] | LNG#/30 mcg EE | **2.0 (0.9-4.1)[p]** |
| BCDSP LNG Study in Marketscan database[110] | LNG/30 mcg EE | **1.3 (0.8-2.0)[β]** |

* NGM = norgestimate; EE = ethinyl estradiol

† Increase in risk of VTE is statistically significant

‡ Pooled odds ratio from references 107 and 113. [Initial 33 months of data: Odds Ratio (95% CI) = 2.5† (1.1-5.5); Separate estimate from 24 months of data on new cases not included in the previous estimate: Odds Ratio (95% CI) = 1.4 (0.5-3.7)]

§ BCDSP = Boston Collaborative Drug Surveillance Program

¶ Pooled odds ratio from references 108, 109 and 111. [Initial 36 months of data: Odds Ratio (95% CI) = 0.9 (0.5-1.6); Separate estimate from 17 months of data on new cases not included in the previous estimate: Odds Ratio (95% CI) = 1.1 (0.6-2.1); Separate estimate from 14 months of data on new cases not included in the previous estimates: Odds Ratio (95% CI) = 2.4† (1.2-5.0)]

\# LNG = levonorgestrel

[p] 48 months of data.

[β] 69 months of data.

In 3 large clinical trials (N= 3,330 with 1,704 women-years of exposure), one case of non-fatal pulmonary embolism occurred during ORTHO EVRA® use, and one case of post-operative non-fatal pulmonary embolism was reported following ORTHO EVRA® use.

ORTHO EVRA® and other contraceptives that contain both an estrogen and a progestin are called combination hormonal contraceptives. As with any combination hormonal contraceptive, the clinician should be alert to the earliest manifestations of thromboembolic disorders (thrombophlebitis, VTE including pulmonary embolism, cerebrovascular disorders, and retinal thrombosis). Should any of these occur or be suspected, ORTHO EVRA® should be discontinued immediately.

Practitioners prescribing ORTHO EVRA® should be familiar with the following information relating to risks:

The use of combination hormonal contraceptives is associated with increased risks of several serious conditions including myocardial infarction, thromboembolism, stroke, hepatic neoplasia, and gallbladder disease, although the risk of serious morbidity or mortality is very small in healthy women without underlying risk factors. The risk of morbidity and mortality increases significantly in the presence of other underlying risk factors such as hypertension, hyperlipidemias, obesity and diabetes.

The information that follows in this section of the package insert is principally based on studies carried out in women who used combination oral contraceptives with higher formulations of estrogens and progestins than those in common use today. The effect of long-term use of combination hormonal contraceptives with lower doses of both estrogen and progestin administered by any route remains to be determined.

Throughout this labeling, epidemiological studies reported are of two types: retrospective or case control studies and cohort studies. Case control studies provide an estimate of the relative risk or odds for developing a disease, namely, a ratio of the disease among oral contraceptive users to that among nonusers or users of a comparator drug product. The odds ratio does not provide information on the actual clinical occurrence of a disease. Cohort studies provide a measure of the incidence of a disease in an exposed population. The relative risk is the ratio of the incidence density in the exposed population relative to the incidence density in a comparator population. Cohort studies also provide a measure of attributable risk, which is the *difference* in the incidence of disease between hormonal contraceptive users and nonusers or comparator drug products. The attributable risk does provide information about the actual occurrence of a disease in the population (adapted from refs. 2 and 3 with the author's permission). For further information, the reader is referred to a text on epidemiological methods.

**1. Thromboembolic Disorders and Other Vascular Problems**

a. Thromboembolism

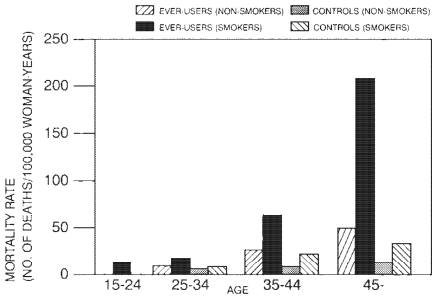
An increased risk of thromboembolic and thrombotic disease associated with the use of hormonal contraceptives is well established. Case control studies have found the relative risk of users compared to nonusers to be 3 for the first episode of superficial venous thrombosis, 4 to 11 for deep vein thrombosis or pulmonary embolism, and 1.5 to 6 for women with predisposing conditions for venous thromboembolic disease.[2,3,19-24] Cohort studies have shown the relative risk to be somewhat lower, about 3 for new cases and about 4.5 for new cases requiring hospitalization.[25] The risk of thromboembolic disease associated with hormonal contraceptives is not related to length of use and disappears after hormonal contraceptive use is stopped.[2] A two- to four-fold increase in relative risk of post-operative thromboembolic complications has been reported with the use of hormonal contraceptives.[9,26] The relative risk of venous thrombosis in women who have predisposing conditions is twice that of women without such medical conditions.[9,26] If feasible, hormonal contraceptives should be discontinued at least four weeks prior to and for two weeks after elective surgery of a type associated with an increase in risk of thromboembolism and during and following prolonged immobilization. Since the immediate postpartum period is also associated with an increased risk of thromboembolism, hormonal contraceptives should be started no earlier than four weeks after delivery in women who elect not to breastfeed.

b. Myocardial Infarction

An increased risk of myocardial infarction has been attributed to hormonal contraceptive use. This risk is primarily in smokers or women with other underlying risk factors for coronary artery disease such as hypertension, hypercholesterolemia, morbid obesity, and diabetes. The relative risk of heart attack for current hormonal contraceptive users has been estimated to be two to six[4-10] compared to non-users. The risk is very low under the age of 30.

Smoking in combination with oral contraceptive use has been shown to contribute substantially to the incidence of myocardial infarctions in women in their mid-thirties or older with smoking accounting for the majority of excess cases.[11] Mortality rates associated with circulatory disease have been shown to increase substantially in smokers, especially in those 35 years of age and older among women who use oral contraceptives. (See Figure 5.)

Figure 5: Circulatory Disease Mortality Rates Per 100,000 Women-Years by Age, Smoking Status and Oral Contraceptive Use




Hormonal contraceptives may compound the effects of well-known risk factors, such as hypertension, diabetes, hyperlipidemias, age and obesity.[13] In particular, some progestins are known to decrease HDL cholesterol and cause glucose intolerance, while estrogens may create a state of hyperinsulinism.[14-18] Hormonal contraceptives have been shown to increase blood pressure among some users (see section 9 in WARNINGS). Similar effects on risk factors have been associated with an increased risk of heart disease. Hormonal contraceptives, including ORTHO EVRA®, must be used with caution in women with cardiovascular disease risk factors.

Norgestimate and norelgestromin have minimal androgenic activity (see CLINICAL PHARMACOLOGY). There is some evidence that the risk of myocardial infarction associated with hormonal contraceptives is lower when the progestin has minimal androgenic activity than when the activity is greater.[97]

c. Cerebrovascular Diseases

Hormonal contraceptives have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes), although, in general, the risk is greatest among older (>35 years), hypertensive women who also smoke. Hypertension was found to be a risk factor for both users and nonusers, for both types of strokes, and smoking interacted to increase the risk of stroke.[27-29]

In a large study, the relative risk of thrombotic strokes has been shown to range from 3 for normotensive users to 14 for users with severe hypertension.[30] The relative risk of hemorrhagic stroke is reported to be 1.2 for non-smokers who used hormonal contraceptives, 2.6 for smokers who did not use hormonal contraceptives, 7.6 for smokers who used hormonal contraceptives, 1.8 for normotensive users and 25.7 for users with severe hypertension.[30] The attributable risk is also greater in older women.[3]

d. Dose-Related Risk of Vascular Disease from Hormonal Contraceptives

A positive association has been observed between the amount of estrogen and progestin in hormonal contraceptives and the risk of vascular disease.[31-33] A decline in serum high-density lipoproteins (HDL) has been reported with many progestational agents.[14-16] A decline in serum high-density lipoproteins has been associated with an increased incidence of ischemic heart disease. Because estrogens increase HDL cholesterol, the net effect of a hormonal contraceptive depends on a balance achieved between doses of estrogen and progestin and the activity of the progestin used in the contraceptives. The activity and amount of both hormones should be considered in the choice of a hormonal contraceptive.

e. Persistence of Risk of Vascular Disease

There are two studies that have shown persistence of risk of vascular disease for ever-users of combination hormonal contraceptives. In a study in the United States, the risk of developing myocardial infarction after discontinuing combination hormonal contraceptives persists for at least 9 years for women 40-49 years who had used combination hormonal contraceptives for five or more years, but this increased risk was not demonstrated in other age groups.[8] In another study in Great Britain, the risk of developing cerebrovascular disease persisted for at least 6 years after discontinuation of combination hormonal contraceptives, although excess risk was very small.[34] However, both studies were performed with combination hormonal contraceptive formulations containing 50 micrograms or higher of estrogens.

**2. Estimates of Mortality from Combination Hormonal Contraceptive Use**

One study gathered data from a variety of sources that have estimated the mortality rate associated with different methods of contraception at different ages (Table 6). These estimates include the combined risk of death associated with contraceptive methods plus the risk attributable to pregnancy in the event of method failure. Each method of contraception has its specific benefits and risks. The study concluded that with the exception of combination oral contraceptive users 35 and older who smoke, and 40 and older who do not smoke, mortality associated with all methods of birth control is low and below that associated with childbirth.

The observation of a possible increase in risk of mortality with age for combination oral contraceptive users is based on data gathered in the 1970's but not reported until 1983.[35] Current clinical recommendation involves the use of lower estrogen dose formulations and a careful consideration of risk factors. In 1989, the Fertility and Maternal Health Drugs Advisory Committee was asked to review the use of combination hormonal contraceptives in women 40 years of age and over. The Committee concluded that although cardiovascular disease risks may be increased with combination hormonal contraceptive use after age 40 in healthy non-smoking women (even with the newer low-dose formulations), there are also greater potential health risks associated with pregnancy in older women and with the alternative surgical and medical procedures that may be necessary if such women do not have access to effective and acceptable means of contraception. The Committee recommended that the benefits of low-dose combination hormonal contraceptive use by healthy non-smoking women over 40 may outweigh the possible risks.[36,37]

Although the data are mainly obtained with oral contraceptives, this is likely to apply to ORTHO EVRA® as well. Women of all ages who use combination hormonal contraceptives, should use the lowest possible dose formulation that is effective and meets the individual patient needs.

**Table 6: Annual Number of Birth-Related or Method-Related Deaths Associated with Control of Fertility per 100,000 Non-Sterile Women, by Fertility Control Method According to Age**

| Method of control and outcome | 15-19 | 20-24 | 25-29 | 30-34 | 35-39 | 40-44 |
|---|---|---|---|---|---|---|
| No fertility control methods* | 7.0 | 7.4 | 9.1 | 14.8 | 25.7 | 28.2 |
| Oral contraceptives, non-smoker† | 0.3 | 0.5 | 0.9 | 1.9 | 13.8 | 31.6 |
| Oral contraceptives, smoker† | 2.2 | 3.4 | 6.6 | 13.5 | 51.1 | 117.2 |
| IUD† | 0.8 | 0.8 | 1.0 | 1.0 | 1.4 | 1.4 |
| Condom* | 1.1 | 1.6 | 0.7 | 0.2 | 0.3 | 0.4 |
| Diaphragm/spermicide* | 1.9 | 1.2 | 1.2 | 1.3 | 2.2 | 2.8 |
| Periodic abstinence* | 2.5 | 1.6 | 1.6 | 1.7 | 2.9 | 3.6 |

Adapted from H.W. Ory, ref. # 35.
* Deaths are birth-related
† Deaths are method-related

**3. Carcinoma of the Reproductive Organs and Breasts**

Numerous epidemiological studies give conflicting reports on the relationship between breast cancer and COC use. The risk of having breast cancer diagnosed may be slightly increased among current and recent users of combination oral contraceptives. However, this excess risk appears to decrease over time after COC discontinuation and by 10 years after cessation the increased risk disappears. Some studies report an increased risk with duration of use while other studies do not and no consistent relationships have been found with dose or type of steroid. Some studies have found a small increase in risk for women who first use COCs before age 20. Most studies show a similar pattern of risk with COC use regardless of a woman's reproductive history or her family breast cancer history.

In addition, breast cancers diagnosed in current or ever oral contraceptive users may be less clinically advanced than in never-users.

Women who currently have or have had breast cancer should not use hormonal contraceptives because breast cancer is usually a hormonally sensitive tumor.

Some studies suggest that combination oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia in some populations of women.[45-48] However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors.

In spite of many studies of the relationship between oral contraceptive use and breast and cervical cancers, a cause-and-effect relationship has not been established. It is not known whether ORTHO EVRA® is distinct from oral contraceptives with regard to the above statements.

**4. Hepatic Neoplasia**

Benign hepatic adenomas are associated with hormonal contraceptive use, although the incidence of benign tumors is rare in the United States. Indirect calculations have estimated the attributable risk to be in the range of 3.3 cases/100,000 for users, a risk that increases after four or more years of use, especially with hormonal contraceptives containing 50 micrograms or more of estrogen.[49] Rupture of benign, hepatic adenomas may cause death through intra-abdominal hemorrhage.[50,51]

Studies from Britain and the U.S. have shown an increased risk of developing hepatocellular carcinoma in long term (≥ 8 years)[52-54,96] oral contraceptive users. However, these cancers are extremely rare in the U.S. and the attributable risk (the excess incidence) of liver cancers in oral contraceptive users approaches less than one per million users. It is unknown whether ORTHO EVRA® is distinct from oral contraceptives in this regard.

**5. Ocular Lesions**

There have been clinical case reports of retinal thrombosis associated with the use of hormonal contraceptives. ORTHO EVRA® should be discontinued if there is unexplained partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions. Appropriate diagnostic and therapeutic measures should be undertaken immediately.

**6. Hormonal Contraceptive Use Before or During Early Pregnancy**

Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy.[56,57] Studies also do not indicate a teratogenic effect, particularly in so far as cardiac anomalies and limb reduction defects are concerned[55,56,58,59], when oral contraceptives are taken inadvertently during early pregnancy.

Combination hormonal contraceptives such as ORTHO EVRA® should not be used to induce withdrawal bleeding as a test for pregnancy. ORTHO EVRA® should not be used during pregnancy to treat threatened or habitual abortion. It is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out. If the patient has not adhered to the prescribed schedule for the use of ORTHO EVRA® the possibility of pregnancy should be considered at the time of the first missed period. Hormonal contraceptive use should be discontinued if pregnancy is confirmed.

**7. Gallbladder Disease**

Earlier studies have reported an increased lifetime relative risk of gallbladder surgery in users of hormonal contraceptives and estrogens.[60,61] More recent studies, however, have shown that the relative risk of developing gallbladder disease among hormonal contraceptive users may be minimal.[62-64] The recent findings of minimal risk may be related to the use of hormonal contraceptive formulations containing lower hormonal doses of estrogens and progestins.

Combination hormonal contraceptives such as ORTHO EVRA® may worsen existing gallbladder disease and may accelerate the development of this disease in previously asymptomatic women. Women with a history of combination hormonal contraceptive-related cholestasis are more likely to have the condition recur with subsequent combination hormonal contraceptive use.

**8. Carbohydrate and Lipid Metabolic Effects**

Hormonal contraceptives have been shown to cause a decrease in glucose tolerance in some users.[17] However, in the non-diabetic woman, combination hormonal contraceptives appear to have no effect on fasting blood glucose.[67] Prediabetic and diabetic women in particular should be carefully monitored while taking combination hormonal contraceptives such as ORTHO EVRA®.

In clinical trials with oral contraceptives containing ethinyl estradiol and norgestimate there were no clinically significant changes in fasting blood glucose levels. There were no clinically significant changes in glucose levels over 24 cycles of use. Moreover, glucose tolerance tests showed no clinically significant changes from baseline to cycles 3, 12 and 24. In a 6-cycle clinical trial with ORTHO EVRA® there were no clinically significant changes in fasting blood glucose from baseline to end of treatment.

A small proportion of women will have persistent hypertriglyceridemia while taking hormonal contraceptives. As discussed earlier (see WARNINGS 1a and 1d), changes in serum triglycerides and lipoprotein levels have been reported in hormonal contraceptive users.

**9. Elevated Blood Pressure**

Women with significant hypertension should not be started on hormonal contraception.[103] Women with a history of hypertension or hypertension-related diseases, or renal disease[70] should be encouraged to use another method of contraception. If these women elect to use ORTHO EVRA®, they should be monitored closely and if a clinically significant persistent elevation of blood pressure (BP) occurs (≥ 160 mm Hg systolic or ≥ 100 mm Hg diastolic) and cannot be adequately controlled, ORTHO EVRA® should be discontinued. In general, women who develop hypertension during hormonal contraceptive therapy should be switched to a non-hormonal contraceptive. If other contraceptive methods are not suitable, hormonal contraceptive therapy may continue combined with antihypertensive therapy. Regular monitoring of BP throughout hormonal contraceptive therapy is recommended.[112] For most women, elevated blood pressure will return to normal after stopping hormonal contraceptives, and there is no difference in the occurrence of hypertension between former and never users.[68-71]

An increase in blood pressure has been reported in women taking hormonal contraceptives[68] and this increase is more likely in older hormonal contraceptive users[69] and with extended duration of use.[61] Data from the Royal College of General Practitioners[12] and subsequent randomized trials have shown that the incidence of hypertension increases with increasing progestational activity.

**10. Headache**

The onset or exacerbation of migraine headache or the development of headache with a new pattern that is recurrent, persistent or severe requires discontinuation of ORTHO EVRA® and evaluation of the cause.

**11. Bleeding Irregularities**

Breakthrough bleeding and spotting are sometimes encountered in women using ORTHO EVRA®. Non-hormonal causes should be considered and adequate diagnostic measures taken to rule out malignancy, other pathology, or pregnancy in the event of breakthrough bleeding, as in the case of any abnormal vaginal bleeding. If pathology has been excluded, time or a change to another contraceptive product may resolve the bleeding. In the event of amenorrhea, pregnancy should be ruled out before initiating use of ORTHO EVRA®.

Some women may encounter amenorrhea or oligomenorrhea after discontinuation of hormonal contraceptive use, especially when such a condition was pre-existent.

Bleeding Patterns

In the clinical trials most women started their withdrawal bleeding on the fourth day of the drug-free interval, and the median duration of withdrawal bleeding was 5 to 6 days. On average 26% of women per cycle had 7 or more total days of bleeding and/or spotting (this includes both withdrawal flow and breakthrough bleeding and/or spotting).

**12. Ectopic Pregnancy**

Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

**PRECAUTIONS**

**Women should be counseled that ORTHO EVRA® does not protect against HIV infection (AIDS) and other sexually transmitted infections.**

**1. Body Weight ≥ 198 lbs. (90 kg)**

Results of clinical trials suggest that ORTHO EVRA® may be less effective in women with body weight ≥ 198 lbs. (90 kg) than in women with lower body weights.

**2. Physical Examination and Follow-Up**

It is good medical practice for women using ORTHO EVRA®, as for all women, to have annual medical evaluation and physical examinations. The physical examination, however, may be deferred until after initiation of hormonal contraceptives if requested by the woman and judged appropriate by the clinician. The physical examination should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology, and relevant laboratory tests. In case of undiagnosed, persistent or recurrent abnormal vaginal bleeding, appropriate measures should be conducted to rule out malignancy or other pathology. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

**3. Lipid Disorders**

Women who are being treated for hyperlipidemias should be followed closely if they elect to use ORTHO EVRA®. Some progestins may elevate LDL levels and may render the control of hyperlipidemias more difficult.

**4. Liver Function**

If jaundice develops in any woman using ORTHO EVRA®, the medication should be discontinued. The hormones in ORTHO EVRA® may be poorly metabolized in patients with impaired liver function.

**5. Fluid Retention**

Steroid hormones like those in ORTHO EVRA® may cause some degree of fluid retention. ORTHO EVRA® should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention.

**6. Emotional Disorders**

Women who become significantly depressed while using combination hormonal contraceptives such as ORTHO EVRA® should stop the medication and use another method of contraception in an attempt to determine whether the symptom is drug related. Women with a history of depression should be carefully observed and ORTHO EVRA® discontinued if significant depression occurs.

**7. Contact Lenses**

Contact lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist.

**8. Drug Interactions**

Changes in Contraceptive Effectiveness Associated With Co-Administration of Other Drugs

If a woman on hormonal contraceptives takes a drug or herbal product that induces enzymes, including CYP3A4, that metabolize contraceptive hormones, counsel her to use additional contraception or a different method of contraception. Drugs or herbal products that induce such enzymes may decrease the plasma concentrations of contraceptive hormones, and may decrease the effectiveness of hormonal contraceptives or increase breakthrough bleeding. Some drugs or herbal products that may decrease the effectiveness of hormonal contraceptives include:

- barbiturates
- bosentan
- carbamazepine
- felbamate
- griseofulvin
- oxcarbazepine
- phenytoin
- rifampin
- St. John's wort
- topiramate

<u>HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors</u>: Significant changes (increase or decrease) in the plasma levels of the estrogen and progestin have been noted in some cases of co-administration of HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors.

<u>Antibiotics</u>: There have been reports of pregnancy while taking hormonal contraceptives and antibiotics, but clinical pharmacokinetic studies have not shown consistent effects of antibiotics on plasma concentrations of synthetic steroids. In a pharmacokinetic drug interaction study, oral administration of tetracycline HCl, 500 mg q.i.d. for 3 days prior to and 7 days during wear of ORTHO EVRA® did not significantly affect the pharmacokinetics of norelgestromin or EE.

Consult the labeling of the concurrently-used drug to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.

Increase in Plasma Hormone Levels Associated With Co-Administered Drugs

Some drugs and grapefruit juice may increase the plasma levels of ethinyl estradiol if co-administered. Examples include:

- acetaminophen
- ascorbic acid
- CYP3A4 inhibitors (including itraconazole, ketoconazole, voriconazole, fluconazole and grapefruit juice)
- HMG-CoA reductase inhibitors (including atorvastatin and rosuvastatin)

Changes in Plasma Levels of Co-Administered Drugs

Data from oral combination hormonal contraceptives indicate that they may also affect the pharmacokinetics of some other drugs if used concomitantly.

Examples of drugs whose plasma levels may be increased (due to CYP inhibition) include:

- cyclosporine
- prednisolone
- theophylline

Examples of drugs whose plasma levels may be decreased (due to induction of glucuronidation) include:

- acetaminophen
- clofibric acid
- lamotrigine (see below)
- morphine
- salicylic acid
- temazepam

Combined hormonal contraceptives have been shown to significantly decrease plasma concentrations of lamotrigine when co-administered likely due to induction of lamotrigine glucuronidation. This may reduce seizure control; therefore, dosage adjustments of lamotrigine may be necessary.

Consult the labeling of concurrently-used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.

**9. Interactions with Laboratory Tests**

Certain endocrine and liver function tests and blood components may be affected by hormonal contraceptives:

a. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.
b. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column or by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG, free T4 concentration is unaltered.
c. Other binding proteins may be elevated in serum.
d. Sex hormone binding globulins are increased and result in elevated levels of total circulating endogenous sex steroids and corticoids; however, free or biologically active levels either decrease or remain unchanged.
e. Triglycerides may be increased and levels of various other lipids and lipoproteins may be affected.
f. Glucose tolerance may be decreased.
g. Serum folate levels may be depressed by hormonal contraceptive therapy. This may be of clinical significance if a woman becomes pregnant shortly after discontinuing ORTHO EVRA®.

**10. Carcinogenesis**

No carcinogenicity studies were conducted with norelgestromin. However, bridging PK studies were conducted using doses of norgestimate (NGM)/EE which were used previously in the 2-year rat carcinogenicity study and 10-year monkey toxicity study to support the approval of ORTHO-CYCLEN® and ORTHO TRI-CYCLEN® under NDAs 19-653 and 19-697, respectively. The PK studies demonstrated that rats and monkeys were exposed to 16 and 8 times the human exposure, respectively, with the proposed ORTHO EVRA® transdermal contraceptive system.

Norelgestromin was tested in in vitro mutagenicity assays (bacterial plate incorporation mutation assay, CHO/HGPRT mutation assay, chromosomal aberration assay using cultured human peripheral lymphocytes) and in one in vivo test (rat micronucleus assay) and found to have no genotoxic potential.

See WARNINGS.

**11. Pregnancy**

Pregnancy Category X. See CONTRAINDICATIONS and WARNINGS.

Norelgestromin was tested for its reproductive toxicity in a rabbit developmental toxicity study by the SC route of administration. Doses of 0, 1, 2, 4 and 6 mg/kg body weight, which gave systemic exposure of approximately 25 to 125 times the human exposure with ORTHO EVRA®, were administered daily on gestation days 7–19. Malformations reported were paw hyperflexion at 4 and 6 mg/kg and paw hyperextension and cleft palate at 6 mg/kg.

**12. Nursing Mothers**

The effects of ORTHO EVRA® in nursing mothers have not been evaluated and are unknown. Small amounts of combination hormonal contraceptive steroids have been identified in the milk of nursing mothers and a few adverse effects on the child have been reported, including jaundice and breast enlargement. In addition, combination hormonal contraceptives given in the postpartum period may interfere with lactation by decreasing the quantity and quality of breast milk. Long-term follow-up of infants whose mothers used combination hormonal contraceptives while breastfeeding has shown no deleterious effects. However, the nursing mother should be advised not to use ORTHO EVRA® but to use other forms of contraception until she has completely weaned her child.

**13. Pediatric Use**

Safety and efficacy of ORTHO EVRA® have been established in women of reproductive age. Safety and efficacy are expected to be the same for post-pubertal adolescents under the age of 16 and for users 16 years and older. Use of this product before menarche is not indicated.

**14. Geriatric Use**

This product has not been studied in women over 65 years of age and is not indicated in this population.

**15. Sexually Transmitted Diseases**

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

**16. Patch Adhesion**

Experience with more than 70,000 ORTHO EVRA® patches worn for contraception for 6-13 cycles showed that 4.7% of patches were replaced because they either fell off (1.8%) or were partly detached (2.9%). Similarly, in a small study of patch wear under conditions of physical exertion and variable temperature and humidity, less than 2% of patches were replaced for complete or partial detachment.

If the ORTHO EVRA® patch becomes partially or completely detached and remains detached, insufficient drug delivery occurs. A patch should not be re-applied if it is no longer sticky, if it has become stuck to itself or another surface, if it has other material stuck to it, or if it has become loose or fallen off before. If a patch cannot be re-applied, a new patch should be applied immediately. Supplemental adhesives or wraps should not be used to hold the ORTHO EVRA® patch in place.

If a patch is partially or completely detached for more than one day (24 hours or more) OR if the woman is not sure how long the patch has been detached, she may not be protected from pregnancy. She should stop the current contraceptive cycle and start a new cycle immediately by applying a new patch. Back-up contraception, such as a condom, spermicide, or diaphragm, must be used for the first week of the new cycle.

**INFORMATION FOR THE PATIENT**

See Patient Labeling printed below.

**ADVERSE REACTIONS**

The following serious adverse reactions with the use of combination hormonal contraceptives, including ORTHO EVRA®, are discussed elsewhere in the labeling:

- Serious cardiovascular events and smoking (see WARNINGS)
- Vascular events, including venous and arterial thromboembolic events (see WARNINGS)
- Liver disease (see WARNINGS and PRECAUTIONS)

Adverse reactions commonly reported by users of combination hormonal contraceptives are:

- Irregular uterine bleeding
- Nausea
- Breast tenderness
- Headache

**Clinical Trials Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to ORTHO EVRA® in 3330 sexually active women (3322 of whom had safety data) who participated in three Phase 3 clinical trials designed to evaluate contraceptive efficacy and safety. These subjects received six or 13 cycles of contraception (ORTHO EVRA® or an oral contraceptive comparator in 2 of the trials). The women ranged in age from 18 to 45 years and were predominantly white (91%).

The most common adverse reactions reported during clinical trials were breast symptoms, headache, application site disorder, nausea, dysmenorrhea and abdominal pain. The most common events leading to discontinuation were application site reaction, breast symptoms (including breast discomfort, engorgement and pain), nausea and/or vomiting, headache and emotional lability.

Adverse drug reactions reported by ≥ 2.5% of ORTHO EVRA®-treated subjects in these trials are shown in Table 7.

**Table 7. Adverse Drug Reactions Reported by ≥ 2.5% of ORTHO EVRA®-treated Subjects in Three Phase 3 Clinical Trials**

| System/Organ Class* Adverse reaction | ORTHO EVRA® (n=3322) |
|---|---|
| **Reproductive system and breast disorders** | |
| Breast symptoms† | 22.4% |
| Dysmenorrhea | 7.8% |
| Vaginal bleeding and menstrual disorders† | 6.4% |
| **Gastrointestinal disorders** | |
| Nausea | 16.6% |
| Abdominal pain† | 8.1% |
| Vomiting | 5.1% |
| Diarrhea | 4.2% |
| **Nervous system disorders** | |
| Headache | 21.0% |
| Dizziness | 3.3% |
| Migraine | 2.7% |
| **General disorders and administration site conditions** | |
| Application site disorder† | 17.1% |
| Fatigue | 2.6% |
| **Psychiatric disorders** | |
| Mood, affect and anxiety disorders† | 6.3% |
| **Skin and subcutaneous tissue disorders** | |
| Acne | 2.9% |
| Pruritus | 2.5% |
| **Infections and infestations** | |
| Vaginal yeast infection† | 3.9% |
| **Investigations** | |
| Weight increased | 2.7% |

* MedDRA version 10.0

† Represents a bundle of similar terms

Additional adverse drug reactions that occurred in < 2.5% of ORTHO EVRA®-treated subjects in the above clinical trials datasets are:

- **Gastrointestinal disorders:** Abdominal distension
- **General disorders and administration site conditions:** Fluid retention[1], malaise
- **Hepatobiliary disorders:** Cholecystitis
- **Investigations:** Blood pressure increased, lipid disorders[1]
- **Musculoskeletal and connective tissue disorders:** Muscle spasms
- **Psychiatric disorders:** Insomnia, libido decreased, libido increased
- **Reproductive system and breast disorders:** Galactorrhea, genital discharge, premenstrual syndrome, uterine spasm, vaginal discharge, vulvovaginal dryness
- **Respiratory, thoracic and mediastinal disorders:** Pulmonary embolism
- **Skin and subcutaneous tissue disorders:** Chloasma, dermatitis contact, erythema, skin irritation

[1] Represents a bundle of similar terms

**Postmarketing Experience**

The following adverse reactions (Table 8) have been identified during postapproval use of ORTHO EVRA®. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

**Table 8. Alphabetical List of Adverse Drug Reactions Identified During Postmarketing Experience with ORTHO EVRA®/EVRA® by System Organ Class***

| System/Organ Class | Adverse Drug Reactions |
|---|---|
| **Cardiac disorders** | Myocardial infarction† |
| **Endocrine disorders** | Hyperglycemia, insulin resistance |
| **Eye disorders** | Contact lens intolerance or complication |
| **Gastrointestinal disorders** | Colitis |
| **General disorders and administration site conditions** | Application site reaction†, edema† |
| **Hepatobiliary disorders** | Blood cholesterol abnormal, cholelithiasis, cholestasis, hepatic lesion, jaundice cholestatic, low density lipoprotein increased |
| **Immune system disorders** | Allergic reaction†, urticaria |
| **Investigations** | Blood glucose abnormal, blood glucose decreased |
| **Metabolism and nutrition disorders** | Increased appetite |
| **Neoplasms benign, malignant and unspecified (Incl cysts and polyps)** | Breast cancer†, cervix carcinoma, hepatic adenoma, hepatic neoplasm |
| **Nervous system disorders** | Dysgeusia, migraine with aura |
| **Psychiatric disorders** | Anger, emotional disorder, frustration, irritability |
| **Reproductive system and breast disorders** | Breast mass, cervical dysplasia, fibroadenoma of breast, menstrual disorder†, suppressed lactation, uterine leiomyoma |
| **Skin and subcutaneous tissues disorders** | Alopecia, eczema, erythema multiforme, erythema nodosum, photosensitivity reaction, pruritus generalized, rash†, seborrheic dermatitis, skin reaction |
| **Vascular disorders** | Arterial thrombosis†, cerebrovascular accident†, deep vein thrombosis†, hemorrhage intracranial†, hypertension, hypertensive crisis, pulmonary embolism†, thrombosis† |

* MedDRA version 10.0
† Represents a bundle of similar terms

**OVERDOSAGE**

Serious ill effects have not been reported following accidental ingestion of large doses of hormonal contraceptives. Overdosage may cause nausea and vomiting, and withdrawal bleeding may occur in females. Given the nature and design of the ORTHO EVRA® patch, it is unlikely that overdosage will occur. Serious ill effects have not been reported following acute ingestion of large doses of oral contraceptives by young children. In case of suspected overdose, all ORTHO EVRA® patches should be removed and symptomatic treatment given.

**DOSAGE AND ADMINISTRATION**

To achieve maximum contraceptive effectiveness, ORTHO EVRA® must be used exactly as directed.

Complete instructions to facilitate patient counseling on proper system usage may be found in the Detailed Patient Labeling.

**Transdermal Contraceptive System Overview**

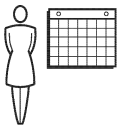
ORTHO EVRA® is a combination transdermal contraceptive that contains 6.00 mg norelgestromin (NGMN) and 0.75 mg ethinyl estradiol (EE). Systemic exposures (as measured by AUC and $C_{ss}$) of NGMN and EE during use of ORTHO EVRA® are higher and peak concentrations ($C_{max}$) are lower than those produced by an oral contraceptive containing norgestimate 250 mcg / EE 35 mcg. (See BOLDED WARNING; CLINICAL PHARMACOLOGY, Transdermal versus Oral Contraceptives).

This system uses a 28-day (four-week) cycle. A new patch is applied each week for three weeks (21 total days). Week Four is patch-free. Withdrawal bleeding is expected during this time.

Every new patch should be applied on the same day of the week. This day is known as the "Patch Change Day." For example, if the first patch is applied on a Monday, all subsequent patches should be applied on a Monday. Only one patch should be worn at a time.

The ORTHO EVRA® patch should not be cut, damaged or altered in any way. If the ORTHO EVRA® patch is cut, damaged or altered in size, contraceptive efficacy may be impaired.

On the day after Week Four ends a new four-week cycle is started by applying a new patch. Under no circumstances should there be more than a seven-day patch-free interval between dosing cycles.



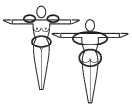
If the woman is starting ORTHO EVRA® for the **first time,** she should **wait until the day she begins her menstrual period.** Either a First Day start or Sunday start may be chosen (see below). The day she applies her first patch will be Day 1. Her "Patch Change Day" will be on this day every week.

- for **First Day Start:** the patient should apply her first patch during the first 24 hours of her menstrual period.

If therapy starts after Day 1 of the menstrual cycle, a non-hormonal back-up contraceptive (such as a condom, spermicide, or diaphragm) should be used concurrently for the first 7 consecutive days of the first treatment cycle.

- for **Sunday Start:** the woman should apply her first patch on the first Sunday after her menstrual period starts. She must use back-up contraception for the first week of her first cycle.

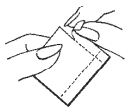
If the menstrual period begins on a Sunday, the first patch should be applied on that day, and no back-up contraception is needed.



**Where to apply the patch.** The patch should be applied to clean, dry, intact healthy skin on the buttock, abdomen, upper outer arm or upper torso, in a place where it won't be rubbed by tight clothing. ORTHO EVRA® should not be placed on skin that is red, irritated or cut, nor should it be placed on the breasts.

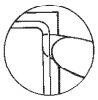
To prevent interference with the adhesive properties of ORTHO EVRA®, no make-up, creams, lotions, powders or other topical products should be applied to the skin area where the ORTHO EVRA® patch is or will be placed.

**Application of the ORTHO EVRA® patch**

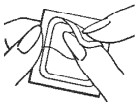


The foil pouch is opened by tearing it along the edge using the fingers.

The foil pouch should be peeled apart and opened flat.



A corner of the patch is grasped firmly and it is gently removed from the foil pouch.



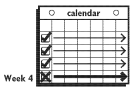
The woman should be instructed to use her fingernail to lift one corner of the patch and peel the patch **and** the plastic liner off the foil liner. **Sometimes patches can stick to the inside of the pouch – the woman should be careful not to accidentally remove the clear liner as she removes the patch.**

Half of the clear protective liner is to be peeled away. (The woman should avoid touching the sticky surface of the patch).

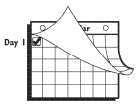
The sticky surface of the patch is applied to the skin and the other half of the liner is removed. The woman should press down firmly on the patch with the palm of her hand for 10 seconds, making sure that the edges stick well. She should check her patch every day to make sure it is sticking.

The patch is worn for seven days (one week). On the "Patch Change Day", Day 8, the used patch is removed and a new one is applied immediately. The used patch still contains some active hormones. Used patches should not be flushed down the toilet. For disposal directions, see HOW SUPPLIED: Special Precautions for Storage and Disposal.

A new patch is applied for Week Two (on Day 8) and again for Week Three (on Day 15), on the usual "Patch Change Day". Patch changes may occur at any time on the Change Day. Each new ORTHO EVRA® patch should be applied to a new spot on the skin to help avoid irritation, although they may be kept within the same anatomic area.




**Week Four is patch-free (Day 22 through Day 28),** thus completing the four-week contraceptive cycle. Bleeding is expected to begin during this time.




**The next four-week cycle is started** by applying a new patch on the usual "Patch Change Day," the day after Day 28, no matter when the menstrual period begins or ends.

Under no circumstances should there be more than a seven-day patch-free interval between patch cycles.

If the ORTHO EVRA® patch becomes partially or completely detached and remains detached, insufficient drug delivery occurs.

***If a patch is partially or completely detached:***

- **for less than one day** (up to 24 hours), the woman should try to reapply it to the same place or replace it with a new patch immediately. No back-up contraception is needed. The woman's "Patch Change Day" will remain the same.
- **for more than one day** (24 hours or more) **OR if the woman is not sure how long the patch has been detached,** SHE MAY NOT BE PROTECTED FROM PREGNANCY. She should stop the current contraceptive cycle and start a new cycle immediately by applying a new patch. There is now a new "Day 1" and a new "Patch Change Day." Back-up contraception, such as a condom, spermicide, or diaphragm, must be used for the first week of the new cycle.

A patch should not be re-applied if it is no longer sticky, if it has become stuck to itself or another surface, if it has other material stuck to it or if it has previously become loose or fallen off. If a patch cannot be re-applied, a new patch should be applied immediately. Supplemental adhesives or wraps should not be used to hold the ORTHO EVRA® patch in place.

**If the woman forgets to change her patch…**

- **at the start of any patch cycle (Week One/Day 1)**: SHE MAY NOT BE PROTECTED FROM PREGNANCY. She should apply the first patch of her new cycle as soon as she remembers. There is now a new "Patch Change Day" and a new "Day 1." The woman must use back-up contraception, such as a condom, spermicide, or diaphragm, for the first week of the new cycle.
- **in the middle of the patch cycle (Week Two/Day 8 or Week Three/Day 15),**
  - for **one or two days** (up to 48 hours), she should apply a new patch immediately. The next patch should be applied on the usual "Patch Change Day." No back-up contraception is needed.
  - for **more than two days** (48 hours or more), SHE MAY NOT BE PROTECTED FROM PREGNANCY. She should stop the current contraceptive cycle and start a new four-week cycle immediately by putting on a new patch. There is now a new "Patch Change Day" and a new "Day 1." The woman must use back-up contraception for one week.
- **at the end of the patch cycle (Week Four/Day 22),**
  Week Four (Day 22): If the woman forgets to remove her patch, she should take it off as soon as she remembers. The next cycle should be started on the usual "Patch Change Day," which is the day after Day 28. No back-up contraception is needed.

  **Under no circumstances should there be more than a seven-day patch-free interval between cycles.** If there are more than seven patch-free days, THE WOMAN MAY NOT BE PROTECTED FROM PREGNANCY and back-up contraception, such as a condom, spermicide, or diaphragm, must be used for seven days. As with combined oral contraceptives, the risk of ovulation increases with each day beyond the recommended drug-free period. If coital exposure has occurred during such an extended patch-free interval, the possibility of fertilization should be considered.

**Change Day Adjustment**

If the woman wishes to change her Patch Change Day she should complete her current cycle, removing the third ORTHO EVRA® patch on the correct day. During the patch-free week, she may select an earlier Patch Day Change by applying a new ORTHO EVRA® patch on the desired day. In no case should there be more than 7 consecutive patch-free days.

**Switching From an Oral Contraceptive**

Treatment with ORTHO EVRA® should begin on the first day of withdrawal bleeding. If there is no withdrawal bleeding within 5 days of the last active (hormone-containing) tablet, pregnancy must be ruled out. If therapy starts later than the first day of withdrawal bleeding, a non-hormonal contraceptive should be used concurrently for 7 days. If more than 7 days elapse after taking the last active oral contraceptive tablet, the possibility of ovulation and conception should be considered.

**Use After Childbirth**

Women who elect not to breastfeed should start contraceptive therapy with ORTHO EVRA® no sooner than 4 weeks after childbirth. If a woman begins using ORTHO EVRA® postpartum, and has not yet had a period, the possibility of ovulation and conception occurring prior to use of ORTHO EVRA® should be considered, and she should be instructed to use an additional method of contraception, such as a condom, spermicide, or diaphragm, for the first seven days. (See Precautions: Nursing Mothers, and Warnings: Thromboembolic and Other Vascular Problems.)

**Use After Abortion or Miscarriage**[106]

After an abortion or miscarriage that occurs in the first trimester, ORTHO EVRA® may be started immediately. An additional method of contraception is not needed if ORTHO EVRA® is started immediately. If use of ORTHO EVRA® is not started within 5 days following a first trimester abortion, the woman should follow the instructions for a woman starting ORTHO EVRA® for the first time. In the meantime she should be advised to use a non-hormonal contraceptive method. Ovulation may occur within 10 days of an abortion or miscarriage.

ORTHO EVRA® should be started no earlier than 4 weeks after a second trimester abortion or miscarriage. When ORTHO EVRA® is used postpartum or postabortion, the increased risk of thromboembolic disease must be considered. (See CONTRAINDICATIONS and WARNINGS concerning thromboembolic disease. See PRECAUTIONS: Nursing Mothers.)

**Breakthrough Bleeding or Spotting**

In the event of breakthrough bleeding or spotting (bleeding that occurs on the days that ORTHO EVRA® is worn), treatment should be continued. If breakthrough bleeding persists longer than a few cycles, a cause other than ORTHO EVRA® should be considered.

In the event of no withdrawal bleeding (bleeding that should occur during the patch-free week), treatment should be resumed on the next scheduled Change Day. If ORTHO EVRA® has been used correctly, the absence of withdrawal bleeding is not necessarily an indication of pregnancy. Nevertheless, the possibility of pregnancy should be considered, especially if absence of withdrawal bleeding occurs in 2 consecutive cycles. ORTHO EVRA® should be discontinued if pregnancy is confirmed.

**In Case of Vomiting or Diarrhea**

Given the nature of transdermal application, dose delivery should be unaffected by vomiting.

**In Case of Skin Irritation**

If patch use results in uncomfortable irritation, the patch may be removed and a new patch may be applied to a different location until the next Change Day. Only one patch should be worn at a time.

**ADDITIONAL INSTRUCTIONS FOR DOSING**

Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing hormonal contraceptives. In case of breakthrough bleeding, as in all cases of irregular bleeding from the vagina, nonfunctional causes should considered. In case of undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If pathology has been excluded, time or a change to another method of contraception may solve the problem.

**Use of Hormonal Contraceptives in the Event of a Missed Menstrual Period**

1. If the woman has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period. Hormonal contraceptive use should be discontinued if pregnancy is confirmed.
2. If the woman has adhered to the prescribed regimen and misses one period, she should continue using her contraceptive patches.
3. If the woman has adhered to the prescribed regimen and misses two consecutive periods, pregnancy should be ruled out. ORTHO EVRA® use should be discontinued if pregnancy is confirmed.

**HOW SUPPLIED**

Each beige ORTHO EVRA® patch contains 6.00 mg norelgestromin and 0.75 mg EE.

Each patch surface is heat stamped with ORTHO EVRA®. Each patch is packaged in a protective pouch.

ORTHO EVRA® is available in folding cartons of 1 cycle each (NDC 0062-1920-15 or NDC 50458-192-15); each cycle contains 3 patches.

ORTHO EVRA® is available for clinic usage in folding cartons of 1 cycle each (NDC 0062-1920-24 or NDC 50458-192-24); each cycle contains 3 patches.

ORTHO EVRA® is also available in folding cartons containing a single patch (NDC 0062-1920-01 or NDC 50458-192-01), intended for use as a replacement in the event that a patch is inadvertently lost or destroyed.

**Special Precautions for Storage and Disposal**

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

Store patches in their protective pouches. Apply immediately upon removal from the protective pouch.

Do not store in the refrigerator or freezer.

Used patches still contain some active hormones. The sticky sides of the patch should be folded together and the folded patch placed in a sturdy container, preferably with a child-resistant cap, and the container thrown in the trash. Used patches should not be flushed down the toilet.

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## DETAILED PATIENT LABELING

**ORTHO EVRA® (norelgestromin/ethinyl estradiol transdermal system)**

**This product is intended to prevent pregnancy. It does not protect against HIV (AIDS) or other sexually transmitted diseases.**

### DESCRIPTION

The contraceptive patch ORTHO EVRA® is a thin, beige, plastic patch that sticks to the skin. The sticky part of the patch contains the following hormones: norelgestromin (progestin) and ethinyl estradiol (estrogen). These hormones are absorbed continuously through the skin and into the bloodstream. On average, the amount of estrogen delivered through the skin produces estrogen exposure that is higher than the exposure when taking a birth control pill containing 35 micrograms of estrogen. Each patch is sealed in a pouch that protects it until you are ready to wear it.

### INTRODUCTION

Any woman who considers using the contraceptive patch ORTHO EVRA® should understand the benefits and risks of using this form of birth control. This leaflet will give you much of the information you will need to make this decision and will also help you determine if you are at risk of developing any serious side effects. It will tell you how to use the contraceptive patch properly so that it will be as effective as possible. However, this leaflet is not a replacement for a careful discussion between you and your healthcare professional. You should discuss the information provided in this leaflet with him or her, both when you first start using the contraceptive patch ORTHO EVRA® and during your revisits. You should also follow your healthcare professional's advice with regard to regular check-ups while you are using the contraceptive patch.

### EFFECTIVENESS OF HORMONAL CONTRACEPTIVE METHODS

Hormonal contraceptives, including ORTHO EVRA®, are used to prevent pregnancy and are more effective than most other non-surgical methods of birth control. When ORTHO EVRA® is used correctly, the chance of becoming pregnant is approximately 1% (1 pregnancy per 100 women per year of use when used correctly), which is comparable to that of the pill. The chance of becoming pregnant increases with incorrect use.

Clinical trials suggested that ORTHO EVRA® may be less effective in women weighing more than 198 lbs. (90 kg). If you weigh more than 198 lbs. (90 kg) you should talk to your healthcare professional about which method of birth control may be best for you.

Typical failure rates for other methods of birth control during the first year of use are as follows:

Implant: <1%
Injection: <1%
IUD: <1-2%
Diaphragm with spermicides: 20%
Spermicides alone: 26%
Female sterilization: <1%
Male sterilization: <1%
Cervical Cap with spermicide: 20 to 40%
Condom alone (male): 14%
Condom alone (female): 21%
Periodic abstinence: 25%
No birth control method: 85%
Withdrawal: 19%

### WHO SHOULD NOT USE ORTHO EVRA®

Hormonal contraceptives include birth control pills, injectables, implants, the vaginal ring, and the contraceptive patch. The following information is derived primarily from studies of birth control pills. The contraceptive patch is expected to be associated with similar risks:

**Do not use ORTHO EVRA® if you smoke cigarettes and are over 35 years old. Smoking increases your risk of serious cardiovascular side effects (heart and blood vessel problems) from hormonal contraceptives, including death from heart attack, blood clots or stroke. This risk increases with age and the number of cigarettes you smoke.**

Some women should not use the ORTHO EVRA® contraceptive patch. For example, you should not use ORTHO EVRA® if you are pregnant or think you may be pregnant. You should also not use ORTHO EVRA® if you have any of the following conditions:

- A history of heart attack or stroke
- Blood clots in the legs (thrombophlebitis), lungs (pulmonary embolism), or eyes
- A history of blood clots in the deep veins of your legs
- An inherited problem that makes your blood clot more than normal
- Chest pain (angina pectoris)
- Known or suspected breast cancer or cancer of the lining of the uterus, cervix or vagina
- Unexplained vaginal bleeding (until your doctor reaches a diagnosis)

- Hepatitis or yellowing of the whites of your eyes or of the skin (jaundice) during pregnancy or during previous use of hormonal contraceptives such as ORTHO EVRA®, NORPLANT®, or the birth control pill
- Liver tumor (benign or cancerous)
- Known or suspected pregnancy
- Severe high blood pressure
- Diabetes with complications of the kidneys, eyes, nerves, or blood vessels
- Headaches with neurological symptoms
- Use of oral contraceptives (birth control pills)
- Disease of heart valves with complications
- Need for a prolonged period of bed rest following major surgery
- An allergic reaction to any of the components of ORTHO EVRA®

Tell your healthcare professional if you have ever had any of these conditions. Your healthcare professional can recommend a non-hormonal method of birth control.

**OTHER CONSIDERATIONS BEFORE USING ORTHO EVRA®**

Hormones from ORTHO EVRA® get into the blood stream and are processed by the body differently than hormones from birth control pills. **You will be exposed to about 60% more estrogen if you use ORTHO EVRA® than if you use a typical birth control pill containing 35 micrograms of estrogen.** In general, increased estrogen may increase the risk of side effects.

The risk of venous thromboembolic events (blood clots in the legs and/or the lungs) may be increased with ORTHO EVRA® use compared with use of birth control pills. Studies examined the risk of these serious blood clots in women who used either ORTHO EVRA® or birth control pills containing one of two progestins (levonorgestrel or norgestimate) and 30-35 micrograms of estrogen. Results of these studies ranged from an approximate doubling of risk of serious blood clots to no increase in risk in women using ORTHO EVRA® compared to women using birth control pills.

You should discuss this possible increased risk with your healthcare professional before using ORTHO EVRA®. Call your healthcare professional immediately if any of the adverse side effects listed under "WARNING SIGNALS" occur while you are using ORTHO EVRA®. (See below.)

Also talk to your healthcare professional about using ORTHO EVRA® if:

- you smoke
- you are recovering from the birth of a baby
- you are recovering from a second trimester miscarriage or abortion
- you are breastfeeding
- you weigh 198 pounds or more
- you are taking any other medications

Also, tell your healthcare professional if you have or have had:

- Breast nodules, fibrocystic disease of the breast, an abnormal breast x-ray or mammogram
- A family history of breast cancer
- Diabetes
- Elevated cholesterol or triglycerides
- High blood pressure
- Migraine or other headaches or epilepsy
- Depression
- Gallbladder disease
- Liver disease
- Heart disease
- Kidney disease
- Scanty or irregular menstrual periods

If you have any of these conditions you should be checked often by your healthcare professional if you use the contraceptive patch.

**RISKS OF USING HORMONAL CONTRACEPTIVES, INCLUDING ORTHO EVRA®**

The following information is derived primarily from studies of birth control pills. Since ORTHO EVRA® contains hormones similar to those found in birth control pills, it is expected to be associated with similar risks:

**1. Risk of Developing Blood Clots**

Blood clots and blockage of blood vessels that can cause death or serious disability are some of the most serious side effects of using hormonal contraceptives, including the ORTHO EVRA® contraceptive patch. In particular, a clot in the legs can cause thrombophlebitis, and a clot that travels to the lungs can cause sudden blocking of the vessel carrying blood to the lungs. Rarely, clots occur in the blood vessels of the eye and may cause blindness, double vision, or impaired vision.

The risk of venous thromboembolic disease (blood clots in the legs and/or the lungs) may be increased with ORTHO EVRA® compared with that of oral contraceptives containing norgestimate and 35 micrograms of estrogen (see the earlier section OTHER CONSIDERATIONS BEFORE USING ORTHO EVRA®). You should discuss this possible increased risk with your healthcare professional before using ORTHO EVRA®. Call your healthcare professional immediately should any of the adverse effects listed under "WARNING SIGNALS" occur while you are using ORTHO EVRA®. (See below.)

If you use ORTHO EVRA® and need elective surgery, need to stay in bed for a prolonged illness or injury or have recently delivered a baby, you may be at risk of developing blood clots. You should consult your doctor about stopping ORTHO EVRA® four weeks before surgery and not using it for two weeks after surgery or during bed rest. You should also not use ORTHO EVRA® soon after delivery of a baby. It is advisable to wait for at least four weeks after delivery if you are not breastfeeding. If you are breastfeeding, you should wait until you have weaned your child before using ORTHO EVRA®. (See also the section on Breastfeeding in General Precautions.)

**2. Heart Attacks and Strokes**

Hormonal contraceptives, including ORTHO EVRA®, may increase the risk of developing strokes (blockage or rupture of blood vessels in the brain) and angina pectoris and heart attacks (blockage of blood vessels in the heart). Any of these conditions can cause death or serious disability.

Smoking and the use of hormonal contraceptives including ORTHO EVRA® greatly increase the chances of developing and dying of heart disease. Smoking also greatly increases the possibility of suffering heart attacks and strokes.

**3. Gallbladder Disease**

Women who use hormonal contraceptives, including ORTHO EVRA®, probably have a greater risk than nonusers of having gallbladder disease.

**4. Liver Tumors**

In rare cases, combination oral contraceptives can cause benign but dangerous liver tumors. Since ORTHO EVRA® contains hormones similar to those in birth control pills, this association may also exist with ORTHO EVRA®. These benign liver tumors can rupture and cause fatal internal bleeding. In addition, some studies report an increased risk of developing liver cancer. However, liver cancers are rare.

**5. Cancer of the Reproductive Organs and Breasts**

Various studies give conflicting reports on the relationship between breast cancer and hormonal contraceptive use. Combination hormonal contraceptives, including ORTHO EVRA®, may slightly increase your chance of having breast cancer diagnosed, particularly after using hormonal contraceptives at a younger age. After you stop using hormonal contraceptives, the chances of having breast cancer diagnosed begin to go back down. You should have regular breast examinations by a healthcare professional and examine your own breasts monthly. Tell your healthcare professional if you have a family history of breast cancer or if you have had breast nodules or an abnormal mammogram.

Women who currently have or have had breast cancer should not use oral contraceptives because breast cancer is usually a hormone-sensitive tumor.

Some studies have found an increase in the incidence of cancer of the cervix in women who use oral contraceptives, although this finding may be related to factors other than the use of oral contraceptives. However, there is insufficient evidence to rule out the possibility that oral contraceptives may cause such cancers.

**ESTIMATED RISK OF DEATH FROM A BIRTH CONTROL METHOD OR PREGNANCY**

All methods of birth control and pregnancy are associated with a risk of developing certain diseases that may lead to disability or death. An estimate of the number of deaths associated with different methods of birth control and pregnancy has been calculated and is shown in the following table.

ORTHO EVRA® is expected to be associated with similar risks as oral contraceptives:

**Annual Number of Birth-Related or Method-Related Deaths Associated With Control of Fertility Per 100,000 Nonsterile Women by Fertility Control Method According to Age**

| Method of control and outcome | 15-19 | 20-24 | 25-29 | 30-34 | 35-39 | 40-44 |
|---|---|---|---|---|---|---|
| No fertility control methods* | 7.0 | 7.4 | 9.1 | 14.8 | 25.7 | 28.2 |
| Oral contraceptives non-smoker† | 0.3 | 0.5 | 0.9 | 1.9 | 13.8 | 31.6 |
| Oral contraceptives smoker† | 2.2 | 3.4 | 6.6 | 13.5 | 51.1 | 117.2 |
| IUD† | 0.8 | 0.8 | 1.0 | 1.0 | 1.4 | 1.4 |
| Condom* | 1.1 | 1.6 | 0.7 | 0.2 | 0.3 | 0.4 |
| Diaphragm / spermicide* | 1.9 | 1.2 | 1.2 | 1.3 | 2.2 | 2.8 |
| Periodic abstinence* | 2.5 | 1.6 | 1.6 | 1.7 | 2.9 | 3.6 |

Adapted from H.W. Ory, ref. #35.

* Deaths are birth-related

† Deaths are method-related

In the above table, the risk of death from any birth control method is less than the risk of childbirth, except for oral contraceptive users over the age of 35 who smoke and pill users over the age of 40 even if they do not smoke. It can be seen in the table that for women aged 15 to 39, the risk of death was highest with pregnancy (7-26 deaths per 100,000 women, depending on age). Among pill users who do not smoke, the risk of death is always lower than that associated with pregnancy for any age group, although over the age of 40, the risk increases to 32 deaths per 100,000 women, compared to 28 associated with pregnancy at that age. However, for pill users who smoke and are over the age of 35, the estimated number of deaths exceeds those for other methods of birth control. If a woman is over the age of 40 and smokes, her estimated risk of death is four times higher (117/100,000 women) than the estimated risk associated with pregnancy (28/100,000 women) in that age group.

In 1989 an Advisory Committee of the FDA concluded that the benefits of low-dose hormonal contraceptive use by healthy, non-smoking women over 40 years of age may outweigh the possible risks.

**WARNING SIGNALS**

If any of these adverse effects occur while you are using ORTHO EVRA®, call your doctor immediately:

- Sharp chest pain, coughing of blood, or sudden shortness of breath (indicating a possible clot in the lung)
- Pain in the calf (indicating a possible clot in the leg)
- Crushing chest pain or tightness in the chest (indicating a possible heart attack)
- Sudden severe headache or vomiting, dizziness or fainting, disturbances of vision or speech, weakness, or numbness in an arm or leg (indicating a possible stroke)
- Sudden partial or complete loss of vision (indicating a possible clot in the eye)
- Breast lumps (indicating possible breast cancer or fibrocystic disease of the breast; ask your doctor or healthcare professional to show you how to examine your breasts)
- Severe pain or tenderness in the stomach area (indicating a possibly ruptured liver tumor)
- Severe problems with sleeping, weakness, lack of energy, fatigue, or change in mood (possibly indicating severe depression)
- Jaundice or a yellowing of the skin or eyeballs accompanied frequently by fever, fatigue, loss of appetite, dark colored urine, or light colored bowel movements (indicating possible liver problems)

**SIDE EFFECTS OF ORTHO EVRA®**

**1. Most Common Side Effects**

The most common side effects of ORTHO EVRA® include nausea, breast symptoms (discomfort, engorgement, or pain), headache, and problems where the patch has been on the skin.

**2. Skin Irritation**

Skin irritation, redness, pain, swelling, itching or rash may occur at the site of application. If this occurs, the patch may be removed and a new patch may be applied to a new location until the next Change Day. Single replacement patches are available from pharmacies.

**3. Vaginal Bleeding**

Irregular vaginal bleeding or spotting may occur while you are using ORTHO EVRA®. Irregular bleeding may vary from slight staining between menstrual periods to breakthrough bleeding which is a flow much like a regular period. Irregular bleeding may occur during the first few months of contraceptive patch use but may also occur after you have been using the contraceptive patch for some time. Such bleeding may be temporary and usually does not

indicate any serious problems. It is important to continue using your contraceptive patches on schedule. If the bleeding occurs in more than a few cycles or lasts for more than a few days, talk to your healthcare professional.

**4. Problems Wearing Contact Lenses**

If you wear contact lenses and notice a change in vision or an inability to wear your lenses, contact your healthcare professional.

**5. Fluid Retention or Raised Blood Pressure**

Edema (fluid retention) with swelling of the fingers or ankles and/or a rise in blood pressure may occur with the use of hormonal contraceptives. If you experience fluid retention, contact your healthcare professional.

**6. Melasma**

A spotty darkening of the skin is possible, particularly of the face. This may persist after use of hormonal contraceptives is discontinued.

**7. Other Side Effects**

Other side effects include weight gain, increased appetite, feeling dizzy, migraine, stomach pain or bloating, vomiting, diarrhea, abnormal taste, acne, muscle spasms, vaginal infections, feeling tired or unwell, painful or heavy periods or periods more frequent than normal, uterine cramps, vaginal discharge and mood problems such as depression, mood swings or anxiety.

**GENERAL PRECAUTIONS**

**1. Weight ≥ 198 lbs. (90 kg)**

Clinical trials suggest that ORTHO EVRA® may be less effective in women weighing 198 lbs. (90 kg) or more compared with its effectiveness in women with lower body weights. If you weigh 198 lbs. (90 kg) or more you should talk to your healthcare professional about which method of birth control may be best for you.

**2. Missed Periods and Use of ORTHO EVRA® Before or During Early Pregnancy**

There may be times when you may not menstruate regularly during your patch-free week. If you have used ORTHO EVRA® correctly and miss one menstrual period, continue using your contraceptive patches for the next cycle but be sure to inform your healthcare professional before doing so. If you have not used ORTHO EVRA® as instructed and missed a menstrual period, or if you missed two menstrual periods in a row, you could be pregnant. Check with your healthcare professional immediately to determine whether you are pregnant. Stop using ORTHO EVRA® if you are pregnant.

There is no conclusive evidence that hormonal contraceptive use causes birth defects when taken accidentally during early pregnancy. Previously, a few studies had reported that oral contraceptives might be associated with birth defects, but these findings have not been seen in more recent studies. Nevertheless, hormonal contraceptives, including ORTHO EVRA®, should not be used during pregnancy. You should check with your healthcare professional about risks to your unborn child from any medication taken during pregnancy.

**3. While Breastfeeding**

If you are breastfeeding, consult your healthcare professional before starting ORTHO EVRA®. Hormonal contraceptives are passed on to the child in the milk. A few adverse effects on the child have been reported, including yellowing of the skin (jaundice) and breast enlargement. In addition, combination hormonal contraceptives may decrease the amount and quality of your milk. If possible, do not use combination hormonal contraceptives such as ORTHO EVRA® while breastfeeding. You should use a barrier method of contraception since breastfeeding provides only partial protection from becoming pregnant and this partial protection decreases significantly as you breastfeed for longer periods of time. You should consider starting ORTHO EVRA® only after you have weaned your child completely.

**4. Laboratory Tests**

If you are scheduled for any laboratory tests, tell your doctor you are using ORTHO EVRA® since certain blood tests may be affected by hormonal contraceptives.

**5. Drug Interactions**

Hormonal contraceptives may interact with lamotrigine, an anticonvulsant used for epilepsy. This may increase the risk of seizures so your physician may need to adjust the dose.

Some medicines and herbal products may make your hormonal contraceptive less effective, including:

- barbiturates
- bosentan
- carbamazepine
- felbamate
- griseofulvin
- oxcarbazepine
- phenytoin
- rifampin
- St. John's wort
- topiramate

Blood levels of estrogen from this hormonal contraceptive may be increased if you take certain medicines or drink grapefruit juice. Also, your hormonal contraceptive may make some other medicines less effective. As with all prescription products, you should notify your healthcare professional of any other medications and herbal products you are taking or plan to take. You may need to use a barrier contraceptive when you take medicines or products that can make hormonal contraceptives less effective.

**6. Sexually Transmitted Diseases**

**ORTHO EVRA® is intended to prevent pregnancy. It does not protect against HIV (AIDS) or other sexually transmitted diseases such as chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B, and syphilis.**

## HOW TO USE ORTHO EVRA®

Instructions for Use

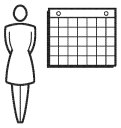
ORTHO EVRA® keeps you from becoming pregnant by transferring hormones to your body through your skin. The patch must stick securely to your skin in order for it to work properly.

This method uses a 28 day (four week) cycle. You should apply a new patch each week for three weeks (21 total days). You should not apply a patch during the fourth week. Your menstrual period should start during this patch-free week.

Every new patch should be applied on the same day of the week. This day will be your 'Patch Change Day.' *For example, if you apply your first patch on a Monday, all of your patches should be applied on a Monday*. You should wear only one patch at a time.

On the day after week four ends, you should begin a new four week cycle by applying a new patch.

**Save these instructions.**



**1**

If this is the **first time** you are using ORTHO EVRA®, **wait until the day you get your menstrual period.** *The day you apply your first patch will be Day 1. Your 'Patch Change Day' will be on this day every week.*

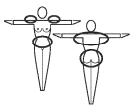
**2**

**You may choose a first day start or Sunday start**

- *for **First Day** start*: apply your first patch during the first 24 hours of your menstrual period

**OR**

- *for **Sunday** start*: apply your first patch on the first Sunday after your menstrual period starts. *You must use back-up contraception, such as a condom, spermicide, or diaphragm for the first week of your first cycle.*
- *The day you apply your first patch will be Day 1. Your 'Patch Change Day' will be on this day every week.*



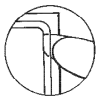
**3**

**Choose a place on your body to put the patch.** Put the patch on your buttock, abdomen, upper outer arm or upper torso, in a place where it won't be rubbed by tight clothing. *Never put the patch on your breasts. To avoid irritation, apply each new patch to a different place on your skin.*

**4**

Open the foil pouch by tearing it along the top edge **and** one side edge.

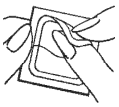
Peel the foil pouch apart and open it flat.



**5**

You will see that the patch is covered by a layer of clear plastic. It is important to remove the patch **and** the plastic together from the foil pouch.

Using your fingernail, lift one corner of the patch and peel the patch and the plastic off the foil liner.



*Sometimes patches can stick to the inside of the pouch – be careful not to accidentally remove the clear liner as you remove the patch.*

**6**

Peel away half of the clear plastic and be careful not to touch the exposed sticky surface of the patch with your fingers.

**7**

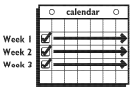
Apply the sticky side of the patch to the skin you've cleaned and dried, then remove the other half of the clear plastic.

Press firmly on the patch with the palm of your hand for 10 seconds, making sure the edges stick well. Run your finger around the edge of the patch to make sure it is sticking properly.

Check your patch every day to make sure all the edges are sticking.

**8**

**Wear the patch for seven days** (one week). On your 'Patch Change Day,' Day 8, remove the used patch. Apply a new patch immediately. *The used patch still contains some active hormones. Used patches should not be flushed down the toilet.* For disposal directions, see Special Precautions for Storage and Disposal below.

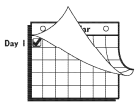



**9**

Apply a new patch for week two (on Day 8) and for week three (on Day 15), on your 'Patch Change Day.' *To avoid irritation, do not apply the new patch to the same exact place on your skin.*

**10**

Do not wear a patch on week four (Day 22 through Day 28). *Your period should start during this week.*




**11**

Begin your next four week cycle by applying a new patch on your normal 'Patch Change Day,' the day after Day 28 – *no matter when your period begins or ends.*

**If your patch has become loose or has fallen off…**

- **for less than one day**, try to re-apply it or apply a new patch immediately. No back-up contraception is needed. *Your 'Patch Change Day' will remain the same.*
- **for more than one day OR if you are not sure for how long,** YOU MAY BECOME PREGNANT – **Start a new four week cycle immediately** by putting on a new patch. *You now have a new Day 1 and a new 'Patch Change Day.' You must use back-up contraception, such as a condom, spermicide, or diaphragm for the first week of your new cycle.*
- do not try to re-apply a patch if it's no longer sticky, if it has become stuck to itself or another surface, if it has other material stuck to it or if it has previously become loose or fallen off. No tapes or wraps should be used to keep the patch in place. If you cannot re-apply a patch, apply a new patch immediately.

**If you forget to change your patch…**

- **at the start of any patch cycle,**
  Week one (Day 1): If you forget to apply your patch, YOU COULD BECOME PREGNANT – *you must use back-up contraception for one week.* Apply the first patch of your new cycle as soon as you remember. *You now have a new 'Patch Change Day' and new Day 1.*
- **in the middle of your patch cycle,**
  Week two or week three: If you forget to change your patch for **one or two days,** apply a new patch as soon as you remember. Apply your next patch on your normal 'Patch Change Day.' No back-up contraception is needed.

  Week two or week three: If you forget to change your patch for **more than two days,** YOU COULD BECOME PREGNANT – **start a new four week cycle as soon as you remember by putting on a new patch.** *You now have a different 'Patch Change Day' and a new Day 1. You must use back-up contraception for the first week of your new cycle.*
- **at the end of your patch cycle,**
  Week four: If you forget to remove your patch, take it off as soon as you remember. Start your next cycle on your normal 'Patch Change Day,' the day after Day 28. No back-up contraception is needed.
- **at the start of your next patch cycle,**
  Day 1 (week one): If you forget to apply your patch, YOU COULD BECOME PREGNANT – apply the first patch of your new cycle as soon as you remember. *You now have a new 'Patch Change Day' and new Day 1. You must use back-up contraception for the first week of your new cycle.*
- ***you should never have the patch off for more than seven days.***

**Other information…**

- Always apply your patch to clean, dry skin. Avoid skin that is red, irritated or cut. Do not use creams, oils, powder or makeup on your skin where you will put a patch or near a patch you are wearing. It may cause the patch to become loose.
- Do not cut, damage or alter the ORTHO EVRA® patch in any way.
- If patch use results in uncomfortable irritation, the patch may be removed and a new patch may be applied to a new location until the next Change Day. Only one patch should be worn at a time.
- Some medicines may change the way ORTHO EVRA® works. If you are taking any medication, you must talk to your healthcare professional BEFORE you use the patch. *You may need to use back-up contraception.*
- Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).
- Single replacement patches are available through your pharmacist.
- For further information log on to **www.orthoevra.com** or call toll free **1-800-526-7736.**

**WHEN YOU SWITCH FROM THE PILL TO ORTHO EVRA®:**

If you are switching from the pill to ORTHO EVRA®, wait until you get your menstrual period. If you do not get your period within five days of taking the last active pill, check with your healthcare professional to be sure that you are not pregnant.

**IMPORTANT POINTS TO REMEMBER**

1. IT IS IMPORTANT TO USE ORTHO EVRA® exactly as directed in this leaflet. Incorrect use increases your chances of becoming pregnant. This includes starting your contraceptive cycle late or missing your scheduled CHANGE DAYS.
2. You should wear one patch per week for three weeks, followed by one week off. **You should never have the patch off for more than seven days in a row.** If you have the patch off for more than seven days in a row and you have had sex during this time, YOU COULD BECOME PREGNANT.
3. **IF YOU ARE NOT SURE WHAT TO DO ABOUT MISTAKES WITH PATCH USE:**
   - Use a BACK-UP METHOD, *such as a condom, spermicide, or diaphragm* anytime you have sex.
   - Contact your healthcare professional for instructions.
4. Do not skip patches even if you do not have sex very often.
5. SOME WOMEN HAVE SPOTTING OR LIGHT BLEEDING, BREAST TENDERNESS OR MAY FEEL SICK TO THEIR STOMACH DURING ORTHO EVRA® USE. If these symptoms occur, do not stop using the contraceptive patch. The problem will usually go away. If it doesn't go away, check with your healthcare professional.
6. MISTAKES IN USING YOUR PATCHES CAN ALSO CAUSE SPOTTING OR LIGHT BLEEDING.
7. If you miss TWO PERIODS IN A ROW contact your healthcare professional because you might be pregnant.
8. The amount of drug you get from the ORTHO EVRA® patch should not be affected by VOMITING OR DIARRHEA.
9. IF YOU TAKE CERTAIN MEDICINES, ORTHO EVRA® may not work as well. Use a non-hormonal back-up method (such as a condom, spermicide, or diaphragm) until you check with your healthcare professional.
10. IF YOU WANT TO MOVE YOUR PATCH CHANGE DAY to a different day of the week, finish your current cycle, removing your third ORTHO EVRA® patch on the correct day. **During week four,** the "patch-free week" (Day 22 through Day 28), you may choose an earlier Patch Change Day by applying a new patch on the day you prefer. You now have a new Day 1 and a new Patch Change Day. **You should never have the patch off for more than seven days in a row.**
11. BE SURE YOU HAVE READY AT ALL TIMES:
    - A NON-HORMONAL BIRTH CONTROL method (such as a condom, spermicide, or diaphragm) to use as a back-up in case of dosing errors.
12. IF YOU HAVE TROUBLE REMEMBERING TO CHANGE YOUR CONTRACEPTIVE PATCH, talk to your healthcare professional about how to make patch-changing easier or about using another method of birth control.
13. Single replacement patches are available through your pharmacist.
14. For Patch replacement, see "How to use ORTHO EVRA®" section.

IF YOU HAVE ANY QUESTIONS OR ARE UNSURE ABOUT THE INFORMATION IN THIS LEAFLET, call your healthcare professional.

**PREGNANCY DUE TO ORTHO EVRA® FAILURE**

The incidence of pregnancy from hormonal contraceptive failure is approximately one percent (i.e., one pregnancy per 100 women per year) if used correctly. The chance of becoming pregnant increases with incorrect use. If contraceptive patch failure does occur, the risk to the fetus is minimal.

**PREGNANCY AFTER STOPPING ORTHO EVRA®**

There may be some delay in becoming pregnant after you stop using ORTHO EVRA®, especially if you had irregular menstrual cycles before you used hormonal contraceptives. It may be best to postpone conception until you begin menstruation regularly once you have stopped using ORTHO EVRA® and want to become pregnant.

There does not appear to be any increase in birth defects in newborn babies when pregnancy occurs soon after stopping hormonal contraceptives.

**OVERDOSAGE**

ORTHO EVRA® is unlikely to cause an overdose because the patch releases a steady amount of the hormones. Do not use more than one patch at a time. Serious ill effects have not been reported when large doses of oral contraceptives were accidentally taken by young children. Overdosage may cause nausea and vomiting. Vaginal bleeding may occur in females. In case of overdosage, contact your healthcare professional or pharmacist.

**OTHER INFORMATION**

Your healthcare professional will take a medical and family history before prescribing ORTHO EVRA® and will examine you. The physical examination may be delayed to another time if you request it and the healthcare professional believes that it is a good medical practice to postpone it. You should be reexamined at least once a year. Be sure to inform your healthcare professional if there is a family history of any of the conditions listed previously in this leaflet. Be sure to keep all appointments with your healthcare professional, because this is a time to determine if there are early signs of side effects of hormonal contraceptive use.

Do not use the drug for any condition other than the one for which it was prescribed. This drug has been prescribed specifically for you; do not give it to others who may want birth control.

If you want more information about ORTHO EVRA®, ask your healthcare professional or pharmacist. They have a more technical leaflet called the Prescribing Information that you may wish to read.

**Special Precautions for Storage and Disposal**

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

Store patches in their protective pouches. Apply to the skin immediately upon removal from the protective pouch.

Do not store in the refrigerator or freezer.

Used patches still contain some active hormones. To help protect the environment and help prevent accidental ingestion by children or pets:

- Fold the sticky sides of the patch together and place it in a sturdy container, preferably with a child-resistant cap or ask your pharmacist for a bottle with a child-resistant cap. Ensure the opening is large enough for a folded patch to go in but small enough that a child's hand cannot enter. If a child-resistant container is unavailable then fold the sticky sides of the patch together and place it in a closable container, such as a sealable bag.
- Throw the container in the trash. Used patches should not be flushed down the toilet.
- Return unused, unneeded, or expired patches to your pharmacist.

ORTHO WOMEN'S HEALTH & UROLOGY™
DIVISION OF ORTHO-MCNEIL-JANSSEN PHARMACEUTICALS, INC.

Mfd. for:
Ortho Women's Health & Urology, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc.
Raritan, New Jersey 08869

Mfd. by:
Janssen Ortho, LLC
Manati, Puerto Rico 00674

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# APPENDIX 2
# EPIDEMIOLOGY STUDY RESULTS BY STUDY INSTALLMENT

Two studies presented results sequentially and this made it possible to examine how the odds ratio varied by calendar time. Both these studies compared ORTHO EVRA to NGM-containing OCs. Odds ratios are shown for VTE and MI + ischemic stroke for the i3 study in Table A1 and for VTE the BCDSP study in Table A2.

**Table A1 Estimates of the Risk of Idiopathic VTE and MI + Ischemic Stroke in Users of ORTHO EVRA Compared With Norgestimate-containing OCs in the i3 Study**

| | OR (95% CI) | |
|---|---|---|
| | VTE | MI + Ischemic Stroke |
| Initial study[a] | 2.42 (1.07 – 5.46) | 0.69 (0.15 – 3.13) |
| StudyExtension[b] | 1.37 (0.51 – 3.67) | 2.02 (0.47 – 8.74) |

[a] Accrual date 4/02 – 12/04
[b] Accrual date 01/05- 12/06

Source: References 89, 90.

**Table A2 Estimates of the Risk of Idiopathic VTE in Users of ORTHO EVRA Compared With Norgestimate-Containing OCs in the BCDSP Study**

| | OR (95% CI), accrual dates |
|---|---|
| Initial study | 0.9 (0.5-1.6), 4/02 – 3/05 |
| First Extension | 1.1 (0.6-2.1), new[a] – 8/06 |
| Second Extension | 2.4 (1.2-5.0), new[a]– 10/07 |

[a] The insurance plans contributing data to the database changed over time. Each update included all cases and controls not included in the previous reports, with an analysis of the new cases and controls, and (cumulative) analysis of all cases and controls ascertained as of that update.

Source Reference 45.

# APPENDIX 3
# TABULATION OF VTE ODDS RATIOS OR RELATIVE RISKS AND ASSOCIATED 95% CONFIDENCE INTERVALS FROM LITERATURE STUDIES

| Comparison | Author, Year | Odds Ratio or Relative Risk (95% CI) |
|---|---|---|
| ORTHO EVRA v LNG or NGM | Jick, 2010a (PharMetrics) | 2.0 (0.9-4.1) |
| | Jick, 2010a (MarketScan) | 1.3 (0.8-2.1) |
| | Dore, 2010 | 2.2 (1.2-4.0) |
| | Jick, 2010b (PharMetrics) | 1.2 (0.9-1.8) |
| ORTHO EVRA v LNG/NGM/NET | FDA, 2011 | 1.55 (1.17-2.07) |
| ORTHO EVRA Meta-Analysis | Johnson & Johnson PRD | 1.5 (1.1-1.9) |
| DSG v LNG or LNG+NGM | Bloemenkamp, 1995 | 2.2 (0.9-5.4) |
| | Jick, 1995 | 2.2 (1.1-4.4) |
| | WHO, 1995 | 2.6 (1.4-4.8) |
| | Spitzer, 1996 | 1.5 (1.1-2.2) |
| | Farmer, 1997 | 1.7 (0.9-3.5) |
| | Bloemenkamp, 1999 | 1.9 (0.8-4.5) |
| | Lewis, 1999 | 1.1 (0.6-2.0) |
| | Todd, 1999 | 1.1 (0.5-2.6) |
| | Farmer, 2000 | 1.0 (0.6-1.6) |
| | Vlieg, 2009 | 2.0 (1.4-2.8) |
| | Lidegaard, 2011 | 2.2 (1.7-3.0) |
| GST v LNG or LNG+NGM | Jick, 1995 | 2.1 (1.0-4.4) |
| | WHO, 1995 | 2.6 (1.4-4.8) |
| | Spitzer, 1996 | 1.5 (1.0-2.2) |
| | Farmer, 1997 | 1.3 (0.7-2.5) |
| | Bloemenkamp, 1999 | 1.9 (0.8-4.5) |
| | Lewis, 1999 | 0.6 (0.3-1.0) |
| | Todd, 1999 | 1.1 (0.5-2.4) |
| | Farmer, 2000 | 1.3 (0.8-2.1) |
| | Vlieg, 2009 | 1.6 (1.0-2.4) |
| | Lidegaard, 2011 | 2.1 (1.6-2.8) |
| DSG + GST v LNG | Hennessy, 2001 | 1.7 (1.3-2.1) |
| NET v LNG | Todd, 1999 | 0.5 (0.2-2.4) |
| | Farmer, 2000 | 0.3 (0.1-1.0) |
| | Lidegaard, 2009 | 1.0 (0.7-1.4) |
| NGM v LNG | Jick, 2006 | 1.1 (0.8-1.6) |
| | Lewis, 1999 | 1.0 (0.5-2.1) |
| | Todd, 1999 | 0.7 (0.2-2.4) |
| | Farmer, 2000 | 1.1 (0.6-2.3) |
| | Lidegaard, 2009 | 1.2 (1.0-1.5) |
| Tri LNG v LNG | Farmer, 2000 | 0.8 (0.3-1.7) |
| DRSP v LNG or Other OCs | Dinger, 2007 | 1.0 (0.6-1.8) |
| | Seeger, 2007 | 0.9 (0.5-1.6) |
| | Lidegaard, 2011 | 2.1 (1.6-2.8) |
| | Vlieg, 2009 | 1.7 (0.7-3.9) |
| | Parkin, 2011 | 3.3 (1.4-7.6) |
| | Jick, 2011 | 2.3 (1.6-3.2) |
| | FDA, 2011 | 1.74 (1.42-2.14) |