Background Document for Joint Meeting of the Advisory Committee for Reproductive Health Drugs and the Drug Safety and Risk Management Advisory Committee

December 9, 2011

NDA 21-180

Ortho Evra

(norelgestromin/ethinyl estradiol transdermal system)

Janssen Pharmaceuticals, Inc.

Indication:

Prevention of Pregnancy

Dosing regimen:

transdermal patch applied once weekly for three weeks

Prepared by

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AMI	Acute myocardial infarction
ATE(s)	Arterial thrombotic event(s)
AUC	Area under the curve
BCDSP	Boston Collaborative Drug Surveillance Program
BMI	Body mass index
CI	Confidence interval
CHC	Combination hormonal contraceptive
CHF	Congestive heart failure
Cmax	Maximum concentration
COC	Combination oral contraceptive
Css	Steady state concentration
% CV	Percent coefficient of variation
DSG	Desogestrel
DVT	Deep vein thrombosis
EE	Ethinyl estradiol
HMO	Health Maintenance Organization
HR	Hazard Ratio
IRR	Incidence rate ratio
IS	Ischemic stroke
LNG	Levonorgestrel
MI	Myocardial infarction
NDI	National Death Index
NGM	Norgestimate
NGMN	Norelgestromin
NHI	Normative Health Information
OR	Odds ratio
PE	Pulmonary embolism
PK	Pharmacokinetics
RDM	Research DataMart
$T_{1/2}$	Elimination half life
UHC	UnitedHealthCare
VTE(s)	Venous thromboembolic event(s)

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the Advisory Committees. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought questions concerning the risk/benefit profile of the Ortho Evra transdermal contraceptive patch to these two Advisory Committees in order to gain the Committees' insights and opinions. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the Advisory Committees. The FDA will not issue a final determination on the issues at hand until input from the Advisory Committee meeting has been considered. The final determination may be affected by issues not discussed at the Advisory Committee meeting.

1. BACKGROUND

1.1 Objective of Meeting

The purpose of this Advisory Committee meeting is to review and discuss the overall risk/benefit profile of the Ortho Evra combination hormonal transdermal patch for the prevention of pregnancy. Like all combination hormonal contraceptives (CHC), Ortho Evra is associated with an increased risk of venous thromboembolic events (VTEs) as compared to nonuse of hormonal contraception. The presentations at the meeting will discuss data suggesting that there is a greater increase in VTE risk with use of Ortho Evra than with use of combination oral contraceptives (COCs) containing 20-35 μg of ethinyl estradiol [EE]). Pharmacokinetic (PK) data demonstrate that the pattern of exposure to the contraceptive hormones is different for Ortho Evra from that seen with COCs, in that Ortho Evra results in higher steady state concentrations and lower peak concentrations. Area under the time-concentration curve (AUC) and average steady state concentrations for EE are about 60% higher for women using Ortho Evra compared to women using a COC containing 35 μg of EE, while peak concentrations (Cmax) for EE are about 25% lower for Ortho Evra. It is unknown whether these changes in PK profiles result in changes in the risk of VTEs or arterial thrombotic events (ATEs).

1.2 Background

Each 20 cm^2 Ortho Evra patch contains the progestin norelgestromin (NGMN) 6 mg and EE 750 μg and a single patch is applied continuously once a week for three consecutive weeks; this dosing is followed by a one week hormone-free interval. Ortho Evra was approved for marketing on November 20, 2001. At the time of approval, the progestin NGMN was a new molecular entity; it is an active metabolite of the progestin norgestimate (NGM), first approved in 1989. Ethinyl estradiol is a widely used and well-characterized estrogen used in the vast majority of COCs. Ortho Evra was the first, and remains the only, transdermal contraceptive product approved for marketing in the US.

The original data in support of the efficacy of Ortho Evra for the prevention of pregnancy was based primarily on three prospective clinical trials that included a total of 3,319 women treated with Ortho Evra who were evaluable for efficacy. This database provided data from over 22,000

28-day cycles of use, and over 600 women completed a full year (13 cycles) of treatment. Efficacy was evaluated by the 12-month Pearl Index, a measure of the pregnancy rate. The Pearl Index is calculated as:

$$\text{Pearl Index} = \frac{\text{(number of "on-treatment" pregnancies) x 13 cycles/year}}{\text{(total number of completed 28-day treatment cycles)}} \times 100$$

In these three studies, there were 16 pregnancies, providing an overall Pearl Index in women aged 35 or younger of 1.07 per 100 women-years of use. The trials included

- a randomized, active-controlled (a triphasic EE/levonorgestrel COC), open-label parallel group study in the US and Canada
- a randomized, active-controlled (a monophasic EE/desogestrel COC), open-label parallel group study in Europe and South Africa
- a single-arm open label study conducted in the US, Europe, Israel, and Australia

The clinical trial results showed reduced efficacy in women weighing 90 kg or more, and this finding is described in labeling for the marketed product.

The safety profile of Ortho Evra in the clinical trials was generally similar to that observed with COCs. Two pulmonary emboli were reported in the trials, both in Ortho Evra users. One woman had no apparent risk factors for VTE, while the other woman used the patch until shortly before she underwent surgery and had an apparent postoperative pulmonary embolus. The calculated point estimate for VTE in the clinical trial safety database was 11.7 per 10,000 women-years of use (95% confidence interval 1.4 – 42.4 VTEs per 10,000 women-years of use), which was believed by the reviewers to be consistent with that observed in COC applications.

1.3 Prevention of Pregnancy

A variety of products are approved for the indication of prevention of pregnancy. Prescription-only drug products include non-hormonal and hormonal contraceptives; hormonal products include oral contraceptives, intrauterine devices, implants, injections, and vaginal rings. Most oral contraceptives combine a progestin with an estrogen; however, progestin-only products are also available with oral, intrauterine, implant and injectable routes of administration. Non-hormonal prescription-only products include devices such as diaphragms and some intrauterine devices (IUDs), while male and female condoms, sponges, and spermicides are available over-the-counter without a prescription.

1.4 Hormonal Contraceptive Products

Combined estrogen/progestin contraceptives, including Ortho Evra, are associated with a number of well-recognized safety concerns, in particular VTEs. Product labeling for this class of drugs includes a boxed warning about the risk of serious cardiovascular events in women over age 35 who smoke, and warnings regarding the risk of thromboembolic disorders and other vascular events.

1.5 Summary and History of Labeling Changes since Approval

Since the 2001 approval, there have been a number of labeling changes to address issues relating to the risk of VTE and to the exposure to the contraceptive hormones seen with Ortho Evra as compared to certain COCs. The most recent labeling revision that pertained to VTE risk was approved on March 23, 2011, and entailed changes to the Boxed Warning to make existing

information about the potential risk of VTE and the PK profile of EE that is associated with the use of Ortho Evra more prominent to healthcare providers. No new information was added in this revision. The Boxed Warning now states:

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.)*

Prior to this, the following labeling revisions were approved:

- May 2005 – revised original labeling to state that exposure to EE with Ortho Evra is greater than that seen with a 20 μg EE COC
- November 2005 – added a warning **in bolded text** indicating that the Ortho Evra AUC for EE was 60% greater than that for a 35 μg EE COC, while the maximum concentration (Cmax) was 25% lower [based on Study NED-1, discussed in Section 2.3.1]
- September 2006 – described a possible increased risk of VTE in Ortho Evra users compared to COC users (based on initial results of two epidemiologic studies comparing Ortho Evra to COCs containing NGM and 35 μg EE). The Ingenix study (described further in Section 4.2) found a statistically significantly increased risk, with an odds ratio of 2.4 and 95% confidence interval (CI) of 1.1-5.5, while the Boston Collaborative Drug

Surveillance Program (BCDSP) did not find an increased risk for Ortho Evra users (odds ratio of 0.9 with 95% CI 0.5-1.6).

- January 2008 – further described a possible increased risk of VTE in Ortho Evra users compared to COC users; this label revision was based on results of another BCDSP epidemiologic study, which compared Ortho Evra to COCs containing levonorgestrel (LNG) and 30 µg EE, as well as on additional months of data from the original BCDSP NGM study. The new BCDSP study used the PharMetrics database to compare Ortho Evra to a LNG-containing COC and found a non-statistically significant increased risk of VTE for Ortho Evra users (odds ratio of 2.0 with 95% CI of 0.9-4.1).
- October 2008 – further described a possible increased risk of VTE in Ortho Evra users compared to COC users (based on further additional months of data from the original BCDSP study that used a NGM comparator). The additional months of data indicated a statistically significant increased VTE risk (odds ratio of 2.4, 95% CI 1.2-5.0), but when all updates for this study were pooled into a single dataset, the increase in risk (odds ratio of 1.2, 95% CI 0.9-1.8) was not statistically significant.
- September 2009 – provided revised data relating to a possible increased risk of VTE in Ortho Evra users compared to COC users (revision to the table regarding risk of VTE, based on reanalysis of epidemiologic data from the Ingenix study, which was found to have had some methodological errors in the original analysis). The reanalysis changed the odds ratio only slightly, to 2.5 (95% CI 1.1-5.5), with the increased risk of VTE for Ortho Evra users in this study remaining statistically significant.
- April 2010 – added new data regarding a possible increased risk of VTE in Ortho Evra users compared to COC users (based on additional months of data from the original Ingenix epidemiologic studies as well as on data from a new BCDSP epidemiologic study in a new database (MarketScan), which compared Ortho Evra to a LNG-containing 30 µg EE COC). The pooled data from the Ingenix study continued to show a statistically significant increased VTE risk of 2.2 (95% CI 1.2-4.0) for Ortho Evra users, while the new BCDSP study did not show a significantly increased risk (odds ratio of 1.3, 95% CI 0.8-2.0).

In addition, several healthcare provider letters or safety advisories were issued by the manufacturer or the FDA addressing these labeling updates/safety concerns from November 2005 through June 2011.

The current description of the epidemiologic data in labeling contains the following table, which is based on the totality of data from each of the respective studies:

Table 1: Comparative Odds Ratios of VTE Risk in Ortho Evra Users

Epidemiologic Study	Comparator Product	Odds Ratio (95% C.I.)
i3 Ingenix NGM Study Ingenix Research Datamart	NGM/35 mcg EE	**2.2* (1.2-4.0)**
BCDSP NGM Study Pharmetrics database	NGM/35 mcg EE	**1.2 (0.9-1.8)**
BCDSP LNG Study Pharmetrics database	LNG/30 mcg EE	**2.0 (0.9-4.1)**
BCDSP LNG Study Marketscan database	LNG/30 mcg EE	**1.3 (0.8-2.0)**

*Statistically significant
NGM - norgestimate, LNG – levonorgestrel
BCDSP - Boston Collaborative Drug Surveillance Program

1.6 Citizen Petition Requesting Withdrawal of Approval for Ortho Evra

In May 2008, Public Citizen filed a citizen petition requesting that FDA withdraw approval for Ortho Evra based on safety considerations, and permit a phased withdrawal from the market during a 6-month transition period. In support of this request, the petitioner cites a higher AUC for EE, a higher variability in EE levels, and a possible doubling of VTE risk as compared to COCs. The petition also alleges that Ortho Evra is associated with an increased risk of estrogenic side effects, has a higher rate of discontinuation and no improvement in contraceptive outcomes as compared to COCs.

FDA will provide a formal response to the petition when all relevant information (including data from the recently completed epidemiologic study funded by FDA) has been considered.

1.7 New FDA Epidemiology data

The FDA recently sponsored a large retrospective cohort study to evaluate use of contraceptive products in a population of prevalent and new users and their risk for a venous and arterial thromboembolic event and/or death. Details of the study and the findings are presented in Section 4.

1.8 Issues for Committee Consideration

The issues for Committee consideration include the following:

A. How do you view the impact of differences between studies, particularly those that provide discrepant results? How do different study designs, study populations, comparator groups and handling of potential confounding factors affect the outcomes of the various studies? Are there other important confounding variables that need to be addressed?

B. What do you believe are the strongest studies/findings?

C. Based on your interpretation of the available epidemiologic studies and the pharmacokinetic data that suggest higher exposure to EE in Ortho Evra users, do you

believe that users of Ortho Evra are at an increased risk of VTE as compared to users of combination oral contraceptives containing ≤ 35 µg of estrogen?

D. Do you believe that the benefits of the Ortho Evra transdermal contraceptive patch for prevention of pregnancy outweigh the risks?

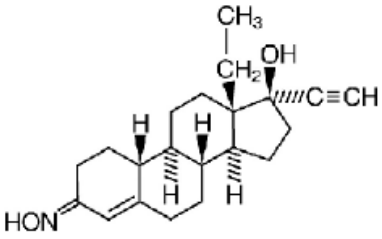
E. Do you believe the current Ortho Evra label adequately reflects the risk/benefit profile for the product?
   If not, in general terms, how would you recommend revising the label; for example,
   a. provide descriptive data about risk,
   b. interpret the findings of the epidemiologic data,
   c. discuss subpopulations of women who might or might not be appropriate users of the product?

F. Are there different studies or re-analyses of existing data that might be conducted that would help clarify the thrombotic/thromboembolic risk and the risk/benefit profile for Ortho Evra?

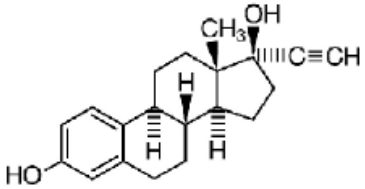
2. CLINICAL PHARMACOLOGY OVERVIEW

2.1 Introduction

Ortho Evra is a thin, matrix-type transdermal contraceptive patch containing 6 mg NGMN and 750 µg EE. The structural formulas of NGMN and EE are:



norelgestromin



ethinyl estradiol

The Ortho Evra patch is applied once weekly for three weeks during each 28-day (four-week) cycle. The fourth week of each cycle is patch-free. The patch should be applied to clean, dry, intact healthy skin on the buttock, abdomen, upper outer arm or upper torso. If a patch is partially or completely detached for less than one day, the woman is instructed to try to reapply it to the same place or to replace it with a new patch. If a patch is detached for more than one day, she is instructed to stop the current contraceptive cycle and start a new cycle immediately by applying a new patch. In this latter case, she would need to use a back-up contraception method during the first week of the new cycle.

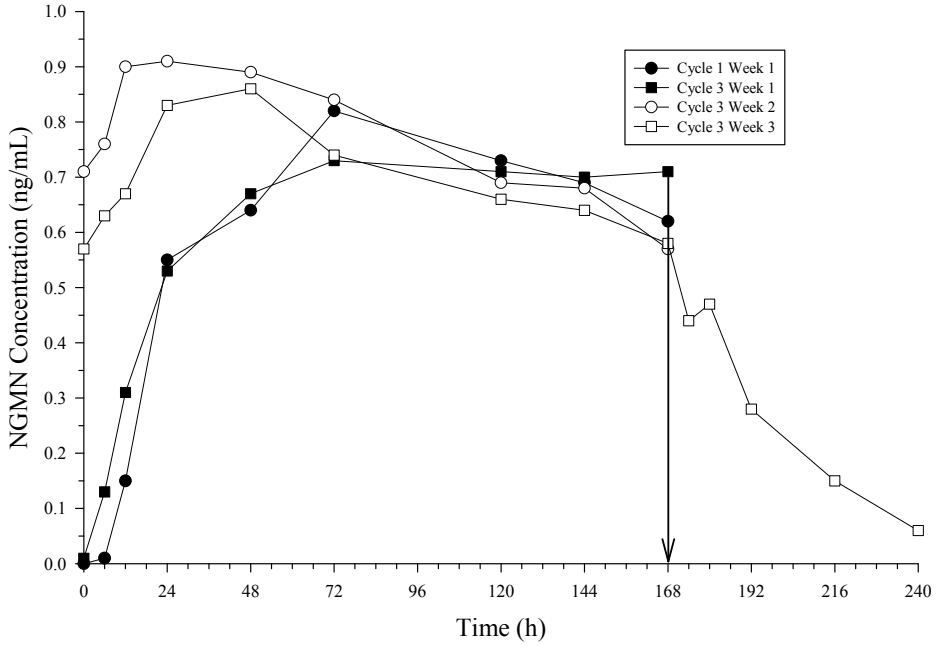
2.2 Pharmacokinetics of EE and NGMN following the application of the Ortho Evra patch

Following a single patch application of Ortho Evra, both serum NGMN and EE concentrations reach a plateau by approximately 48 hours. Steady state is reached within two weeks of application. The mean serum steady state concentrations range is 0.305–1.53 ng/mL for NGMN and 11.2–137 pg/mL for EE.

The mean PK profiles following a single patch application to the buttock during Cycle 1 and for all three weekly applications during Cycle 3 are shown in Figure 1 and Figure 2 for NGMN and EE, respectively. Systemic exposure data for NGMN and EE, as measured by steady state concentration (C_{ss}) and area under the concentration versus time curve (AUC) from time zero to time of patch removal at 168 hours (AUC_{0-168}), are summarized in Table 2.

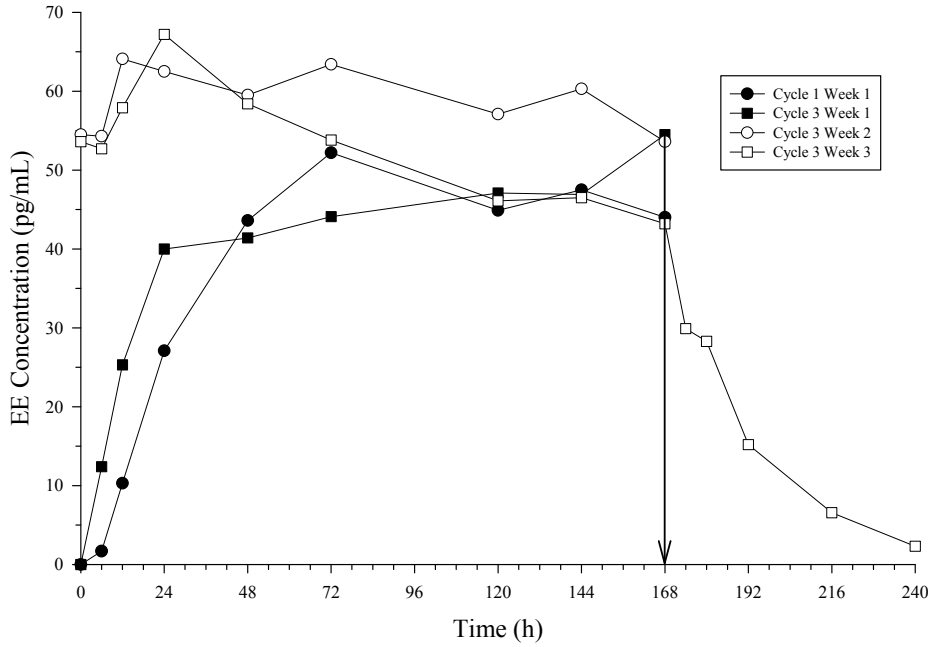
Upon removal of the patch, serum concentrations of EE and NGMN decline and reach concentration near the assay's lower limit of quantitation within three days (see Figure 1 and Figure 2). The mean elimination half-life ($t_{1/2}$) values for NGMN and EE observed across different studies are approximately 28 hours and 17 hours, respectively.

Figure 1: Mean Serum NGMN Concentrations (ng/mL) in Healthy Female Volunteers following Application of Ortho Evra for Three Consecutive Cycles (Vertical arrow indicates time of patch removal)



Source: Figure 1 from current product labeling

Figure 2: Mean Serum EE Concentrations (pg/mL) in Healthy Female Volunteers following Application of Ortho Evra for Three Consecutive Cycles (Vertical arrow indicates time of patch removal.)



Source: Figure 2 from current product labeling

Table 2: Mean (% CV*) Pharmacokinetic Parameters of NGMN and 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)

*% CV is % of Coefficient of variation = 100 (standard deviation/mean);
C_{ss} = steady state concentration; AUC_{0-168} = area under the concentration vs. time curve from 0 -168 hours; $t_{1/2}$ = elimination half life; nc = not calculated
Source: Table 1 from current product labeling

Comment

Note that the summary of PK information above is generated from the available data from many studies and the absolute values from any single study (e.g., $t_{1/2}$ in Table 2) may not exactly match the overall conclusion across studies.

2.3 Comparison of Relative EE and NGMN Exposure between Ortho Evra and COCs

Ortho Evra was designed to deliver EE and NGMN over a seven-day period while COCs are administered on a daily basis. The relatively flat concentration-time profile for NGMN and EE following application of Ortho Evra is in contrast to the daily peak/trough fluctuation observed following daily dosing of COC products.

There are two PK studies, namely, Study NED-1 and Study PHI-017 that evaluated the relative systemic exposure of Ortho Evra and selected COC products. Detailed description and results of the two PK studies are discussed below.

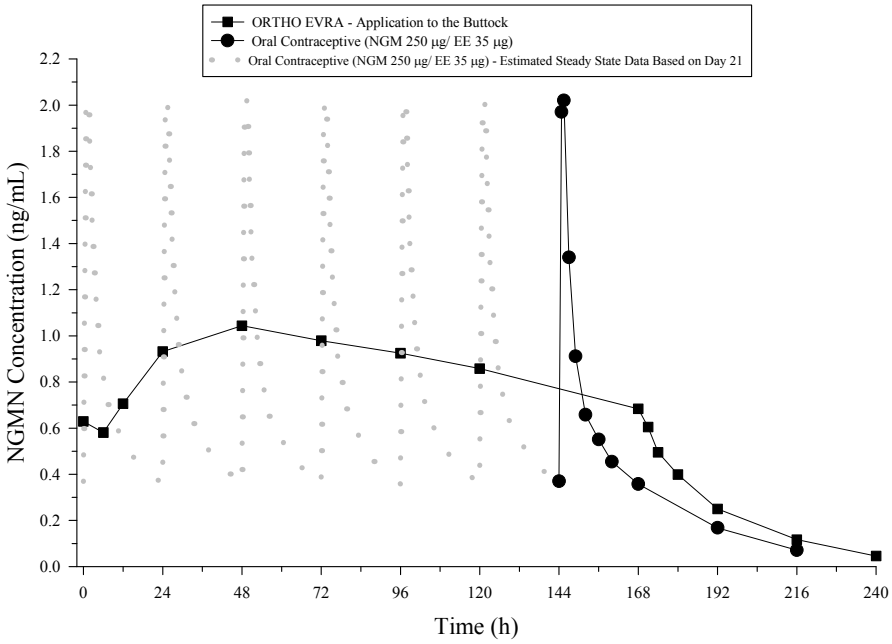
2.3.1 Study NED-1

Study NED-1 evaluated the relative NGMN and EE exposure of the Ortho Evra patch and the COC Cilest. Cilest is a monophasic (i.e., contains the same amount of hormone in all active tablets) 21-day COC containing 250 µg NGM and 35 µg EE per daily dose (NGM rapidly metabolizes into NGMN following oral administration). Cilest is not approved in the US. The US product with the same NGM and EE content is marketed as Ortho-Cyclen.

This was a single center, randomized, open-label, two-way crossover study in 36 healthy female subjects (age 18-48 years). The open-label treatment phase included two 28-day cycles of one treatment, a washout period of 28 days, and a cross-over to two 28-day cycles of the other treatment. Subjects placed an Ortho Evra patch on the abdomen or the buttock once weekly for three consecutive weeks during each of two cycles in one treatment period. In the other treatment period, they received Cilest tablets daily for 21 days of each cycle.

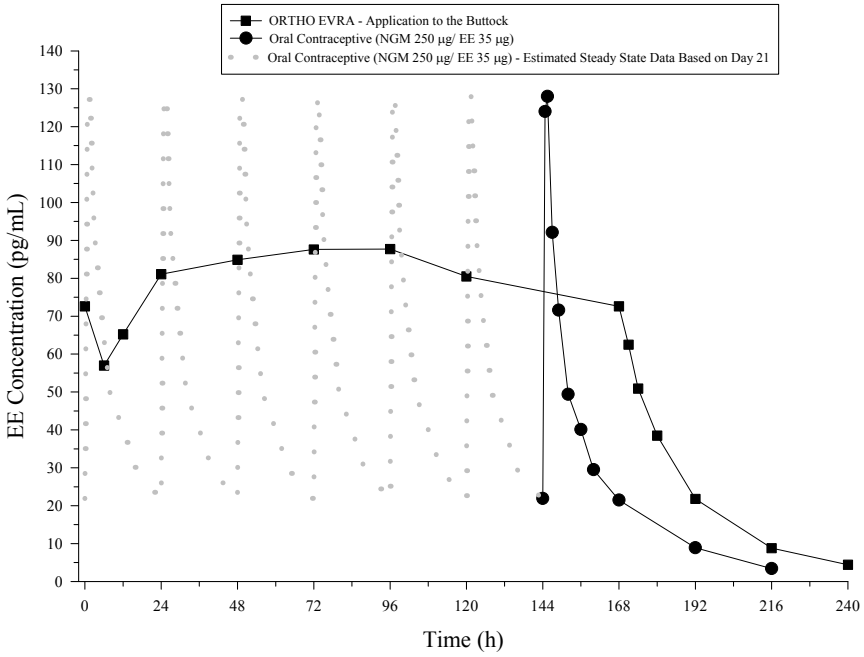
PK was assessed at Week 1 of Cycle 1 and Week 3 of Cycle 2. Figure 3 and Figure 4 present mean PK profiles for NGMN and EE following administration of Cilest compared to the seven-day Ortho Evra patch applied to the buttock during Week 3 of Cycle 2 (i.e., at steady state). The PK profiles for Ortho Evra following application to the abdomen are similar (data not shown). Table 3 shows the mean (% CV) PK parameters.

Figure 3: Mean Serum Concentration-Time Profiles of NGMN following Once-daily Administration of Cilest for 2 Cycles or Application of Ortho Evra to the Buttock for 2 Cycles in Healthy Female Volunteers. [Cilest: Cycle 2, Days 15-21, Ortho Evra: Cycle 2, Week 3]



Note: dotted gray plots are simulated concentration**.**
Source: Figure 3 from current product labeling

Figure 4: Mean Serum Concentration-Time Profiles of EE following Once-daily Administration of Cilest for 2 Cycles or Application of Ortho Evra to the Buttock for 2 Cycles in Healthy Female Volunteers. [Cilest: Cycle 2, Days 15-21, Ortho Evra: Cycle 2, Week 3]



Note: dotted gray plots are simulated concentration**.**
Source: Figure 4 from current product labeling

Table 3: Mean (%CV) NGMN and EE Steady State Pharmacokinetic Parameters following Application of Ortho Evra (Cycle 2, Week 3) and Once-daily Administration of Cilest (Cycle 2, Day 21) in 32 Healthy Female Volunteers

PK parameter	Ortho Evra	Cilest	Ratio, Ortho Evra/Cilest
NGMN[a]			
Cmax (ng/mL)	1.12 (33.6)	2.16 (25.2)	0.52
AUC_{0-168} (ng*h/mL)	145 (36.8)	123 (30.2)[b]	1.18
C_{ss} or C_{avg} (ng/mL)	0.888 (36.6)	0.732 (30.2)[c]	1.21
EE			
Cmax (pg/mL)	97.4 (31.6)	133 (27.7)	0.73
AUC_{0-168} (pg*h/mL)	12,971 (33.1)	8,281 (26.9)[b]	1.57
C_{ss} or C_{avg} (pg/mL)	80.0 (33.5)[d]	49.3 (26.9)[c]	1.62

Cilest contains 35 µg EE and 250 µg NGM per daily dose
[a]NGM in Cilest is rapidly metabolized to NGMN following oral administration
[b]Average weekly exposure, calculated as AUC_{24} x 7
[c]C_{avg}
[d]C_{ss}

Source: Adapted from Table 2 from current product labeling

The results indicated that systemic exposure (measured as AUC) of NGMN and EE following Ortho Evra application was higher than that for Cilest, both after Week 1, Cycle 1 (data not shown) and Week 3, Cycle 2. In contrast, Cmax values were higher in subjects administered Cilest. Under steady state conditions, for Ortho Evra, AUC_{0-168} and C_{ss} for EE were 57% and 62% higher, respectively, while the C_{max} was 27% lower compared to Cilest.

2.3.2 Study PHI-017

Study PHI-017 evaluated the relative bioavailability of Ortho Evra and three different COC products, namely Triphasil, Alesse, and Mercilon (Table 4). Triphasil is a triphasic COC (i.e., the amount of estrogen and progestin varies over the treatment cycle).

Table 4: Composition of OC Products

OC Product	Active tablets per 28-day cycle	Comment
Triphasil	50 µg LNG/ 30 µg EE for 6 days, 75 µg LNG/ 40 µg EE for 5 days, 125 µg LNG/ 30 µg EE for 10 days	A triphasic COC
Alesse	100 µg LNG/ 20 µg EE for 21 days	
Mercilon	150 µg DSG/ 20 µg EE for 21 days	Not approved in the US.

LNG: levonorgestrel; DSG: desogestrel

Study PHI-017 was a single center, open-label, two-period, cross-over study in 35 healthy female subjects (age 18-44 years). They were assigned to one of three groups:

- Group 1: Triphasil once daily for 21 days or Ortho Evra one patch weekly for three weeks (3 patches)
- Group 2: Alesse once daily for seven days or Ortho Evra for one week
- Group 3: Mercilon once daily for seven days or Ortho Evra for one week

Within each group, subjects were randomized to receive either the COC treatment or Ortho Evra followed by the other treatment during the second treatment period, according to a randomization schedule.

Both EE and progestin concentrations were evaluated in this study. The progestins in the COCs studies are different than that in Ortho Evra and the results are not discussed further.

The results for EE are shown in Table 5. The results indicated that EE exposure (AUC) following application of Ortho Evra was **2.1-fold higher** than Triphasil (this product contains 30 µg EE), **2.8-fold higher** than Alesse (this product contains 20 µg EE) and **3.1-fold higher** than Mercilon (this product contains 20 µg EE). The Cmax of EE following application of Ortho Evra ranged from 27% lower to 9% higher, depending on the specific COC and its EE content.

Table 5: Ortho Evra and OC PK Parameters, by Treatment Cohorts

Treatment Cohort	Treatment Group	AUC_{0-168} [pg*h/mL], mean (%CV)	EE AUC ratio, Ortho Evra/OC	C_{max} [pg/mL], mean (%CV)	EE C_{max} ratio, Ortho Evra/OC
Cohort 1	Triphasil [30 µg EE]* (week 3)	5,025 (25.6)	2.1	93.7 (26.8)	0.87
	Ortho Evra (week 3)	10,761 (33.4)		81.9 (37.6)	
Cohort 2	Alesse [20 µg EE] (week 1)	2,607 (25.0)	2.8	56.5 (20.0)	1.09
	Ortho Evra (week 1)	7,367 (36.4)		61.8 (38.4)	
Cohort 3	Mercilon [20 µg EE] (week 1)	2,478 (24.0)	3.1	55.0 (25.6)	1.07
	Ortho Evra (week 1)	7623 (33.2)		58.6 (33.8)	

* Triphasil is a triphasic product containing 30 µg EE for 6 days, 40 µg EE for 5 days, and 30 µg EE for 10 days. PK sampling was done on days 15 – 21 for this comparison.

Source: FDA internal review of Study PHI-017 study report

2.3.3 Summary of EE Results from Studies NED-1 and PHI-017

In Study NED-1, EE exposure (based on AUC values) in volunteers treated with Ortho Evra was 60% higher than that in volunteers treated with a COC (Cilest) containing 35 µg EE. In Study PHI-017, EE exposure in volunteers treated with Ortho Evra was 2-3 fold higher than that in volunteers treated with daily Triphasil, Alesse, or Mercilon (COCs containing 20-30 µg of EE). Cmax values for EE following application of Ortho Evra ranged from 27% lower to 9% higher depending on the specific COC and its EE content (see Table 6).

Table 6: Relative EE Exposure (AUC) Comparison between Ortho Evra and Select COCs

Study #	OC comparators[a]	EE AUC Ratio of patch/OC	EE C_{max} Ratio of patch/OC
NED-1	Cilest – 35 µg EE	1.57	0.73
PHI-017	Triphasil – 30 µg EE[b]	2.1	0.87
	Alesse – 20 µg EE	2.8	1.09
	Mercilon – 20 µg EE	3.1	1.07

[a]COC comparators contain EE and different progestins;
[b]Triphasil is a triphasic product containing 30 µg EE for 6 days, 40 µg EE for 5 days, and 30 µg EE for 10 days. PK sampling was done on days 15 – 21 for this comparison.

3. DATA ON EFFICACY AND COMPLIANCE WITH USE OF ORTHO EVRA

3.1 Original NDA Data Based on US and European Experience

When the product was reviewed and approved in November 2001, it was anticipated that the seven-day patch would result in better compliance and therefore better effectiveness compared to a contraceptive method that required daily administration. This seemed logical, as the user would need to apply the transdermal patch only once weekly for each of three consecutive weeks instead of remembering to take a daily pill. Studies and surveys have consistently shown that first year pregnancy rates during typical use of COCs is ~9%[1], whereas the one-year pregnancy rates in clinical trials of approved COCs range between 1-3%. Poor compliance is the primary reason given to explain the difference in effectiveness between typical use of marketed products and effectiveness in clinical trials. Compliance can refer to use compliance (pills, patch, or ring are used daily according to instructions) or continuation compliance (a prescription is filled on time and use of the product is continued from cycle to cycle). This distinction must be noted as the various studies from the medical literature are discussed below.

The original NDA submission included three large phase 3 studies, CONT-002, -003, and -004; each study was designed to accumulate information about the contraceptive efficacy, vaginal bleeding patterns, and safety of the Ortho Evra regimen in generally healthy women, age 18 to 45 years, who elected to use transdermal hormonal contraception for the prevention of pregnancy. Each study was multicenter, open-label, 6 or 13-cycles, to evaluate efficacy and safety with the transdermal patch. Study 002 was non-comparative and conducted in 31 centers in the United States and 42 outside the US, while Studies 003 and 004 were comparative, with Study 003 using the COC Mercilon and conducted in 65 centers in European countries and South Africa, and Study 004 using the COC Triphasil and conducted in 39 US and 6 Canadian centers.

The Audet et al article[2] reports only on Study 004, the US/Canadian trial comparing the contraceptive patch with a COC. In the study, 1,400 participants were randomized in a ratio of 4:3 to receive either the Ortho Evra contraceptive patch or a triphasic COC; the first third of the participants were enrolled for 13 cycles and the remainder for 6 cycles. The overall Pearl index rate was numerically lower in the patch group (1.24) than in the COC group (2.18), although the differences between the treatments were not statistically significant. In the patch group, five pregnancies occurred among 811 women treated for 5,240 cycles. In the COC group, seven pregnancies occurred among 605 women treated for 4,167 cycles.

Compliance was determined by daily dosing (and weekly patch replacement) noted on diary cards and included all cycles in which adequate dosing information was available. Perfect compliance was defined as 21 consecutive days of drug-taking, which could include the use of replacement patches, followed by a 7 day drug-free interval. For patch users, no patch could be worn for more than 7 days. If one or more pills were missed (not taken daily), then the COC cycle was non-compliant. Compliance with the dosing schedule of the patch was better than that of the COC among all six different age groups (the youngest group was < age 20; the oldest was ≥ age 40). The mean proportion of cycles that demonstrated perfect compliance was 88.2% in the patch group and 77.7% in the COC group ($p < 0.001$).

Comment

Per protocol, if a subject missed taking one active pill on any given day, the cycle was counted as non-compliant. It must be noted, however, that patch subjects were given 3 reserve patches; if a patch partially lifted or fell off and a replacement patch was used the same day, then the cycle was still considered to be compliant. The comparative US/Canadian study showed 88.2% compliant cycles for the Ortho Evra patch and 77.7% compliance for the pill users. In typical (actual) use, however, an extra patch is often not available, so compliance will likely be lower.

In the three clinical trials combined, the reason for a patch change was the following:

- **Scheduled change: 92.2 %**
- **Partially lifted: 2.9**
- **Patch fell off: 2.6**
- **Other: 1.6**
- **Skin reaction: 0.6**

It is plausible that the compliance rate with the 7-day patch would be better compared to a COC pill that is to be taken daily. With a COC, if a pill is missed, the instructions are clear about doubling up (taking the missed pill + the current day's pill) as soon as possible. What is not precisely known is the actual risk of pregnancy if one or two pills are missed and how the risk varies during different cycle weeks of pill use. The Division does not have data for the incidence of one and two missed pills that were taken as soon as recognized in the comparator COC arm in this trial. Although the pregnancy rate was numerically lower with use of the patch, the difference between the two treatments was not statistically significant, so no definitive conclusion can be drawn about better compliance equating with better contraceptive efficacy.

The Urdl et al article[3] reports on Study 003, conducted in Europe and South Africa. In this trial, 1,489 women received a contraceptive patch (N= 846) or a COC (N= 643) for 6 or 13 cycles. The overall/perfect use Pearl Indices were 0.88/0.66 with the patch and 0.56/0.28 with the COC, not statistically significantly different. Compliance was higher in all age groups with the patch (overall 96.5%) compared to the COC (overall 90.6%). The percentage of patch users being very satisfied with patch use increased with age, whereas it did not in the COC group. The authors concluded that contraceptive efficacy of the patch is comparable to that of COCs, but patch compliance is consistently better in all age groups.

Comment

The protocols for the US 004 trial and the European 003 trial and the number of enrolled subjects were essentially the same. In the European trial, the compliance for 6-13 cycles of use was noticeably higher than in the US trial for both the patch (96.5 vs. 88.2) and COC users (90.6 vs. 77.7), and higher than what is found with typical use US data. This higher compliance did translate into better Pearl indices for both treatments arms in Study 003 compared to the US trial. This has been a common finding in the Division's experience – that pregnancy rates in European contraceptive trials are lower compared to rates in US

trials. This difference in effectiveness may reflect both differences in compliance in the two populations as well as the impact of the greater prevalence of obesity in the US population.

Although COC users had a lower Pearl index than patch users in Study 003, the difference was not statistically significant.

3.2 Other Data from the Medical Literature

A search was made of the medical literature to help evaluate 1) whether compliance or continuation rates are better with the 7-day Ortho Evra patch compared to use of a daily COC or a 21-day vaginal ring (NuvaRing), and 2) whether a difference in compliance translates to a difference in contraceptive efficacy.

Discontinuation Patterns:
We found two articles that analyzed large databases for prescription refills for hormonal contraception. The articles are discussed here.

Murphy and Brixner[4] did a retrospective descriptive analysis within an administrative claims database (the Institute of Health Care Information Solutions and its National Benchmark Database) of nearly 250,000 women aged 15-40 years with a pharmacy benefit. The women had at least one new hormonal contraception prescription during the study period (1999 to March 31, 2004) and no prescription in the previous 6 months. Filled contraceptive prescriptions were grouped into several categories, including delivery system (oral, transdermal, vaginal ring, and injectable), dose, progestin type, and monophasic vs. triphasic formulations. In each, a baseline number of women was established who filled a first prescription for a contraceptive formulation in the specified category. The percentage of these women who filled a prescription for a contraceptive in the same category within three months' time was then determined. Continuation or change rates were compared within each group. Summary results showed that COCs were the least likely to be discontinued at three months; injectables were the most likely. COC formulations associated with increased risk of discontinuation (odds ratios above 1.3 for $\geq$ 5% increased discontinuation rate) included very low dose (20–25 μg EE) pills containing norethindrone acetate or NGM, as compared to a COC with the same progestin and a higher dose of estrogen. Five percent of the baseline eligible women used the transdermal patch; they were 1.6 times more likely to have discontinued at three months than users of COCs (95% CI 1.5-1.7). The study did not have access to clinical or socioeconomic data, and the authors were unable to assess for confounding and potential bias.

Comment

This study is limited to discontinuation data at three months for a very large number of women (35 health plans representing approximately 38 million unique members in 2004). There are no data on contraceptive efficacy or reasons for discontinuation of the original prescription. The authors recognize that poor adherence to contraceptive use has many different factors and is recognized as a common problem. Relative to the focus of this current Advisory Committee meeting, the most impressive finding from this study is the odds ratio of 1.6 for Ortho Evra for discontinuation at three months.

Nelson, et al[5] analyzed longitudinal prescription refills from the Verispan database from 99% of retail pharmacies in the United States between October 2003 and August 2005 for specific branded hormonal contraceptives. Only women who could be tracked for the entire study period were included in the analysis. The authors calculated refill rates for Ortho Evra, NuvaRing, Depo Provera, and five branded COCs (including one extended-cycle product), and for different

age groups. Refill data were available for nearly 1.7 million women for 240 days (eight months) and for almost 1 million women for 420 days (14 months). After 30 days, a range of 59-75% of women refilled their prescriptions for the eight products on a timely basis. By three months, only 48-61% of women returned for timely refills. By 12 months, 16-35% of women had consistently refilled their original prescriptions. Very young teens (age 14-16 years) had refill rates for most methods that were at least as good as those of older women.

Table 7: Prescription Refill Rates (%) over Time

Method	Starting N*	Percent Refilled at				
		30 Days	90 Days	180 Days	12 Months	18 Months
Patch	433,403	68.4	49.8	38.9	25.9	21.6
Ring	96,598	59.4	51.1	40.4	26.2	23.2
COCs 28-day cycle	917,519	72.7	55.2	43.8	28.9	20.1

*Population recruited from October 2003 through December 2004
Source: Adapted from Tables 1 and 2 from the article (pp 784 and 785). Data for the two 3-month methods, OC Seasonale and injectable Depo Provera, are not included.

The authors' conclusions were that these low rates of timely refill in actual practice indicate that few women had the potential for correct and consistent contraceptive use. Products with extended cycles (Seasonale and Depo-Provera) or a new progestin (drospirenone) had higher refill rates than did other 28-day products. These high discontinuation rates suggest that barriers to successful utilization and/or access of contraceptives exist.

Comment
This is an analysis of prescription refill rates over 3-18 months from a very large database. The transdermal patch refill rates were consistently lower by 3.0 to 5.4% than the averaged 28-day rates for the 4 branded COCs from 3 to 12 months. At 18 months, however, the patch refill rate was higher by 1.5%. The overall impression here is that the prescription refill rate for women continuing with the same COC is slightly better than the refill rate with the transdermal patch. Although this article does not address the question of actual correct administration of product (use compliance) or contraceptive efficacy, the data do not support the notion that continuation with a 7-day patch is better than with a COC.

We found four comparative studies in the medical literature that evaluated continuation rates and, in some studies, pregnancy rates in high risk populations. Although the studies have limitations, they do provide comparative data.

1. Creinin et al[6] reported on a randomized trial at ten university medical centers between June 2005 and September 2006 to evaluate if the contraceptive ring or patch was more acceptable, as measured primarily by continuation rates, to women who had already been using an oral contraceptive, but were interested in switching to a non-daily, combined hormonal contraceptive. Five hundred women were randomly assigned to use the contraceptive ring (N=249) or contraceptive patch (N=251) for four consecutive menstrual cycles, starting with their next menses. Participants returned for a single follow-up visit during the fourth cycle for an evaluation, which included a questionnaire to assess acceptability and adverse effects.

Rates of completion of three cycles were 94.6% (95% CI 91.0–97.1%) and 88.2% (95% CI 83.4–92.0%) for ring and patch users, respectively (p = 0.03). Of these women, 71.0% of ring users

and 26.5% of patch users planned to continue their method after the study ($p < 0.001$). All women were switching from daily COC use. Women switching to the patch were significantly more likely than women switching to the ring to experience longer menstrual periods (38% compared with 9%), increased dysmenorrhea (29% compared with 16%), frequent nausea (8% compared with 1%), frequent mood swings (14% compared with 8%), and frequent skin rash (12% compared with 2%) and were less likely to experience frequent vaginal discharge (8% compared with 17%). Ring users preferred the ring to the oral contraceptive ($p < 0.001$), and patch users preferred the oral contraceptive to the patch ($p < 0.001$). Adverse effects as noted and complaints about product use (skin rash, poor adherence, difficulty removing) were the reasons patch users preferred COC use. No contraceptive efficacy data was collected during this study. Women noted use problems with both products. The patch fell off at least once during any three-week use period in 46% of women and the ring was expelled at least once during any three-week use period in 20% of women ($p < 0.001$).

Comment

This study was limited to three months of follow-up and had no data on contraceptive efficacy. Patch continuation compliance was 88%. What is notable are the following:

- **The side effect profile (longer periods, dysmenorrhea, nausea, mood swings) for the patch was noticeably worse than for the ring; these may be related to the higher estrogen exposure with the patch compared to the ring**
- **Patch users preferred COC use to the 3-month use of the patch**
- **46% of users had a patch fall off at least once during any 3-week use period; an additional 3.8% removed a patch during a 3-week use period**

2. Bakhru and Stanford[7] conducted a prospective study in 1,230 hormonal contraceptive-naïve women at three Planned Parenthood clinics in the Rochester-Syracuse area. The subjects self-selected their contraceptive method (patch use N=651; COC use N=579). Discontinuation, adverse effects, and pregnancy outcomes were catalogued. The primary outcome was time to discontinuation of the patch or pill. Survival analyses with life tables and Cox proportional hazards were used to assess acceptability and compliance. Pearl Indices were calculated for both the pill and patch. Subjects were a racially diverse group of predominantly single women. Eighty-nine percent of the study population met the study definition of being at high risk for a future unintended pregnancy or pregnancy termination. Loss to follow-up after the first clinic visit was higher among patch users (45.2% versus 29.5%, $p < 0.001$). Verified continued use beyond the first three cycles was lower with patch users (67% versus 89%, $p < 0.001$). At one year of follow-up, 76% of COC users and 57% of patch users continued their original method ($p = 0.004$). The most common reason to discontinue either the patch or the pill was to switch to another contraceptive method.

The 3,206 cycles captured in this study resulted in a Pearl Index of 3.62 for the pill and 14.84 for the patch. For subjects who used the patch after continuous use was established at three cycles, the absolute risk for unintended pregnancy was 3.46%. Differences in the baseline demographic and contraceptive practices may account for this discrepancy although, in multivariate analysis, patch users continued to do worse. The authors found users of the contraceptive patch to have significantly higher discontinuation and unintended pregnancy rates compared to the women who chose to use a COC in this high-risk population.

Comment

This was not a randomized trial. The patch group (53% of the total) had more minorities (43% vs. 15%), prior births (40% vs. 7%), and abortions (59% vs. 10%) than the COC group,

although by the authors' criteria, the two groups were essentially at the same "high-risk" status (90.5% of patch users and 87.2% of COC users). The authors acknowledge that they did not expect to see the resultant findings, and that prior controlled studies have shown greater compliance with the contraceptive patch in both adults [Archer DF et al, Contraception 2004; Burkman RT, Am J Obst Gyn 2004] and teens [Rubinstein ML, et al, J Adolesc Health 2004; Harel Z et al, J Pedi Adolesc Gyn 2005]. It should be noted, however, that the Archer and Burkman articles are based on the clinical trials that supported approval of the Ortho Evra NDA where "typical use" is not the same as typical use in an uncontrolled non-clinical setting.

There is little information on the calculations for the Pearl Indices, but the absolute risk of 3.46% for an unintended pregnancy for patch users seems reasonable. Data for the calculation of the Pearl index of 14.8 with use of the Ortho Evra patch are not given.

3. Thurman AE et al[8] did an observational prospective cohort study to evaluate the repeat teen pregnancy rates within one year of delivery in Charleston, SC. The 252 teens (age 11-19) choose the patch (N=55), a COC (N=55) or Depo Provera (N=142); 72% were African American and 96% qualified for Medicaid insurance. The primary outcome measure was a repeat pregnancy within 12 months of the index delivery. Secondary outcome variables were contraceptive continuation rates, reasons for discontinuation, side effects, and condom usage. The results at the one-year follow-up showed repeat pregnancy rates were 14.2%, 29.7%, and 31.8% among Depo Provera, COC, and patch users respectively (p= 0.02), and most pregnancies occurred after 6 months postpartum. Original COC users (76%) and Depo Provera users (79%) were reported to be using some form of hormonal contraception one year postpartum, while only 55% of patch users reported such use (see Table 8). Self-reported condom use was similarly low among all cohorts and at all time intervals. The authors concluded that the patch offers no advantage over COC use in terms of preventing repeat teen pregnancies within one year of a delivery.

Table 8: Continuation Rates (%) and Use of Contraception at 3 and 12 Months Follow-up

Method	Continuation at 90 Days	No Method at 90 Days	Continuation at 12 Months	Using Another Method at 12 Months	No Method at 12 Months
Patch	71.4	20.4	48.3	6.9	44.8
COCs	51.2	34.2	52.0	24.0	24.0
Depo Provera	75.7	24.3	66.7	12.2	21.1

Source: Adapted from Table 3 from the article (pg 64). Data for switching to another hormonal method at 90 days are not included.

Comment

The study population here is definitely high-risk for repeat pregnancy having already had a delivery at age 11 to 19. The most consistent contraceptive use was with the Depo Provera cohort which probably is why they had the lowest repeat pregnancy rate. The low continuation rate for COC users at three months is hard to explain given the same continuation rate at 12 months. The overall impression is that in this study the compliance (continued use of original product) and pregnancy rates (contraceptive efficacy) for the patch and OC users were basically the same at 12 months postpartum in this high risk group of young users.

4. Raine et al[9] did a 12-month longitudinal cohort study of women (N=1,387) age 15-24 years attending public family planning clinics and choosing to initiate the patch (N=370), ring (N=233), Depo Provera (N=279), or COCs (N=387). Two-thirds of the participants were adolescents. Participants completed follow-up assessments at three, six, and 12 months after

baseline. Life table analysis was used to estimate rates of contraceptive continuation. The approximate continuation rate at three months was 37% for patch users and 62% for COC users. The continuation rate (per 100 person-years) at 12 months was low for all methods; however, it was lowest for patch and Depo Provera initiators, 10.9 and 12.1 per 100 person- years, respectively ($p < 0.003$); continuation among ring initiators was comparable to pill initiators, 29.4 and 32.7 per 100 person-years, respectively ($p = 0.06$). Discontinuation was independently associated with method initiated and younger age. The only factors associated with higher continuation of any contraception method were 1) greater intent to use the method, and 2) being in school or working. The pregnancy rates (per 100 person-years) were highest for patch and ring initiators (30.1 and 30.5), and comparable for pill and Depo Provera initiators (16.5 and 16.1; $p < 0.001$).

The authors concluded that the patch and the ring may not be better options than the pill or Depo Provera for women at high risk for unintended pregnancy.

Table 9: Continuation Rates (%) at 3 and 12 Months Follow-up and Pregnancy Rate

Method	Continuation at 90 Days	Continuation at 12 Months per 100 women/yr	Pregnancy Rate per 100 women/years*
Patch	37	10.9	30.1
Ring	55	29.4	30.5
COCs	62	32.7	16.5
Depo Provera	30	12.1	16.1

*****Overall pregnancy rate was 22.9
Source: Adapted from Figure 1 from the article (pg 367). Data for switching to another hormonal method or using no method are not available.

Comment

For using the same initial contraceptive method, this 12-month study found much better continuation rates for ring and COC users at both three and 12 months compared to patch and Depo Provera users. The majority of patch and Depo Provera users discontinued their method by four months. Overall, 53% of the women switched to another method during the 12 months and 20% stopped their initial method and did not use another effective method. The most common reason for discontinuation of the methods was side effects, with this reason noted by 26% of ring users, 33% of COC users, 34% of patch users, and 46% of Depo Provera users. It is noteworthy that the pregnancy rate for the patch and ring was twice that of COC and Depo Provera users (roughly 30% vs. 16%).

The following table (Table 10) is a summary of the findings from the previously summarized eight studies.

Table 10: Comparative Ortho Evra Compliance, Continuation, Efficacy Data

1° Author (year)	Correct Use Compliance	Continuation or Refill Rate over time	Efficacy Data	Reviewer Comment
Audet (2001) Clinical trial - **Patch vs. COC**	Patch - 89% COC - 78%	Data not given	Patch Pearl Index - 1.24, better than COC 2.18	6-13 cycle trial - patch efficacy numerically but not statistically better
Urdl (2005) Clinical trial - **Patch vs. COC**	Patch - 97% COC - 91%	Data not given	Patch Pearl - 0.88, worse than COC 0.56	6-13 cycle trial - COC efficacy numerically but not statistically better
Murphy (2008) Rx database - **All methods**	Patch odds ratio for risk of discontinuation compared to COC use = 1.6	Patch - 52% refill at 3 months COC - 62% at 3 months	None	~250,000 women in database with data for only 3 months
Nelson (2008) Rx database - **All methods**		COC refill rate to 12 months was better than patch rate	None	Huge Rx database 3-18 month follow-up
Creinin (2008) N=500 Clinical trial - **Patch vs. ring**		Patch - 88% at 3 months; Ring - 95% at 3 months	None	Women content with a COC; adverse event profile worse with the patch
Bakhru (2006) N=1230 Naïve users - **Patch vs. COC**		Patch - 67% at 3 months and 57% at 12 months COC- 89 & 76%	Pill efficacy better than the patch	High-risk Planned Parenthood population
Thurman **(2007)** N=252 **Patch, COC, or Depo Provera**		Patch - 71% at 3 months and 48% at 12 months COC - 51 & 52%	None	1 year follow-up post teen delivery; teens age 11-19
Raine (2011) N=1387 **Patch, ring, COC, Depo Provera**		Patch - 37% & 11% at 3 & 12 months. Depo Provera – 30% & 12% at 3 and 12 months Ring - 55% & 30% at 3 and 12 months COC - 62% & 33% at 3 and 12 months	Pregnancy rate at 12 months Patch: 30% Depo Provera: 16% Ring: 31% COC: 17%	1 year follow-up for women age 15-24 at family planning clinic

Source: Composite data from 8 studies in peer-reviewed medical literature**.**

The following summary table (Table 11) shows the comparative refill or continuation rates.

Table 11: Comparative Refill or Continuation Data for Ortho Evra vs. COC

Study	3-Month Refill or Continuation	12-month Refill or Continuation	Reviewer Comment
Murphy (2008)	Patch - 52% COC - 62%		~250,000 women in database with only 3-month data
Nelson (2008)	Patch - 50% COC - 55%	Patch - 26% COC - 29%	Huge Rx database 3-18 month follow
Creinin (2008)	Patch - 88% Ring - 95%		Women who had been using a COC; but desired a switch to a non-daily method
Bakhru (2006)	Patch - 67% COC - 89%	Patch - 57% COC - 76%	High-risk clinic population
Thurman (2007)	Patch - 71% COC - 51%	Patch - 48% COC - 52%	High risk teens (age 11-19) post delivery
Raine (2011)	Patch - 37% COC - 62%	Patch - 11% COC - 33%	At-risk women age 15-24 at public clinic

Source: Composite data from studies in peer-reviewed medical literature**.**

3.3 Conclusions for Use Compliance and Continuation Compliance

Two of the studies had only three-month data and the remaining four had 12-month data. The data come from three very different sources:

- Two large comparative clinical trials for the original 2001 approval of Ortho Evra
- Two large prescription databases for refills of hormonal contraception
- Four comparative, non-randomized, clinical trials with predominantly younger women, most of whom were considered at high risk for pregnancy

3.3.1 NDA Clinical Trials

Although the two NDA clinical trials have the largest amount of data and probably the most accurate data, their structure is far from the typical use setting found in all the other studies. Follow-up visits, instructions to subjects, supply of drug product (including three reserve patches for all Ortho Evra users), and other factors make the environment closer to ideal use rather than typical use. Trial subjects do not have the option to switch to another method, although they do have the option to withdraw from the study. In any case, these two trials showed an overall use compliance of 89% and 97% for patch users and 78% and 91% for COC users for up to 12 months of use. In these two controlled studies, use compliance was numerically better in the subjects using the patch.

3.3.2 Prescription Databases (up to March 2004 and August 2005)

Data for 3 months: based on large prescription databases, both the articles found a numerically lower refill rate for patch users compared to COC users, although the difference was only 5-10%. What is notable is that the range for all refills was 50-62%, which means that 38-50% of the

women either switched to another method (not determined in this study) or did not use any contraceptive method.

Data for 12 months: the huge database from the Nelson study showed similar refill rates for both patch users and COC users, but the refill rates for the original product were only 26-29%. At 18 months, the refill rate was 21.6% for patch users and 20.1% (range of 8.8 to 31.5%) for users of four branded COCs. The authors noted that:

> "very young women had refill rates for most methods that were at least as good as those for older women. These low rates of timely refill rates in actual practice indicate that few women had the potential for correct and consistent contraceptive use. New methods with extended cycles [Seasonale was included] or a new progestin [Yasmin was included] had higher rates than did the other 28-day products."

Comment
The Division's conclusion is that patch users had a numerically lower continuation rate than COC users based on the prescription refill data. The two studies, however, do not provide any data for actual use compliance or contraceptive effectiveness.

3.3.3 Comparative, Non-randomized, Clinical Trials (not NDA-related Trials)

These four trials are closer to typical use of four methods of hormonal contraception, namely, patch (Ortho Evra), COCs, ring (NuvaRing), and injectable (Depo Provera). As noted in Table 10 and Table 11 above, the three-month refill or continuation rates ranged from 37 to 88% for patch users, 51-89% for COC users, and 95% for ring users (one study only). What is more useful is the 12-month data, as it is well known that women who switch their method of contraception usually do so in the first 3-6 months of use of a given method. The 12-month data from three studies shows that refill or continuation rates ranged from 11 to 57% for patch users and 33-76% for COC users. The study populations were generally younger women at risk or high risk of pregnancy, so the results are not generalizable to all women of reproductive age. Nonetheless, the results show that continuation or refill rates for patch users were numerically lower than found with COC users.

3.4 Conclusions for Contraceptive Efficacy

The two 6-13 cycle NDA clinical trials had conflicting data for contraceptive efficacy for patch users and COC users. The US trial 004 showed a lower Pearl index for patch users while the European trial 003 showed a lower Pearl index for COC users. In both trials, however, the Pearl index for patch users was in an acceptable range of 0.88-1.34, and the difference from COC users was not statistically significant. Both articles conclude that "contraceptive efficacy of the patch is comparable to the OC" used in the NDA clinical trial.

Only two of the non-NDA clinical trials addressed contraceptive efficacy and neither was conducted as an efficacy trial. Both enrolled younger women at public family planning clinics. Bakhru et al had a high initial Pearl Index for patch users, but found that for subjects who had established acceptability for patch use the absolute risk for unintended pregnancy was 3.46%. Raine et al found the 12-month pregnancy rate for initial patch users at 30% compared to 31% for ring users, and 17% for COC users.

Comment
The Division's conclusion is that the data from clinical trials do not support the notion that contraceptive efficacy with patch use is better than with COC use. Rather, efficacy appears

to be comparable to that of COC use, and lower in certain high-risk populations when studied over time.

4. POST MARKETING ASSESSMENT OF THE RISK OF THROMBOTIC AND THROMBOEMBOLIC EVENTS IN ORTHO EVRA USERS

4.1 Overview

4.1.1 Standard Postmarketing Pharmacovigilance

From the time of approval (November 20, 2001), FDA has reviewed reports of thrombotic and thromboembolic events submitted to the FDA's Adverse Event Reporting System (AERS) for users of Ortho Evra. Based on these voluntarily or spontaneously submitted reports and drug use data (e.g., numbers of prescriptions) "reporting rates" for these events were calculated and compared to reporting rates for several (including some newly approved) combined hormonal contraceptives (CHCs). These comparisons suggested slightly higher reported risks for these events in users of Ortho Evra (see Table 12). The potential increase appeared to be greater when only women 30 years of age or younger were considered.

Table 12: Reporting Rates* (Events per 100,000 PY***), Approval - 2005**

	All Ages		< 30 Years	
	NGMN	**Comparators**	**NGMN**	**Comparators**
Pulmonary Embolism	**3.7**	**0.6-2.7**	**2.1**	**0.4-1.6**
Acute Myocardial Infarction	**0.3**	**--**	**0.1**	**--**
Stroke	**2.2**	**0.2-1.2**	**1.5**	**0.0-0.4**
Death	**0.7**	**0.2-0.5**	**0.4**	**0.0-0.1**

**Dispensed Total Prescriptions (TRX) by demographic segments obtained from IMS HEALTH, National Prescription Audit Plus™. Age distributions were obtained from IMS Health, National Disease and Therapeutic Index™. Includes 28 average days on therapy assumed for all hormonal contraceptives evaluated. < CLEARED BY IMS HEALTH November 2005 >*

***Adjudicated events reported to FDA Adverse Events Reporting System (AERS)*

**** PY = Person/prescription years of exposure, estimated from the use data*

It is not possible to obtain precise estimates of the absolute or relative risk of thrombotic and thromboembolic events using data in the AERS database because of a number of factors. Among these are under-reporting of adverse events, imprecise data on the number of women at risk, and often limited data about comorbid conditions and concomitant medications that may have affected the reported cases. Reliance on voluntary reporting of events to FDA to compare reporting rates for thrombotic events across CHCs became more challenging as concerns about the safety of Ortho Evra were reported in the media. It was unclear whether the increase in reported events was related to an increased awareness of safety concerns, particularly for younger women, or whether the reports reflected a true increase in risk with the transdermal product. Because of these limitations, the FDA requested that the manufacturer conduct an epidemiologic study to better assess the risk of thrombotic and thromboembolic events in users of Ortho Evra.

4.1.2 Overview of Common Epidemiologic Study Designs

For the purposes of this review, the following epidemiologic designs will be discussed.

A **cohort study** starts by identifying subjects who have been exposed or not exposed to CHCs as a possible cause of the disease outcome. After exposed subjects are selected, they are followed in time to observe the frequency (incidence) with which they develop the disease outcome. Because these studies are often population-based, they allow calculation of the incidence of the disease outcome. The ratio of the incidences observed in the exposed and non-exposed cohorts is called the **Relative Risk**. This design is useful for evaluating the effects of a given exposure and can identify a number of different disease outcomes that may be related to an exposure. The FDA-funded study uses a cohort design.

In contrast, **case-control studies** first identify subjects with and without the disease outcome of interest, and then look back in time to see if the subjects had different rates of exposure to CHCs. Because all cases, by definition, have the disease, these studies do not provide reliable estimates of the incidence of the disease in the study population. The comparative risk estimate they use to assess the association of risk factors under consideration (in this review, the association between CHC exposure related to risk of VTE or ATE) is called the **Odds Ratio**. Under certain conditions, the Odds Ratio is a good approximation of the Relative Risk. This design is useful for evaluating risk factors associated with a given disease, including drug therapies.

Nested case-control studies are something of a hybrid design. In a nested case-control study, cases and controls are identified from a cohort of individuals exposed to the CHCs of interest to explore additional factors that might predict risk, including exposure. Cases, therefore, are identified not at the time of entry into the study, but as events of interest that occur while the cohort is followed through time. Controls are selected at the time a case is identified. Controls could later become cases if they subsequently experience an event of interest. Incidence rates are readily calculated using the cohort design. The risk estimates represented by odds ratios in the nested case-control analysis usually align closely with the relative risk estimates from the incident cohort analysis, as long as all cases and representative controls are included.

Although both the i3 Ingenix and the BCDSP studies are reported as nested case-control studies, in fact, cases and controls were selected based on whether the subjects were current users of the study CHCs. Both study protocols are unclear as to how the exposure cohorts were created.

4.1.3 Epidemiologic Studies about Ortho Evra

Several studies conducted after Ortho Evra approval provide data about the risk of VTE and other thrombotic and thromboembolic events in Ortho Evra users compared to users of various CHCs. These studies are summarized in Appendix A. Four were initiated and/or submitted to FDA by the Sponsor. Based on the FDA's request, the manufacturer of Ortho Evra initially funded two epidemiologic studies, both of which were based on information in claims databases (see Section 4.2.2). Because of concerns that the increased exposure to EE (compared to COCs with 30-35 μg of EE) might increase the risk of VTEs in users of Ortho Evra, both of these studies were designed to compare Ortho Evra to COCs that contained 35 μg of EE and the progestin NGM (the precursor of the progestin in Ortho Evra). In 2006, at the request of the EMA, the Sponsor funded an additional epidemiologic study in which Ortho Evra was compared to COCs that contained 30 μg of EE and the progestin LNG, rather than NGM. This study, which provided results characterized by the investigators as "not consistent with any of our previous studies on this subject" was followed by another study using LNG as a comparator in a different database.

FDA, however, had concerns about the ability of the manufacturer's epidemiologic studies to identify all VTEs, ATEs and deaths (including sudden deaths) and the study methods proposed to evaluate the most common thrombotic and thromboembolic events with this product. In addition, examining drug utilization data, FDA noted that use of certain recently approved products, including Ortho Evra, was increasing in the Medicaid population, and became interested in the prescribing patterns, and possible patient behaviors that could affect risk. The FDA subsequently initiated a study to allow exploration of these issues for several CHCs, including Ortho Evra.

Sponsor-funded Studies

The Sponsor contracted with two groups of investigators to perform the studies. Using the UnitedHealthCare database, the i3 Ingenix study compared the risk of VTE, myocardial infarction (MI), and ischemic stroke (IS) and death between users of Ortho Evra and users of COCs that contained NGM and 35 μg of EE; this study was able to validate cases identified by claim codes with information from the medical charts.

The Boston Collaborative Drug Surveillance Program (BCDSP) study also evaluated non-fatal idiopathic VTE, MI and IS, comparing Ortho Evra users in the PharMetrics database to users of a COC containing NGM and 35 μg EE; no chart review confirmation of cases was possible for this study.

Two additional BCDSP studies compared non-fatal idiopathic VTE risk between new Ortho Evra users and new users of a LNG-containing COC that also contained 30 μg of EE; the two analyses differed in that they drew their study populations from two different claims databases (PharMetrics/IMS and MarketScan). These two studies were reported in a single publication[10]. Again, no chart review confirmation of cases was possible for these studies.

These four studies have generated several publications for the i3 Ingenix study[11, 12] and for the BCDSP studies[10, 13, 14, 15, 16].

FDA-funded Study

The FDA-funded study[17] was conducted at two HMO sites (Kaiser Permanente Northern and Southern California) and two state Medicaid programs (Tennessee and Washington), each associated with an academic institution. This cohort study was designed to assess the risk for VTE, MI and IS for various recently approved study contraceptives (including Ortho Evra) vs. a composite of frequently prescribed products that contained the progestins LNG, norethindrone, or NGM combined with 20 μg to 35 μg of EE. This study was also able to validate cases identified by claims codes with information from the medical charts including outpatient deep vein thromboses (DVTs) at a single site.

4.2 Details of Manufacturer- and FDA-funded Epidemiologic Studies

4.2.1 Study Objectives

Sponsor-funded Studies

The objectives for the both the i3 Ingenix study and the BCDSP study using a NGM comparator were to:

1. Estimate the relative risks of AMI and IS combined in current users of Ortho Evra compared to current users of COCs that contained NGM and 35 μg EE, with special

attention to duration of use of the treatment that the subjects were on just before the adverse event occurred.

2. Estimate the relative risks of other endpoints (VTE, IS, and AMI) separately in current users of Ortho Evra compared to current users of the NGM-containing COC, with special attention to duration of use of the treatment that the subjects were on just before the adverse event occurred.

The objectives for the two nested case-control BCDSP studies using a LNG comparator were to:

1. Estimate the relative risks of non-fatal idiopathic VTE (DVT and PE) in new users of Ortho Evra compared to new users of COCs that contained LNG and 30 μg EE.
2. Conduct a stratified analysis to estimate the risk of VTE in new users compared to non-new users by calendar year.

FDA-funded Study

The objectives of the FDA study were to:

1. Determine prevalence and incidence rates for VTE and ATE and all-cause and cause-specific mortality in women exposed to three relative new hormonal contraceptives (Ortho Evra, Yasmin or its generic equivalent, and NuvaRing) compared to older frequently prescribed low estrogen hormonal contraceptives containing the progestins LNG, NGM, or norethindrone (this phase has been completed and is described here).
2. Identify medical, pharmacological, and behavioral characteristics from claims and medical records to assess predictors of increased risk for VTE, ATE, and death (to be completed at a later date, if possible).

4.2.2 Population Sources

Sponsor-funded Studies

The population sources varied over studies

Ingenix

The i3 Ingenix group evaluated thrombotic and thromboembolic risks of Ortho Evra compared to NGM-containing COCs using their proprietary Normative Health Information (NHI) database (also referred to at different periods of the study as the Research DataMart [RDM] and UnitedHealthCare [UHC] in the published manuscripts and submitted reports). This healthcare database captures health insurance claims from large US commercial health insurers and affiliates that generate data for payment of healthcare services. Importantly, this database contains identifying information that allows the investigators to verify outcome with medical charts and is linkable to death files

BCDSP

The BCDSP group evaluated thrombotic and thromboembolic risks of Ortho Evra compared to NGM-containing COCs using the PharMetrics/IMS database (referred to as PharMetrics for the remainder of this review). The later studies of Ortho Evra compared to LNG-containing COCs used the same PharMetrics database in one study and the MarketScan database in the other.

Both the PharMetrics and the MarketScan* databases contain longitudinal information on US covered lives, mostly those younger than age 65 years of age.

PharMetrics data are generated by managed care and other health plans throughout the US. MarketScan data are generated by large self-insured employers and a smaller number of health insurance plans. Both databases contain information on pharmaceuticals, medical services (with diagnoses recorded) and procedures, as well as demographic information on all subjects. Both databases, however, contain de-identified records, which at the time of the study, were not linkable to other US databases and did not allow for obtaining medical records for verification of events.

FDA-funded Study

The FDA-funded study included two HMO sites (Kaiser Permanente Northern and Southern California) and two state Medicaid programs (Tennessee and Washington), each associated with an academic institution. Kaiser Permanente maintains computerized files of eligibility, outpatient visits, hospitalizations, medical procedures, emergency room visits, laboratory testing, and outpatient drug prescriptions for all its members. Mortality information, including underlying cause of death as recorded on death certificates, is periodically updated with data obtained from the California Department of Health, Center for Health Statistics**.** Tennessee Medicaid (TennCare) is an expanded version of the joint federal-state Medicaid program that finances medical care for qualifying low income persons. The TennCare data are contained in several different files that include filled prescriptions, inpatient admissions, outpatient visits, and other types of care. The Washington State Medicaid program is similar to that in Tennessee.

4.2.3 Study Time Period

Sponsor-funded Studies

The time period initially evaluated for the i3 Ingenix study was April 1, 2002 through December 31, 2004, with a subsequent extension of the study through December 31, 2006.

For the BCDSP study that compared Ortho Evra with NGM-containing COCs, the initial analyses included users from April 1, 2002 through March 31, 2005. The extensions were completed incrementally. The first update encompassed the time period from April 1, 2002 through September 2006; the second update included the time period from April 1, 2002 through October 31, 2007.

The PharMetrics analysis comparing Ortho Evra with LNG-containing COCs spanned the time period from April 1, 2002 through March 31, 2006. The MarketScan analysis comparing Ortho Evra with LNG-containing COCs spanned the time period from April 1, 2002 through December 31, 2007.

FDA-funded Study

The time period for the FDA-funded study was January 1, 2001 through December 31, 2007.

4.2.4 Study Population

Women who were 15 to 44 years of age as of April 1, 2002 were considered for both Sponsor-funded studies comparing Ortho Evra to NGM-containing COCs. The FDA-funded study

* *MarketScan, Commercial Claims and Encounters (CCAE) owned by Thomson Healthcare's, Medstat Division*

included women age 10 to 55 years. Cases and controls in the Sponsor-funded studies and current users in the FDA-funded study were required to have six months of continuous enrollment in the database prior to the index date. All studies excluded women with cancer other than non-melanoma skin cancer and other diseases noted below.

4.2.5 Entry Criteria

The i3 Ingenix and the BCDSP studies used the same basic design, but with some differences. Both initially identified all possible outcomes of interest that occurred during the study time period among women who were ever exposed to Ortho Evra or NGM-containing COCs.

Sponsor-funded Studies

Ingenix

Additional selection factors included:

- Possible cases of VTE (DVT and PE), AMI, IS and other thromboembolic events were identified using broad claims (ICD9, CPT, and HCPCS) codes, relevant diagnostic tests, and anticoagulant therapy to identify possible inpatient and outpatient DVTs and PEs. These cases were initially reviewed by clinicians to assess the probability of being an incident case based on the chronology of occurrence. Final selected cases were confirmed by review of medical records.
- Inclusion as a case or a control required six months of enrollment in the database before the case index date (the date the relevant event occurred) and exposure to one of the study drugs (Ortho Evra or NGM-containing COC) in the six months before the index date. Current use was defined as having a study drug dispensed on the index date; and recent use was defined as having a supply of study drug in the prior six months but not as recently as the index date.
- Deaths were identified based on inpatient discharge codes and codes indicative of demise, such as those for ambulance services, resuscitation, cardiac arrest followed by complete cessations of services. The study also linked records to the NDI database for the years for which NDI information was available; in actuality, this only included the records of women identified between 2002 and 2006 who disenrolled prior to the end of 2006.
- Chronologically plausible incident cases were verified with information available from the medical charts

BCDSP

In addition to baseline exclusion criteria that were similar to those used in the i3 Ingenix study, the BCDSP selected only non-fatal, idiopathic cases for evaluation. Both cases and controls had to have six months of enrollment and had to be current users of the study contraceptives. Cases were also identified using more rigorous selection criteria than those employed by i3 Ingenix because, due to the de-identification of the cases, they could not be validated using medical charts.

- Cases were women with codes for VTE (DVT or hospitalized PE) at any time during the study period who also had a subsequent claim for an anticoagulant and evidence of stopping the study contraceptive after diagnosis. Only idiopathic cases (those without known risk factors for VTE) were included in the study. Therefore, potential cases with

history of anticoagulant medication, recent major surgery, trauma, epilepsy, or pregnancy were excluded.

- IS cases were defined as having an ICD9 code during the study period and who were hospitalized. Potential cases with treated hypertension, diabetes, angina, congestive heart failure, cardiac dysrhythmias, or other chronic heart disease were excluded, as were cases with recent major surgery, trauma, or pregnancy.
- AMI cases were those with ICD9 codes for acute myocardial infarction or acute coronary revascularization who were hospitalized. Potential cases with treated hypertension, diabetes, angina, congestive heart failure, cardiac dysrhythmias, or other chronic heart disease were excluded, as were cases with history of anticoagulant medication, epilepsy, recent major surgery, trauma, or pregnancy.

For the i3 Ingenix and BCDSP studies, four controls per case were selected. Controls with the same birth year were randomly selected from all cohort members enrolled at the case index date who were at risk of becoming a case following the case index date. Controls had the same inclusion (current use of Ortho Evra or NGM-containing COC at the case index date) and exclusion criteria (history of anticoagulant medication, recent major surgery, trauma, epilepsy, or pregnancy) imposed as the case.

FDA-funded Study

Because the FDA-funded study was designed as a cohort analysis, the study entry criteria were applied to create the exposure cohort. A woman was excluded if she had evidence of a serious or life-threatening illness (sickle cell disease, cystic fibrosis, cerebral palsy, cancer, HIV, organ transplant, liver failure, severe congestive heart failure, renal failure, respiratory failure, or hospitalization for AMI, stroke, or VTE) during the six-month pre-exposure eligibility period. Criteria for these illnesses included inpatient claim(s) for the illness.

4.2.6 Exposure Definitions

All studies reviewed evaluated thrombotic and thromboembolic risk in current users of study contraceptives, although some studies also captured information on past, or former, use.

Sponsor-funded studies

In case-control studies, exposure is the outcome of interest. However, both studies selected cases and controls based on their current and recent use of only two specific products, Ortho Evra and the comparator, as the exposure (i.e., rather than evaluating the risk of any type of CHC exposure). All other contraceptive use, including no use, was ignored. No information is presented as to whether this design would provide similar results to a stratified nested-case control analysis.

Both studies have similar definitions of current and recent use around the index date:

- Current use was defined as having a recorded claim for a study contraceptive whose filled use extended to within 28 (Ingenix) or 30 (BCDSP) days before the index date of the event or beyond the index date.
- Recent use was defined as having a recorded claim for a study contraceptive whose filled use ended in the 90 day time period prior to the current use period (as defined above). These women had claims that suggested they had been exposed to the CHC within the

four months preceding the event, but not within the month immediately preceding the event.

For the i3 Ingenix group, it is possible that the new prescription received by a woman for the NGM product soon after the study start date of April 1, 2002 could still be a renewal of a prescription for one that expired just prior to the start of the study. Thus, although they appeared to be new users (because their subsequent prescription was written after the study start date), they actually were continuing users. However, because Ortho Evra was a newly marketed product at the time the study started, women could not have been using it prior to the study start date.

This was handled differently in the BCDSP, which employed a definition that required that subjects have no study CHC use for 120 days (four months) prior to the study start date, although this definition was later eased in the 2nd update. Women using Ortho Evra and NGM-containing COCs in the BCDSP study had to have a new prescription filled no earlier than April 1, 2002, with evidence of no study contraceptive fill in the preceding four months. The implication of these decisions, which likely resulted in including women with a different duration of exposure, is discussed further in Section 4.4.2.

Although not restricting NGM use completely to new use, the i3 Ingenix investigators did capture information on a) non- or past-use (past use defined as time after "recent use" had ended), and b) switching products used and exposure to non-study contraceptives in the six months prior to the index date. The first report from this group further classified exposure to allow the analyses to be restricted to new users or adjusted for type of exposure. These additional classification variables were:

1. New Initiator: no exposure to **any** hormonal contraceptive in the four months before the start of the course of therapy
2. Switcher: exposure to any other non-study hormonal contraceptive in the four months before the start of the course of therapy
3. Unknown: no apparent exposure to any hormonal contraceptive, but information about exposure was not known for the full four months before the start of the course of therapy
4. Interrupted: a break in the use of a contraceptive for more than 28 days in the four months before the start of the course of therapy, followed by resumption of the same drug

FDA-funded Study

In the FDA-funded study[17], exposure was used to create the study cohorts and not evaluated as a study endpoint. Two exposure cohorts were created. The first was a cohort of prevalent users, where exposure was defined as having a prescription filled for a study CHC during the study period. A subject could appear in multiple cohorts of current users as long as the study eligibility criteria were met. The new user cohort, however, was restricted to subjects who had a new study CHC filled during the study period, with documentation of no CHC fills (whether of a study CHC or a non-study CHC) in the prior six months. No re-entry was allowed in the new user cohort (i.e., subjects could be classified as new users only once); as soon as subjects began using a study CHC, even if they later discontinued and then restarted or switched to a new study CHC, they were no longer considered to be new users. Incident cases were identified only during an

episode of current use. Current use was defined as the exposure period that began with the fill date of the CHC prescription and continued through 42 days after the end of the prescription.

4.2.7 Analyses

Sponsor-funded Studies

Both Sponsor-funded study groups analyzed study results using conditional logistic regression analyses conditioned on the variables used to match cases and controls (index date and year of birth). I3 Ingenix also adjusted for initiator status. Covariates were considered for inclusion if including them in the model produced more than 10% change in the estimate, but no covariate reached that level in either study and therefore none were included as adjustments.

Ingenix

The i3 Ingenix investigators completed a staged analysis of claims-derived information on outcomes and risk factors[18], claims-derived risk factors with chart-verified outcomes[19], and finally claims and chart-derived risk factors with chart verified outcomes[20]. This last analysis included linkage to NDI information[21]. The same sequence of analyses was repeated for the two-year update[22]. Both the internal and published reports presented information on VTEs and ATEs as requested by the FDA.

BCDSP

The BCDSP investigators, on the other hand, did not have the capability to validate outcome with charts nor could they link to the NDI. They completed the initial Ortho Evra and NGM-containing COC VTE analyses in 2005 and published them in 2006[23, 13].

This group also completed in 2009 and published[10] in 2010 an analysis comparing Ortho Evra with LNG-containing contraceptives using both the PharMetrics and the MarketScan databases. Information on ATEs was summarized in a published manuscript in 2007[15] and in an updated report[24].

FDA-funded Study

The FDA-funded study analyzed the hazard of developing VTE, AMI or IS using a Cox Proportional Hazards model that adjusted for age, site, and calendar year. The study calculated the Hazard Ratio (HR) for these outcomes for Ortho Evra vs. two different comparison groups; one included LNG-, NGM- and norethindrone-containing COCs and one included only LNG-containing COCs that had 30 μg of EE. Incidence data were calculated using the Poisson Regression Model.

4.3 Summary of Results

4.3.1 VTE Risk

The relative risk values reported in the Ortho Evra label (Table 1) were based on only idiopathic cases for all four studies. FDA chose to report these estimates because they allowed comparison of risk estimates over the different studies that were based on similar case definitions. Because the BCDSP studies included only idiopathic cases, this was the common case definition that could be used.

Results for the four Sponsor-funded studies and the FDA-funded study are shown in Table 13.

Table 13 Relative Risk of VTE for Ortho Evra Users in the Various Studies

Study/Database	Comparator	Relative Risk	95% CI
I3 Ingenix[12]	NGM	2.0[a]	1.2-3.3
BCDSP, PharMetrics	NGM	1.2[b]	0.9-1.8
BCDSP, PharMetrics	LNG	2.0[c]	0.9-4.1
BCDSP, MarketScan	LNG	1.3[d]	0.8-2.1
FDA	LNG, NGM, NETA	1.6[e]	1.2-2.1
FDA	LNG[f]	1.3[e]	1.0-1.8

NGM = norgestimate; NETA = norethindrone acetate

[a] Approximated by odds ratio, for chart-verified cases, idiopathic and non-idiopathic, based on all pooled data from all phases of the study

[b] Approximated by odds ratio for nonfatal, idiopathic cases, based on pooled data from all phases of the study

[c] Approximated by odds ratio for idiopathic VTEs

[d] Approximated by odds ratio for idiopathic and non-idiopathic VTEs

[e] Approximated by hazard ratio for All Users adjusted for age, site, and year of study entry, based on all VTEs (inpatient and outpatient)

[f] LNG-containing COCs with 30 μg EE

As noted by the odds ratios for idiopathic cases that was reported in labeling, as well as the published data based on all cases, the Sponsor-funded i3 Ingenix study found a twofold increased risk of VTE among Ortho Evra users compared to users of a COC containing NGM and 35 μg EE. In contrast, the results from the BCDSP NGM study found no increased risk for non-fatal, idiopathic VTE among Ortho Evra users.

The BCDSP also reported results of the analyses from two databases that compared Ortho Evra with LNG-containing COCs that also contained 30 μg EE. These analyses reported lower odds ratios than those reported by i3 Ingenix and the confidence intervals all included 1, suggesting no increase in risk.

The FDA-funded study reported that the HR for VTE for All Users of Ortho Evra was increased compared to either the comparator group of four COCs or to LNG-containing COCs with 30 μg EE.

4.3.2 ATE Risk

The relative risk of ATE events in the Sponsor-funded i3 Ingenix and the FDA-funded studies are displayed in Table 14. No studies found an increased risk of ATE for Ortho Evra users.

Table 14 Relative Risk of ATE for Ortho Evra Users in i3 Ingenix and FDA Studies

Study/Database	Comparator	Relative Risk	95% CI
I3 Ingenix[12]	NGM	0.9[a]	0.3-2.5
FDA	LNG, NGM, NETA	1.0[b]	0.6-1.7
FDA	LNG[c]	0.8[b]	0.5-1.4

NGM = norgestimate; NETA = norethindrone acetate

[a] Approximated by odds ratio for AMI and IS combined

[b] Hazard ratio for All Users adjusted for age, site and year of study entry

[c] LNG-containing COCs with 30 μg EE

The number of ATE (AMI and IS) cases in the Sponsor-funded studies was very small and risk estimates could not be reliably calculated. In the LNG MarketScan study, the BCDSP investigators merely listed the AMI cases but did not attempt to estimate risks.

The FDA-funded study did not show an increased risk of ATE for All Users or New Users of Ortho Evra whether they were compared with all comparator COCs or the LNG comparator. However, the number of cases also was very small, so it is possible that there was not sufficient statistical power to examine this outcome.

4.4 Study Differences and Methods Issues

The similarities and differences between the different studies have been highlighted in the previous sections of this summary. Beginning with the initial BCDSP results that showed no increased risk of VTE, discussions among the investigators, the Sponsor, and the Agency concerning the study methods have provided valuable information. This section will discuss some of these issues.

4.4.1 Design: Cohort, Incidence, Case-control, and Nested Case-control

The Sponsor initially proposed to use a nested case-control design for both the i3 Ingenix and BCDSP NGM studies to evaluate the risk of ATE and VTE among women using Ortho Evra compared with women using NGM-containing COCs. As described in Section 4.1.2, in a nested case-control study, the initial study population consisted of a cohort of individuals exposed to the CHC of interest. Cases and controls were later identified as events of interest occur while the cohort is followed through time.

In the Sponsor-funded studies, however, cases and controls were selected from a population of women 15 to 44 years of age who were current or recent users of the specific study contraceptives anytime between April 1, 2002 and December 31, 2004 (without necessarily first creating an exposure cohort). FDA had a real concern as to whether incidence rates obtained with this method would be representative of true incidence rates because only cases and controls with current or recent exposure to the study CHC were included. The exposure of women who stopped study CHCs as well as women exposed to non-study CHCs or who did not have current or recent CHC exposure was ignored. FDA had concerns about limiting cases and controls to current Ortho Evra and NGM-containing COC users[25] and requested the Sponsor to provide claims-based and medically verified ATE and VTE incidence rates.

The investigators did provide crude incidence rates with the first reports submitted to the Agency and in the initial published manuscripts[11, 13] for the NGM studies done by i3 Ingenix and BCDSP, although it remains unclear how these rates were derived. No overall updated Ortho Evra/NGM-containing COC incidence rate information was provided in the final reports for the updates. BCDSP included incidence rates when comparing Ortho Evra with LNG-containing COCs in the PharMetrics and MarketScan analyses and incidence rates by age and contraceptive type in their 2007 report.

Table 15 displays the incidence rates, the incidence rate ratios (IRRs) and the odds ratios or hazard ratios derived from the different studies. This table demonstrates that, despite variation between studies in the incidence rates, which are likely related to differences in methodology and case and exposure definitions, the relative risk estimates (i.e., IRRs, ORs, or HRs) remain relatively consistent across studies.

Table 15: Incidence Rates per 10,000 person-years, Incidence Rate Ratios, and Relative Risks of Idiopathic VTEs

	ORTHO EVRA		NGM COC		Relative Risk Results^			
Study/Database	**Incidence**	**95% CI**	**Incidence**	**95% CI**	**IRR***	**95% CI**	**OR****	**95% CI**
I3 Ingenix, 2007	4.1	2.5-6.3	1.8	1.3-2.0	2.2	1.3-3.8	2.1	1.0-4.0
BCDSP PharMetrics, 2006	5.3	3.6-7.6	4.2	2.9-5.8	1.1	0.7-1.8	0.9	0.5-1.6
	ORTHO EVRA		**LNG COC**		**Relative Risk Results**			
	Incidence	**95% CI**	**Incidence**	**95% CI**	**IRR**	**95% CI**	**OR****	**95% CI**
BCDSP PharMetrics, 2010	5.6	3.9-8.0	3.8	2.3-6.2	1.5	#	1.9	1.1-3.3
BCDSP MarketScan, 2009, 2010	2.5	1.9.-3.4	2.0	1.5-2.6	1.3	0.9-1.9	1.3	0.9-1.8
	ORTHO EVRA		**COMPARATOR COCs†**		**Relative Risk Results**			
	Incidence	**95% CI**	**Incidence**	**95% CI**	**IRR***	**95% CI**	**HR*****	**95% CI**
FDA Study, All Users	10.7	#	5.9	#	2.5	1.9-3.2	1.6	1.2-2.1
FDA Study, New Users	19.0	#	8.4	#	2.1	1.4-3.0	1.4	0.9-2.0
	ORTHO EVRA		**LNG COC**		**Relative Risk Results**			
	Incidence	**95% CI**	**Incidence**	**95% CI**	**IRR***	**95% CI**	**HR*****	**95% CI**
FDA Study, All Users	10.7	#	6.5	#	2.3	1.7-3.1	1.3	1.0-1.8
FDA Study, New Users	19.0	#	9.1	#	2.1	1.4-3.2	1.2	0.8-1.9

CI = Confidence Intervals; IRR = incidence rate ratio; OR = odds ratio
NGM – norgestimate-containing contraceptive; LNG = levonorgestrel-containing contraceptive
^ Depending on the design of the study, the relative risk may be best approximated by the IRR, the OR, or the HR
** Age adjusted Incidence Rate Ratios provided for the NHI studies and the FDA study.*
*** Matched on year of birth and index year.*
**** Adjusted for age, site, and calendar year*
† Includes NGM, norethindrone, and LNG products that also contain 20-35 µg of EE
 # Confidence intervals not specified

For all studies, the incidence rates were higher for Ortho Evra than for the comparator contraceptive. The incidence rates observed in the MarketScan database were lower than those observed in the PharMetrics database, although, more importantly, the risk ratios were similar. Due to the methodology used, the comparable age- and site-adjusted incidence rates per 10,000 person years in the FDA-funded study were generally twice as high as those reported for the Sponsor-funded studies. While the IRRs for All Users were similar to the age-adjusted ratios in the i3 Ingenix study, the adjusted relative hazards were lower than the odds ratios reported by i3 Ingenix.

Based on these data, age-adjusted incidence rates reported from an exposure-based cohort study of currently exposed women (the FDA study) were generally higher and possibly more inclusive than when the information was obtained using an exposure cohort assembled after case selection from a population-based case-control design (the Sponsor studies). The differences seen in the two BCDSP analyses that use a similar study design, but different population sources (PharMetrics and MarketScan) underscore the importance of considering the contribution of population differences in a study. This is further supported in the FDA study, where nearly 65% of Ortho Evra use was in the Medicaid population. The VTE risk for All Users was lower in the Medicaid population (HR 1.4; 95% CI: 0.9-2.0) than in the population from the Kaiser sites (HR 2.1; 95% CI: 1.4-3.2), as discussed in Section 4.4.6.

Comment

Differences in results obtained from exposure-based cohort designs compared to case-control designs need further evaluation. Differences across studies may also be related to differences in the populations included in the study. With today's increased computing power, evaluating whether differences exists between these two designs and population characteristics should be possible.

4.4.2 Exposure – Current Users vs. New Users and Switchers

Although both of the initial Sponsor-funded studies evaluated thrombotic and thromboembolic risks associated with current and recent exposure to Ortho Evra and NGM-containing COCs, the BCDSP investigators imposed a new-user design for both Ortho Evra and NGM product. Eligible subjects could have no claim for a study contraceptive in the four months prior to the index date.

The i3 Ingenix investigators did not require that NGM be restricted to new initiators although the fact that Ortho Evra was a newly approved product meant that women having initial use of Ortho Evra were new initiators of this product. This was not the case for NGM-containing COCs. To control for use, in addition to age and index year, the i3 investigators adjusted for initiator status. A new initiator was defined as having no claim for any contraceptive in the four months prior to the index data, a definition that differed from the BCDSP definition, which classified new users based only on their lack of prior use of study contraceptives. In addition, the i3 Ingenix investigators examined the risks for each exposure group separately.

In the final report[26] of the Ortho Evra/LNG studies, the BCDSP investigators also examined the results among naïve and non-naïve users, where non-naïve users were defined as having four months of prior contraceptive history in their records and naïve users had no history. Although the definitions of new/naive user or initiator vary across studies and population sources, a comparison of the associated VTE risks and results is summarized in Table 16.

Table 16: Comparison of Risk Estimates for Ortho Evra for VTE by Study and New Use Status

Data Source	Risk Estimate	95% CI	Database (Comparator)
Overall Study Population			
Studies – Published Results			
i3 Final Report 2010[12] All Users	2.0*	1.2-3.3	UHC (NGM)
BCDSP Final Combined 2007[14] Idiopathic cases only	1.0*	0.7-1.5	PharMetrics (NGM)
Studies – from Study Reports			
FDA-Funded Study[17] All Users	1.6†	1.2-2.1	Kaiser + Medicaid (COMP)
Initiators or New/Naïve Users			
Studies – From Study Reports			
i3 Initiators[22] June 23, 2009	1.8**	0.8-3.8	UHC (NGM)
BCDSP All Naïve+ Users 2009[26]	1.4**	0.8-2.3	MarketScan (LNG)
FDA-Funded Study[17] New Users‡	1.4‡	0.9-2.0	Kaiser + Medicaid (COMP)
Not-New and Not-Naïve Users			
Studies – From Study Reports			
I3 Final Report[22] June 23, 2009	2.2**	1.1-4.5	UHC (NGM)
BCDSP Not-New User[24] May 20, 2008***	2.4**	1.2-5.0	PharMetrics (NGM)

** OR, Matched on year of birth, index year for both studies and initiator status for the i3 Ingenix study.*

† HR, All users defined as having a new prescription during the study period; matched on age, site and calendar year.

COMP = NGM-, LNG- and NETA-containing COCs

*** OR, Adjusted for year of birth and index year*

+ Naïve User = Users with at least 4 months of history in the database prior to their first study drug.

‡ HR,' New user defined as having a first prescription during the study period and no prior contraceptive use in the six months prior to first use; matched on age, site, and calendar year

****Update exposures not limited to women who had 4 months study contraceptive-free period*.

Adjusted or matched VTE risk among non-new users appears to be higher than that in new users in both Sponsor-funded studies regardless of comparator used (OR 2.2-2.4 vs. OR 1.4-1.8). Although the relative hazard ratios are lower in the FDA-funded study compared to the odds ratios in the Sponsor studies, All Users (HR: 1.6) are also seen to be at higher risk compared to New Users (HR: 1.4) but the differences are small.

It is unclear whether switchers contribute to the increased VTE risk associated with non-new (non-naïve) users in the studies or whether this group includes a mix of switchers and lower-risk survivors. All studies captured information on switchers, and the i3 Ingenix group adjusted for initiator status. The BCDSP study did not adjust for switching in the analysis, and it is unclear how they incorporated this information and what contribution switching made to their analyses. Another study (not discussed in this review) suggested that switchers, particularly switchers

following a break in contraceptive use, appear to be at increased VTE risk. Therefore, if users are predominantly switchers when a new contraceptive such as Ortho Evra is introduced into the market, the potentially higher risk estimates for switchers is likely to influence the overall risk estimates found. The differences between new user and non-new users reported by the studies may be related to other unmeasured factors not adequately characterized, or factors not completely controlled.

Comment

Although the definitions used are not truly comparable, information on risk by user status provides valuable insight in explaining differences observed across studies. When exposure definitions are more closely aligned between studies, reported risk estimates are surprisingly similar and differences disappear. Whether the confidence intervals include or excludes 1 depends almost entirely on the number of users in the groups being compared.

4.4.3 Claims Only vs. Validated Risk Estimates

The i3 Ingenix study initially explored differences in risk estimates using cases identified only by claims codes and later used validated cases as the basis for the analysis. All reported VTE risk estimates for cases and controls, matched on year of birth and index year, are shown in Table 17.

The i3 Ingenix investigators were able to verify most cases with medical charts ("chart verified" in Table 17) and to verify some covariates as well ("subset" in Table 17.)

Of the 1,487 potential AMI, IS, or VTE events that occurred in the population from which the i3 Ingenix nested case-control study was drawn, 400 events (192 patients) met study eligibility criteria. Of these, medical records for 290 (73%) were successfully abstracted. The positive predictive value (PPV) for the VTE claims identification was 91%. The PPV was only 83% in the FDA-funded study. In other studies, the PPV has been reported to be as high as 99%[27]. In the i3 Ingenix study, however, only 16 of the possible 111 AMI (14%) and 19 of the 68 strokes (27%) were confirmed.

Risk estimates for VTE are presented in Table 17. Results based on validated cases demonstrate a trend that the risk estimates increase but the confidence intervals widen, likely due to the decrease in the number of cases and controls. Therefore, results reported in studies that validate codes with medical records are likely to report higher VTE risk estimates than studies reporting only claims-based cases. However, the BCDSP VTE case definition is more specific than merely using ICD9 claims codes.

Table 17: i3 Ingenix Analyses: Risk of VTE by Case Claims-based and Chart Verified Definition

	OR	95% CI
Claims codes*	1.6**	0.9-2.9
Chart Verified	2.1	1.0-4.1
Revised 2006 Final Report	2.0	1.0-4.0
Case & Covariate Chart Abstracted Subset	3.1	1.1-8.7

OR = odds ratio; CI = confidence interval

** Includes claims associated with diagnostic codes for other arterial, ocular, and venous sinus thrombotic events.*

*** Odds ratios from conditional logistic regression; adjusted for essential hypertension, hyperlipidemia/hypercholesterolemia, diabetes mellitus, obesity/abnormal weight gain, cardiac dysrhythmias, CYP 3A4 inhibitor use*

4.4.4 Fatal Thrombotic and Thromboembolic Cases

To identify all possible cases, records of all women in the study population who disenrolled from the health plan prior to December 31, 2006, and who did not have evidence of subsequent re-enrollment were linked to the NDI database in the i3 Ingenix study. The NDI search identified 20 fatal AMIs, four (20%) not previously identified and 113 fatal VTEs, only five (4%) of which were not previously identified. No deaths occurred in the Ortho Evra-exposed group. Inclusion of these deaths in the analysis did not change the risk estimates significantly.

The FDA-funded study was the only other study to attempt to identify deaths not captured by the medical system. The sites in this study, however, were able to link directly to state vital statistics on an ongoing basis and matching accuracy is likely more robust. Nonetheless, the results were similar to the i3 Ingenix NDI search in that very few additional cases were identified.

Comment
Making the effort to identify deaths not captured by claims information does not appear to change the risk estimates significantly.

4.4.5 Case Restrictions – Idiopathic vs. All Cases

The BCDSP investigators restricted their analyses to idiopathic thrombotic and thromboembolic events, whereas the i3 Ingenix investigators included all validated events but analyzed the idiopathic cases in a secondary analysis. The BCDSP definitions of idiopathic conditions have varied over time as risk factors for VTE are identified, but for the Ortho Evra/NGM study[23], cases with strong risk factors such as use of an anticoagulant medication (indicating past history of VTE), recent major surgery, trauma, epilepsy, or recent pregnancy were excluded. Unless there are differences in the contraceptive options offered to women who experience trauma, pregnancy, surgery, or other concomitant illnesses, there may be no reason to exclude cases based on these high risk conditions. Adjustments during analysis should be able to control for these concomitant high risk conditions. Nonetheless, the BCDSP investigators imposed this restriction in all their CHC studies.

As a result of the discussions surrounding this issue, the i3 Ingenix investigators stratified their analyses and presented risk estimates for VTE and ATE for all cases, and for idiopathic cases (Table 18). The BCDSP investigators also submitted a report that compared the VTE risks for idiopathic cases as well as for all cases when comparing Ortho Evra vs. LNG-containing COC users. The odds ratios for the idiopathic group show either a higher risk or the same risk estimate as for all VTE cases when comparing two hormonal contraceptives but generally the confidence limits are wider, likely due to fewer cases included in the idiopathic group.

Table 18: Risk of VTE by Restricted and Unrestricted Case Definition

	All Cases		Idiopathic Cases Only	
	OR	95% CI	OR	95% CI
I3 Ingenix (Ortho Evra vs. NGM)	2.0	1.2-3.3	2.2	1.2-4.0
BCDSP PharMetrics (Ortho Evra vs. LNG)	1.3	0.9-1.8	1.3	0.8-2.0

OR = odds ratio; CI = confidence interval;

4.4.6 Age

The investigators for the Sponsor-funded studies matched cases and controls on age and index date and analyzed the data using conditional logistic methods. Therefore the effect of age could

not be evaluated in the case-control analyses. Nonetheless, the BCDSP 2005 Final Report presented crude incidence rates stratified by age group, which show a dramatic increase in the incidence of VTE risk by age in both groups:

Table 19: Incidence Rates per 10,000 Women-Years by Age

Age (years)	Ortho Evra	NGM
15 to 29	2.1	3.0
30 to 39	9.5	4.3
40+	18.5	20.7

The BCDSP investigators also published VTE odds stratified by age groups for the Ortho Evra analyses vs. NGM- or LNG-containing COCs using the PharMetrics database and Ortho Evra vs. LNG using the MarketScan database to assess the residual effects of age using case-control pairs matched on index year. When Ortho Evra is compared to LNG (Table 20), the odds ratios show a slightly bimodal distribution with elevated residual effect of age on VTE risk for women younger than 30 years of age and for women 40 to 44 years of age after matching on index date. This was not observed for the Ortho Evra vs. NGM comparisons using the combined estimates of idiopathic cases presented in the 2007 report. The magnitude of risk may be dependent on the case definition; however, the true age effect is difficult to assess in populations matched on year of birth.

Table 20: Odds ratio for VTE Risk by Age Group

	PharMetrics (NGM) Jan 16 2007 combined		PharMetrics (LNG) Jun 15, 2007		MarketScan (LNG) Apr 3 2009	
Age (year)	OR Idiopathic	95% CI	OR All Cases	95% CI	OR All Cases	95% CI
< 30	0.8	0.4-1.5	1.9	0.8-4.3	1.5	0.8-2.6
30-39	1.2	0.6-2.4	1.3	0.5-3.0	1.0	0.6-1.7
40-44	0.9	0.4-2.4	6.9	1.3-37.4	1.5	0.6-3.8

OR = odds ratio; CI = confidence intervals
Note: Cases and controls matched on index year

The FDA-funded study did not match on age but rather adjusted for age in the analyses. The effect of age, therefore, could be evaluated. Investigators chose not to pre-specify the age relationship. Instead, the Cox models were stratified by 5-year age intervals with the exact age included as a continuous covariate in the regression model to provide additional control for potential residual confounding within the age strata. This provided tight control for age, freed the investigators from having to pre-specify the form of the relationship between age and outcomes in the regression models, but also allowed for the independent evaluation of the age effect. This provided important information about the effect of age.

First, the age-specific VTE and ATE incidence rates increased with age for Ortho Evra. This was true for both New Users and All Users although the rates were higher in New Users. Incidence rates in the FDA-funded study were higher than those reported by other investigators.

Secondly, in the FDA-funded study, the mean age for women filling prescriptions for Ortho Evra at all sites combined is lower than the mean age in either of the comparison groups (either the overall comparator group or the LNG comparator group). Generally Ortho Evra users were

younger than women using the comparators (52% vs. 45% of women younger than 25 years respectively). The Medicaid sites also had proportionally more (73%) women age 10 to 24 years compared to the Kaiser sites, and also showed a lower VTE risk compared to those at the Kaiser sites. However, age differences do not likely explain all differences seen in risk estimates.

In the FDA-funded study, which used the Cox Proportional Hazards model, age was adjusted more tightly (five-year age strata and actual age within each stratum) as were site, and calendar year. The FDA-funded study noted a significant interaction with age and study site as well.

Comment

Age is an important confounder in the contraceptive studies and matching on year of birth without additional adjustments or other stratification in the analyses may not sufficiently control for residual confounding. But other confounders may be important also, because age may also be a proxy for other risk factors.

4.4.7 Other Confounders

The risk of VTE may be higher among women with gynecological problems. Of interest, the i3 Ingenix group compared the 2005-2006 VTE risk estimates adjusted for gynecological disorders with the combined 2002-2006 VTE risk estimates that did not include this adjustment. The gynecological (Gyn) disorders used for the adjustment included endometriosis, disorders of menstruation, inflammatory disease of ovary, pelvic, peritoneum, inflammatory disease of cervix, vagina, and vulva, and uterine leiomyoma.

The Gyn-adjusted VTE risk estimate provided in the report was lower (OR 1.5; 95% CI: 0.7-3.6) and no longer statistically significant compared to the overall matched risk estimate for the entire 2002-2006 study (OR 2.0; 95% CI: 1.2-3.3). Although the Gyn-adjusted VTE risk estimate was reported only in a 2005-2006 update, the unadjusted 2005-2006 VTE risk estimates were reported in an interim report[28]. This unadjusted 2005-2006 VTE risk estimates (OR 2.1; 95% CI: 1.2-3.6) does not differ substantially from the published estimates (OR 2.0; 95% CI: 1.2-3.3). Of interest is whether any possible channeling bias (selective prescribing) by providers exists whereby they prescribe CHCs for non-contraceptive benefits that may be afforded by these products and whether these women are independently at increased risk of VTE due to their gynecologic condition.

In further support this concept, the BCDSP investigators provided univariate estimates of the covariates selected for analysis[10]. When comparing currently exposed (Ortho Evra and LNG) cases and controls, the covariate for gynecological disorders (menstrual disorders, endometriosis, uterine fibroids) was associated with a twofold increased risk of VTE in the MarketScan database (OR 2.0; 95% CI: 1.2-3.5). This trend, however, was not seen in the PharMetrics database (OR 1.2; 95% CI: 0.5-3.2).

Finally, none of the claims-based studies, including the FDA-funded study, adjusted for important known confounders such as body mass index (BMI), smoking, personal and family history of VTE, and lifetime use of hormonal contraceptives. The contribution of these covariates to increasing VTE risks needs to be independently assessed. Preliminary analyses of drug use data suggest that Ortho Evra users may have slightly higher BMI than users of other contraceptives; these data are included in Appendix C.

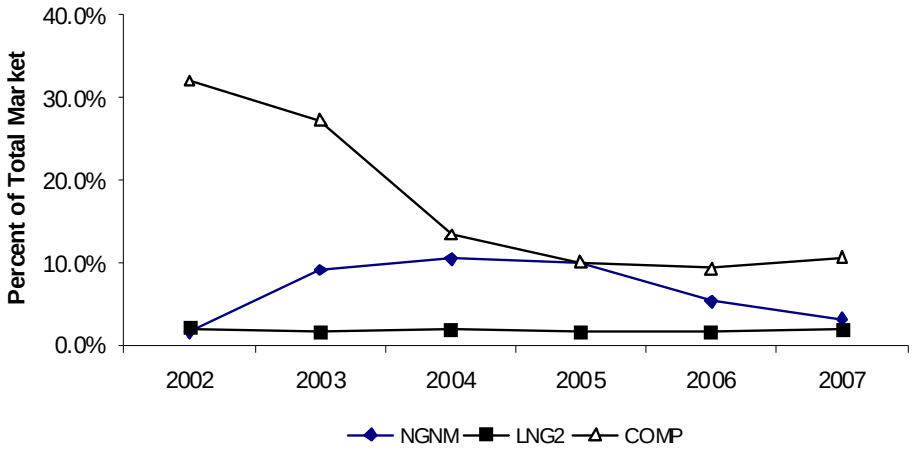
4.4.8 Changes in CHC Product Use over Time

The Sponsor-funded studies compared current and recent users of Ortho Evra with NGM- and LNG-containing COCs between the years 2002 and 2007. Limiting use data to the time period

covered by the Ortho Evra studies, an examination of CHC trends in the market share data displayed in Figure 5 demonstrates that use of Ortho Evra (NGMN) has been decreasing since 2005, whereas LNG use in the US remained low, but relatively stable. Taken together, Ortho Evra and LNG represent less than 20% of hormonal contraceptives used in the marketplace according to the projected numbers obtained from *SDI Vector One*® databases. Overall drug use data is provided in Appendix C.

An important question is whether the population of users differed over the study period and, if so, whether this difference is reflected in the observed risk estimates.

Figure 5: Total Prescriptions for Selected CHCs as Proportion of the Total Market, 2002-2007



Source: SDI Vector One®: National, Years 2002-2007; Data Extracted September 2011. NGMN= Norelgestromin-containing contraceptive (Ortho Evra); LNG = levonorgestrel-containing contraceptive; COMP = includes norgestimate-, norethindrone acetate- and levonorgestrel-containing contraceptives

None of the studies specifically addressed differences in risk over time but rather matched cases and controls on the index date or adjusted for calendar year (FDA study). Because of the matching, the time effect could not be evaluated. The BCDSP investigators, however, did assess the residual effect of time in the case-control pairs matched on year of birth. The reports comparing Ortho Evra with LNG show the residual effect of experiencing a VTE by year. Odds ratios from both the PharMetrics and MarketScan databases for all cases are shown in Table 21. Results from the PharMetrics database suggest a slightly higher VTE risk in 2003, a time soon after Ortho Evra market approval, with another smaller increase in 2005. The risk estimates from the MarketScan database did not show any residual effect of time since market approval but did show a decrease around 2005-2006, then a return to the more stable earlier estimates. The dip may reflect the dramatic decrease of Ortho Evra prescriptions in 2005.

Therefore, after adjusting for index year and age, differences in VTE risks are not likely due to the effect of year, but may be related more specifically to the differences in population sources used for comparison.

Table 21: Odds Ratios for VTE Risk by Calendar Year

	PharMetrics (LNG comparator)		MarketScan (LNG comparator)	
	OR	**95% CI**	**OR**	**95% CI**
2003	5.7	0.7-46.6	1.6	0.4-6.5
2004	0.8	0.3-2.0	1.6	0.8-3.2
2005	3.0	1.2-7.2	1.2	0.6-2.3
2006	1.9	0.3-10.3	0.7	0.3-1.5
2007	--	--	1.4	0.6-3.5

OR = odds ratio; CI = confidence interval.
Note: Cases and controls matched on year of birth

5. Conclusions

None of the studies to date provides a definitive answer as to the safety of Ortho Evra with regard to thrombotic and thromboembolic events. The entire body of studies provides conflicting evidence that cannot be easily reconciled by considering any single difference among studies. Most of these studies have unique strengths and limitations, but the challenge lies in trying to reconcile multiple methodological differences between studies conducted in very different populations, often using different comparators and different exposure definitions.

- Claims-based algorithms to identify VTE events have a high positive-predictive value (91% for i3 Ingenix) but risk estimates tend towards the null if the definition is too broad, due to the inclusion of cases that may not be truly new cases (see Table 17).
- Use of a more restrictive case definition (e.g., idiopathic cases as opposed to all cases) does not explain the differences reported between the two Sponsor studies.
- Risk increases with age, but even after matching on age and index year, there may continue to be an impact of age or age-related factors on the results if not further adjusted.
- Population differences across databases, in addition to age, may explain some of the differences in risk estimates. Of concern is the possible channeling of specific CHC products on the basis of their non-contraceptive benefits to women who could be at higher risk of VTE based on the medical conditions that led to such channeling (e.g., gynecological disorders).
- Prescriptions have remained relatively stable over time for LNG, but have decreased for Ortho Evra. Comparing risks for different contraceptives over time may be sensitive to changes in prescribing patterns. Including a time covariate or adjusting for year in the analyses may control for some of this effect.
- Differences in exposure definitions across study designs may be responsible for larger risk differences. The risk estimates in the Sponsor's and other studies demonstrate that when exposure definitions are closely aligned, risk differences reported are similar.
- Depending on the definition used, new users of a newly marketed contraceptive are likely to include mainly switchers rather than true initiators (defined as no CHC use prior to current use). Comparing new users of a newly marketed product with new users of an

older marketed product may be more reflective of the differences in the populations of contraceptive users rather than differences between products

6. Future Activities

Even prior to the introduction of Ortho Evra, some newer contraceptive products have been observed to be associated with increased risk for thrombotic and thromboembolic events. The Agency would like to explore whether channeling of newer products to patients already at higher risk for these events may play a role. The FDA-funded study was originally designed to be the first phase in a two-part study designed to address many of the unresolved questions perceived by the Agency as possibly providing explanations for the differences in risks.

Based on the current studies, it is unclear whether the increased risk seen for thrombotic and thromboembolic events in some of the epidemiologic studies is actually due to use of Ortho Evra. However, because two of the studies indicate an increased risk associated with the use of Ortho Evra, FDA believes that these issues warrant Advisory Committee input. Therefore, we would like the Advisory Committee (a) to discuss how best to interpret and communicate the findings from the epidemiologic studies and (b) to consider the overall risk/benefit profile of Ortho Evra.

The Agency also advocates further study of the issue of thrombotic and thromboembolic risk associated with the use of CHCs in general as part of a larger effort to better understand this risk, particularly for all newer CHCs. Such studies should include the following features, which have been identified in our reviews as being crucial to understanding these risks:

1. Population source
    a. The use of the contraceptive products in the study population must be well-understood with regard to patient characteristics and indication. The description should include the impact of formularies on prescribing choices, age of patients by product dispensed, indications for treatment by product dispensed, and comorbid conditions of patients prescribed each product.
    b. All product comparisons need to be done within that one population source.
    c. Studies must be US population-based; not voluntary or selective, so as to be representative of the population source.
    d. When matching in the study design, characteristics of users who cannot be matched should be fully described.
2. Design: An exposure cohort should be assembled. An incident cohort within this exposure cohort would include a nested case-control design that includes all cases and selected controls at the case index date to evaluate risk factors that contribute to the increased risk. All cases and controls would be selected from within the incidence or exposure cohort.
3. Consistent and more comprehensive exposure definitions, to include lifetime exposure to contraceptives as opposed to just what is in the claims histories.
4. More complete capture and adjustment for variables that have not been controlled adequately or at all in prior studies:
    a. Age

b. Non-contraceptive indications (whether the woman uses the product for such an indication instead of, or in addition to, the contraception indication), particularly where such use that may increase the risk for thrombotic and thromboembolic events
c. Other comorbid conditions that may increase the risk for thrombotic and thromboembolic events (e.g., gynecological conditions)
d. Confounders typically unmeasured in claims studies
    i. BMI
    ii. Smoking
    iii. Family history of thrombotic and thromboembolic events
    iv. Personal history of thrombotic and thromboembolic events

In addition, there is a need for further study to examine and quantify the risk for thrombotic and thromboembolic events in women with a variety of conditions that can be either indications for contraceptive use or comorbid conditions among contraceptive users, that may increase risk. Risk should be examined in these women, independently of their use of contraceptive products. These conditions include:

- Polycystic ovary syndrome (PCOS)
- Acne (moderate to severe, possibly as a marker for a systemic condition)
- Hirsutism and alopecia
- Dysmenorrhea, menorrhagia, and other menstrual disorders
- Migraines
- Premenstrual dysphoric disorder (PMDD)
- Other gynecological disorders such as endometriosis, leiomyoma, vaginal and ovarian inflammation, infertility, etc
- HIV and cancer

7. References

[1] Trussell J. 2011. Contraceptive Failure in the United States. Contraception; 83:397-404.

[2] Audet M-C, et al. 2001. Evaluation of Contraceptive Efficacy and Cycle Control of a Transdermal Contraceptive Patch vs an Oral Contraceptive. JAMA; 285, No 18:2347-54.

[3] Urdl W, et al. 2005. Contraceptive efficacy, compliance and beyond: factors related to satisfaction with once-weekly transdermal compared with oral contraception. Euro J of Obstet and Gyn and Repro Biol; 121:202-210.

[4] Murphy PA, Brixner D. 2008. Hormonal contraceptive discontinuation patterns according to formulation: investigation of associations in an administrative claims database. Contraception; 77:257-263.

[5] Nelson AL, Westhoff C, Schnare SM. 2008. Real-world patterns of prescription refills for branded hormonal contraceptives- a reflection of contraceptive discontinuation. Obstetrics & Gynecology;112 (4):782-787.

[6] Creinin MD, et al. 2008. Multicenter comparison of the contraceptive ring and patch: a randomized controlled trial. Obstetrics and Gynecology; 111(2):267-277.

[7] Bakhru A, Stanford N. 2006. Performance of contraceptive patch compared with oral contraceptive pill in a high-risk population. Obstetrics and Gynecology; 108(2):378-86.

[8] Thurman AR, et al. 2007. Preventing teen pregnancy: postpartum depot medroxyprogesterone acetate, oral contraceptive pills, or the patch? Journal of Pediatric Adolescent Gynecology; 20:61-65.

[9] Raine TR, et al. 2011. One-year contraceptive continuation and pregnancy in adolescent girls and women initiating hormonal contraceptives. Obstetrics Gynecology;117(2):363-71.

[10] Jick SS, Hagberg KW, Hernandez R, and Kaye JA. 2010. Postmarketing study of Ortho Evra® and levonorgestrel oral contraceptives containing hormonal contraceptives with 30 mcg of ethinyl estradiol in relation to nonfatal venous thromboembolism. Contraception 81:16-21.

[11] Cole JA, Norman H, Doherty M, and Walker AM. 2007. Venous Thromboembolism, Myocardial Infarction, and Stroke among Transdermal Contraceptive System Users. Obstetrics & Gynecology; 109(2): 339-346. Erratum 2008: 111(6):1449.

[12] Dore DD, Norman H, Loughlin J, Seeger JD. 2010. Extended case-control study results on thromboembolic outcomes among transdermal contraceptive users. Contraception; 81:408-413.

[13] Jick SS, Kaye JA, Russmann S, and Jick H. 2006. Risk of nonfatal venous thromboembolism in women using a contraceptive transdermal patch and oral contraceptives containing norgestimate and 35 μg of ethinyl estradiol. Contraception; 73:223-228.

[14] Jick S, Kaye JA, Li L and Jick H. 2007. Further results on the risk of nonfatal venous thromboembolism in users of the contraceptive transdermal patch compared to users of oral contraceptives containing norgestimate and 35 μg of ethinyl estradiol. Contraception; 76:4-7.

[15] Jick SS and Jick H. 2007. The Contraceptive Patch in Relation to Ischemic Stroke and Acute Myocardial Infarction. Brief Reports. Pharmacotherapy; 27:218-220.

[16] Jick SS, Hagberg KW, Hernandez R, and Kaye JA. 2010. Postmarketing study of Ortho Evra® and levonorgestrel oral contraceptives containing hormonal contraceptives with 30 mcg of ethinyl estradiol in relation to nonfatal venous thromboembolism. Contraception 81:16-21.

[17] FDA Office of Surveillance and Epidemiology. Combined hormonal contraceptives (CHCs) and the risk of cardiovascular disease endpoints. http://www.fda.gov/downloads/Drugs/DrugSafety/UCM277384.pdf

[18] i3 Drug Safety. 2005. The Risk of Venous Thromboembolism, Myocardial Infarction, and Ischemic Stroke Among Women Using the Transdermal Contraceptive System Compared with Women Using Norgestimate-Containing Oral Contraceptives with 35 μg Ethinyl Estradiol. First Interim Report, Nested Case Control Study. October 28, 2005.

[19] i3Drug Safety. 2006. The Risk of Venous Thromboembolism, Myocardial Infarction, and Ischemic Stroke Among Women Using the Transdermal Contraceptive System Compared with Women Using Norgestimate-Containing Oral Contraceptives with 35 μg Ethinyl Estradiol. Interim Report, Nested Case Control Study. February 9, 2006.

[20] i3 Drug Safety. 2006. The Risk of Venous Thromboembolism, Myocardial Infarction, and Ischemic Stroke Among Women Using the Transdermal Contraceptive System Compared with Women Using Norgestimate-Containing Oral Contraceptives with 35 μg Ethinyl Estradiol. Draft Final Report, Nested Case Control Study. June 30, 2006.

[21] i3 Drug Safety. 2009. The Risk of Venous Thromboembolism, Myocardial Infarction, and Ischemic Stroke Among Women Using the Transdermal Contraceptive System Compared with Women Using Norgestimate-Containing Oral Contraceptives with 35 μg Ethinyl Estradiol, Nested Case Control Study. Revised Final Report, January 22, 2009 (Originally issued on August 3, 2006.

[22] i3 Drug Safety. 2009. The Risk of Venous Thromboembolism, Myocardial Infarction, and Ischemic Stroke Among Women Using the Transdermal Contraceptive System Compared with Women Using Norgestimate-Containing Oral Contraceptives with 35 μg Ethinyl Estradiol, Nested Case Control Extension. Final Report, June 23, 2009.

[23] Boston Collaborative Drug Surveillance Program. 2005. Final Report, Postmarketing Study of ORTHO EVRA™ in Relation to Non-Fatal Venous Thromboembolism. September 21, 2005.

[24] Boston Collaborative Drug Surveillance Program. 2008. Report on the 2007 Update on Postmarketing Study of ORTHO EVRA™ in Relation to Non-Fatal Venous Thromboembolism, Ischemic Stroke, Acute Myocardial Infarction, and Cerebral Vascular Sinus Thrombosis. May 20, 2008.

[25] Ouellet-Hellstrom R. 2005. Review of the Final Report: Postmarketing Study of ORTHO EVRA™ in Relation to Non-Fatal Venous Thromboembolism. Reports Submitted to Johnson & Johnson by the Boston Collaborative Drug Surveillance Study Results, September 21, 2005. PID D050578, November 9, 2005.

[26] Boston Collaborative Drug Surveillance Program. 2009. Postmarketing Study of ORTHO EVRA™ and Levonorgestrel Oral Contraceptives Containing Hormonal Contraceptives with 30 μg of EE in Relation to Non-Fatal Venous Thromboembolism. Final Report. April 3, 2009.

[27] Lidegaard Ø, Nielsen LH, Skovlund CW, Skjeldestad FE, and Løkkegaard E. 2011. Risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogen doses: Danish cohort study, 2001-9. BMJ 2011;343:d6423 doi: 10.1136/bmj.d6423.

[28] i3 Ingenix. 2008. The Risk of Venous Thromboembolism, Myocardial Infarction, and Ischemic Stroke Among Women Using the Transdermal Contraceptive System Compared to Women Using Norgestimate-Containing Oral Contraceptives With 35 μg Ethinyl Estradiol Nested Case-Control Study. Interim Report. June 18, 2008.

[29] Jick S, Hagberg, K. 2010. ORTHO-EVRA and venous thromboembolism: an update. Contraception; 81:452-453.

Appendix A

Ortho Evra Nested Case-Control Studies

Appendix A: Ortho Evra Nested Case-Control Studies

Author(s) Study Time Period	Outcome	Database	CHC	Person Years	Cases	Controls	Odds Ratios (95% CI)	Incidence/ 10,000	IRR (95% CI)
I3 Ingenix – medical chart validated cases - VTE									
Cole 2007[11] Apr 2002-Dec 2004	VTE	UHC	NGMN NGM	49,048 202,344	20 37	41 150	2.0 (1.0-4.1) Reference	4.1 1.8	2.2 (1.3-3.8) Reference
Dore 2010[12] Combined Apr 2002-Dec 2006	VTE	UHC	NGMN NGM	NR NR	39 63	90 263	2.0 (1.2-3.3) Reference	NR NR	--- ---
Boston Collaborative Drug Surveillance Program (BCDSP) - VTE* - de-identified databases									
Jick 2006[13] Apr 2002-Mar 2005	VTE*	PharMetrics	NGMN NGM	58,752 88,571	31 37	127 139	0.9 (0.5-1.6) Reference	5.3 (3.6-7.5) 4.2 (2.9-5.8)	1.1 (0.7-1.8) Reference
Jick Year2 2007[14] Apr 2005-Sep 2006	VTE*	PharMetrics	NGMN NGM	NR NR	20 36	72 140	1.1 (0.6-2.1) Reference	NR NR	
Jick Year3 2010[29] Oct 2006-Oct 2007	VTE*	PharMetrics	NGMN NGM		19 19	42 106	2.4 (1.2-5.0)	NR NR	--- ---
Jick2010 Combined[29] Apr 2002-Oct 2007	VTE*	PharMetrics	NGMN NGM		70 92	241 385	1.2 (0.9-1.8)	NR NR	--- ---
Jick 2010[16] Apr 2001-Mar 2006 Jan 2004-Dec 2007	VTE* VTE*	PharMetrics MarketScan	NGMN LNG_30 NGMN LNG_30	53,755 42,153 186,473 251,001	30 16 47 50	109 98 160 222	2.0 (0.9-4.1) Reference 1.3 (0.8-2.1) Reference	3.8 (2.3-6.2) 5.6 (3.9-8.0) 2.5 (1.9-3.4) 2.0 (1.5-2.6)	NR NR NR NR

** Idiopathic cases*
CHC –combined hormonal contraceptive; CI – confidence interval; PY – person-years; NR = not reported
VTE – venous thromboembolic events
NGMN – norelgestromin-containing contraceptive; NGM – norgestimate-containing contraceptive; LNG – levonorgestrel-containing contraceptives
UHC – United HealthCare; also referred to as Normative Health Information (NHI) database
Reference numbers refer to references at the end of the primary document

Appendix A: Ortho Evra Nested Case-Control Studies (Continued)

I3 Ingenix –– medical chart validated cases - AMI and Stroke

Author(s) Study Time Period	Outcome	Database	CHC	PY	Cases	Controls	Odds Ratios (95% CI)	Incidence/ 100,000 PY	IRR (95% CI)
Cole 2007[11]	AMI	UHC	NGMN	49,048	3	9	2.1 (0.3-15.5)	6.1	1.8 (0.5-6.8)
Apr 2002-Dec 2004			NGM	202,344	7	34	Reference	3.5	Reference
	Stroke	UHC	NGMN	49,048	0	6	0.0	--	--
			NGM	202,344	10	30	--	4.9	--
Dore 2010[12] Combined	AMI	NHI	NGMN	NR	5	18	1.2 (0.3-4.7)	NR	--
Apr 2002-Dec 2006			NGM	NR	11	50	Reference	NR	
	Stroke	NHI	NGMN	NR	2	10	0.6 (0.1-3.2)	NR	--
			NGM	NR	15	50	Reference	NR	
BCDSP - AMI and stroke - de-identified databases									
Jick 2007[15]	AMI*	PharMetrics	NGMN	58,752	1	--	--	1.7 (0.04-9.5)	0.2 (0.0-1.7)
Apr 2002-Mar 2005			NGM	88,571	7	--	--	7.9 (3.2-16.3)	Reference
	Stoke*	PharMetrics	NGMN	58,752	8	--	--	13.6 (5.9-26.8)	1.20 (0.4-3.4)
			NGM	88,571	10	--	--	11.3 (5.45-20.8)	Reference

** Idiopathic cases*
CHC –combined hormonal contraceptive; CI – confidence interval; PY – person-years; NR = not reported
AMI – acute myocardial infarction/
NGMN – norelgestromin-containing contraceptive; NGM – norgestimate-containing contraceptive; LNG – levonorgestrel-containing contraceptives
UHC – United HealthCare; also referred to as Normative Health Information (NHI) database
Reference numbers refer to references at the end of the primary document

Appendix B

FDA Review of Final Report of FDA-Funded Study Entitled "Combined Hormonal Contraceptives (CHCs) and the Risk of Cardiovascular Disease Endpoints"

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology
Epidemiologist Study Comparison Review

Date:	November 3, 2011
Reviewer(s):	Rita Ouellet-Hellstrom, PhD, MPH Associate Director FDA Principal Investigator (PI) Division of Epidemiology II (DEPI II)
Office Director	Gerald Dal Pan, MD, MHS, Acting Director Office of Surveillance and Epidemiology (OSE)
Division Director	Judy Staffa, PhD, RPh, Director Division of Epidemiology II (DEPI II)
Drug Name(s):	3.0 mg of drospirenone with 30 µg of ethinyl estradiol (EE) (Yasmin); 6.0 mg norelgestromin with 750 µg EE (Ortho Evra); 11.7 mg etonogestrel/2700 µg EE (NuvaRing); ***Comparators*** 0.10 mg of levonorgestrel/20 µg EE (LNG1) 0.15 mg levonorgestrel and 30 µg EE (LNG2) 1.0 mg norethindrone acetate/20 µg EE (NETA) 0.18 – 0.25 mg of norgestimate/35 µg EE (NGM)
Subject:	Review of the FDA-funded Study: Combined Hormonal Contraceptive (CHC) and the Risk of Cardiovascular Disease Endpoints; October 22, 2011 v2.
OSE RCM #:	2008-1629
TSI #:	770
TEAM MEMBERS	David J Graham, MD, MPH (OPE) Marlene Hammer (OSE) Adrienne Rothstein, Pharm D (DPV II) Mark Miller, Pharm D (DPV II) Daniel Davis, MD, MPH (DRUP) Mark Levenson, PhD (DB7)
Acknowledgements	Patty Greene, Pharm D (DEPI II), Drug Use Specialist CDR David Money, MPH, RPh, USPHS

This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.

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EXECUTIVE SUMMARY

Several contraceptive products approved in 2001 quickly became very popular forms of contraception, particularly among young women, and were considered relatively safe because of their lower estrogen content compared to older hormonal products. Safety concerns for serious thrombotic and thromboembolic adverse events as well as death, however, became a public concern soon after their market introduction.

Although several epidemiologic studies were initiated by the manufacturers of these new contraceptive products at the request of U.S. and European regulatory authorities around the time of their approval, the studies were designed mainly to evaluate one specific product compared to one or a group of other contraceptive products. In addition, based on reports submitted to the Adverse Event Reporting System (AERS), the FDA had concerns about the ability of some of the epidemiologic studies to identify and characterize all thrombotic and thromboembolic events and deaths (including sudden deaths) that could be related to these products.

For these reasons, FDA sponsored an epidemiologic study involving data from insurance claims and medical record data. The objective of the FDA-funded study was to assess cardiovascular risks, including the risk of thrombotic and thromboembolic events and death. The newer products selected for study were those that had sufficient numbers of users to allow for an evaluation of these risks compared to those associated with use of older, more frequently prescribed contraceptives at the sites selected. If an increased risk was observed, the FDA-funded study would subsequently attempt to assess user characteristics and prescribing patterns that might help explain the increased risk. It was recognized at the time that a more in-depth assessment of potential reasons for increased risk would not be possible using only claims and electronic medical records and would require physician and patient contact, something that could be conducted later if needed.

The FDA-funded study was conducted at two HMO sites (Kaiser Permanente North and South California) and two state Medicaid programs (Tennessee and Washington) each associated with an academic institution. In addition to having access to data from a large group of young reproductive age women, reasons for selecting study sites included: 1) the ability of the investigators to validate study outcomes with medical records; 2) the ability of the sites to link to state vital status files to identify deaths quickly; and 3) the ability of the sites to facilitate physician and patient contact if and when needed. Diversity of populations was favored over similarity to maximize the capture of possible reasons for an increased risk if observed.

The FDA-funded study was designed as a retrospective cohort study of women age 10 to 55 years who were current users of the study contraceptives from January 1, 2001 to December 31, 2007. Two exposure cohorts, one of current users and the other of new users, were created for evaluation. The study contraceptives included Yasmin (3.0 mg of

drospirenone/30 μg of ethinyl estradiol)[a], referred to as DRSP in this review; Ortho Evra (6.0 mg norelgestromin and 0.750 μg EE), (referred to as NGMN); and the NuvaRing (0.18–0.25 mg etonorgestrel/ 2700 μg EE) referred to as ETON in this review. Although known to be underpowered, ETON was included nonetheless because of its potential to provide information on continuous hormonal exposure along with Ortho Evra.

For each study contraceptive in the primary analysis, the comparison group included a composite of frequently prescribed products that contained the progestin levonorgestrel, norethindrone, or norgestimate combined with 20 μg to 35 μg of ethinyl estradiol (COMP). As a secondary analysis following recent published studies, comparisons of the risk for serious thrombotic and thromboembolic events were also made for each study contraceptive with the levonorgestrel products containing 30 μg of estrogen (LNG2).

As expected, age-specific incidence rates per 10,000 person-years (PY) adjusted for site show a VTE and ATE risk increasing with age for DRSP, NGMN, and COMP. These rates were higher in New Users than All Users. Among All Users but not New Users, age and site-adjusted VTE incidence rates per 10,000 PY were higher for the exposure CHCs (DRSP - 10.2; NGMN – 9.8; ETON - 11.9) than for COMP (6.0) or LNG2 (6.6).

Similar to the EURAS study, age- and site-adjusted ATE incidence rates per 10,000 PY were higher for COMP (1.4) and LNG2 (1.6) than DRSP (1.1) and NGMN (1.1). Age-adjusted mortality rates were also slightly higher in the comparator groups also but only for All Users in the FDA-funded study.

In the Cox Proportional Hazard analyses which adjusted for age, site, and year of entry into the study, results show an increased VTE risk for DRSP (HR = 1.7), NGMN (HR = 1.6), and ETON (HR = 1.6) when compared to COMP in All Users and only for DRSP in New Users. Comparisons with LNG2 in these analyses show an increased risk only for DRSP for All Users and New Users. The increased VTE risks were reported for women younger than 35 years of age and the increased ATE risk was reported for women 35 years of age and older only for DRSP.

The results of the FDA-funded study are consistent with the published studies demonstrating an increased VTE risk among current users of DRSP and NGMN, particularly among women younger than 35 years of age. This study is also the first to report an increased ATE risk among older DRSP users. Linkage to state mortality files did not reveal any large discrepancy in missed ATE and VTE case identification. The increased VTE risk reported for ETON needs further evaluation because it is a new finding.

This study also demonstrated the importance of considering differences in population sources, population characteristics, and comparators when comparing one product type with another. Possible channeling by clinicians towards prescribing some CHCs for specific non-contraceptive benefits provided by these products (e.g., dysmenorrhea,

[a] *Although Yaz contains the same amount of drospirenone (3.0 mg) as Yasmin, it contains only 20 μg of ethinyl estradiol (EE) instead of 30 and is taken for an additional 3 days. Yaz was not included in the FDA-funded study nor was it analyzed in any of the studies discussed or referenced in this review.*

menorrhagia, acne, Polycystic Ovarian Syndrome) in addition to contraception needs to be considered.

The study was carefully done, is comprehensive, and all hospitalized outcomes have been validated with medical records. One site also validated outpatient deep vein thrombosis (DVTs). In addition, the study was able to link records to state mortality files, evaluated two different exposure cohorts (All Users and New Users), and the contribution of known confounders in two very different US populations (Medicaid and large HMO).

Like other claims-based studies, however, the study is limited in that it captures only information available in the claims databases or in electronic medical records for cases only. Limitations also include the absence of data on key covariates (obesity/ body mass index (BMI), smoking, personal and family history of VTE, lifetime use of hormonal contraceptives) and the inability to validate all outpatient DVTs by chart review (except at only one site). The small number of ATEs limited the power for analyses of these outcomes, though the rates were consistent with published data.

The FDA-funded study as well as most postmarketing studies, however, identified all users of study combined hormonal contraceptives (CHCs) from claims databases or electronic medical records. Therefore, the studies very likely would capture the experience of all CHC users, not just the experience of women who use CHCs mostly for contraception. And even though some studies excluded women with known risk factors for experiencing VTEs, none have assessed possible channeling by prescribers and potential risk associated with CHC use for non-contraceptive benefits. If women using CHCs mostly for the non-contraceptive benefits of CHCs are at increased risk of VTE by nature of their condition, and if specific CHC products are preferred in treating those conditions (channeling), then differences in risk estimates observed between the CHC products would be attributed to a specific product but would more likely be the result of the health condition.

None of the studies to date provides a definitive answer as to the safety of DRSP and NGMN with regard to thrombotic and thromboembolic events (TTE). The entire body of studies provides conflicting evidence that cannot be easily reconciled by any single difference among studies. Most of these studies have unique strengths and limitations, but the challenge lies in trying to reconcile multiple methodological differences between studies conducted in very different populations, often using different comparators and different exposure definitions. There is a history that newer contraceptive products are observed to have associations with increased risk for thrombotic and thromboembolic events, and the Agency would like to better understand whether channeling of newer products to patients already at higher risk for these events may play a role. The FDA-funded study was originally designed to be the first phase in a multi-phase study designed to address many of the unresolved questions perceived by the Agency to possibly provide alternative explanations for the risks seen, other than the individual drugs themselves.

Since FDA cannot at this time determine whether the increased risk seen for thrombotic and thromboembolic events in some of the epidemiologic studies is actually not due to use of the DRSP and NGMN products, we believe that, because of the consistency in recent reports for an increased risk, product labeling should reflect that very real possibility. However, the Agency advocates further study of this issue, as part of a larger

effort to better understand the risk for thrombotic and thromboembolic events associated with all newer contraceptive agents. Such studies should assure the comparability of population sources, study design, exposure definitions, and adequate capture and adjustment of age, non-contraceptive co-indications, other co-morbid diseases (e.g. ob/gynecological conditions), and known confounders such as BMI, smoking, and personal and family history of thrombotic and thromboembolic events.

The Final Report, presenting results from the risk assessment phase of this study achieved its objectives.

1 BACKGROUND

Several contraceptive products approved in the early 2000's quickly became very popular forms of contraception, particularly among young women, and were considered relatively safe because of their lower estrogen content compared to older hormonal products containing ≥ 50 μg of ethinyl estradiol (EE). Safety concerns for serious thrombotic and thromboembolic adverse events as well as death, however, became a public concern soon after their market introduction. Between 2002 and 2010, over 800 million prescriptions[b] for combined hormonal contraceptives (CHCs) have been dispensed, the majority of which were dispensed to women younger than 35 years of age. Of these, 55 million were prescriptions for the 3 mg drospirenone with 30 μg ethinyl estradiol (EE), 41 million were for norelgestromin with 0.75 μg EE prescriptions, and 28 million were for the approximately 11.7 mg etonorgestrel with 2700 μg EE.

These safety concerns stimulated adverse event reporting, which made appropriate review and interpretation of the reports received in FDA's Adverse Event Reporting System (AERS) challenging. Despite a low incidence of venous thromboembolic events in this population, an increase in risk for these adverse events among users could put many young women at risk of a major life-threatening event. FDA was concerned about its ability to interpret the postmarketing information available in the AERS database.

1.1 DROSPIRENONE

In May 2001, Yasmin (3.0 mg of drospirenone/30 μg EE), referred to as DRSP in this review, was the first drospirenone-containing contraceptive to be approved for contraception in May 2001 in the United States. Yaz was the second drospirenone containing contraceptive approved for contraception in March 2006. Although Yaz contains the same amount of drospirenone (3.0 mg) as Yasmin, it contains only 20 μg of ethinyl estradiol (EE) compared to Yasmin's 30 μg. In addition, one active Yaz pill is taken over 24 instead of 21 days. Yaz was also approved for premenstrual dysphoric disorder (PMDD) in October 2006, and acne in January 2007. None of the studies published to date (including the FDA-funded study) evaluated the VTE and ATE risk for Yaz that contains 20 μg EE.

Although labels for hormonal contraceptives (including Yasmin and Yaz) warn prescribers and users of the increased thrombotic risks associated with use of

[b] *Source: SDI Vector One®: National, Years 2002-2010 Data Extracted September 2011.*

contraceptive steroids, due to its spironolactone-like activity, drospirenone-containing contraceptive labels also contraindicate its use in women with

- Renal insufficiency
- Hepatic dysfunction
- Adrenal Insufficiency

The progestin drospirenone was thought to increase cardiac arrhythmia risks and sudden deaths among users because of its propensity to increase potassium levels. The label, therefore, has a bold warning that long-term users of drugs that could increase serum potassium such as NSAIDS, potassium-sparing diuretics, potassium supplementation, ACE inhibitors, angiotensin-II receptor, heparin and aldosterone antagonists "should have their serum potassium levels checked during the first treatment cycle" with a drospirenone product.

At approval in 2001, the Division of Reproductive and Urologic Drug Products (DRUP) requested a postmarketing plan and evaluation at the time of approval and modified later to include thrombotic and thromboembolic events and deaths. When concerns of thrombotic and thromboembolic risks surfaced, a US postmarketing study to assess the risks of venous thromboembolic events (VTE) as well as arterial thrombotic events (ATE) and death was initiated in addition to the European (German) Study.

Two prospective observational studies were funded by the sponsor and were ongoing at the time the FDA-funded study was initiated. The European Active Surveillance Study (EURAS)[1] included DRSP users and two groups of comparators: LNG and other contraceptives. Once enlisted, each woman was contacted every six months during the study period to obtain information on adverse events and changes in contraceptive use. The study implemented a very aggressive loss-to-follow-up protocol. The US-based study, conducted by i3 Ingenix[2,3], identified DRSP initiators quarterly for the first year beginning June 11, 2001 then semiannually through June 30, 2004 during which time the investigators matched each DRSP user to two other contraceptive initiators based on their respective propensity scores or probability of being prescribed DRSP. Neither of these two studies showed any increased risk of VTE, ATE, or death associated with use of DRSP compared to any comparator group evaluated. These studies capture the experience of contraceptive users who had comparable baseline characteristics and, in the EURAS study, used these products mainly for contraception.

While the FDA-sponsored study was underway, several retrospective observational studies[4, 5, 6, 7] were published that did show an increased risk for VTE associated with use of DRSP. Neither these two sponsor-funded studies nor any of the studies published since nor the FDA-funded study has evaluated the VTE and ATE risks associated specifically with the product Yaz which contains a lower dose of EE although taken over 24 days instead of the 21 days for Yasmin.

1.2 NORELGESTROMIN

Ortho Evra (6.0 mg norelgestromin with 0.75 μg EE), (referred to as NGMN in this review), is a combination transdermal patch approved for the prevention of pregnancy on November 20, 2001. Like labels for most hormonal contraceptives, the NGMN label

warns prescribers and users of the possible increased thrombotic risks associated with being overweight and smoking. Because systemic estrogen exposure levels for the NGMN patch during use were reported to be 55% to 60% higher and peak concentrations lower than those produced by an oral contraceptive containing 0.18 to 0.25 mg norgestimate with 35 μg EE, FDA had concerns about the safety of the product.

The two postmarketing studies conducted by the sponsor were case-control studies.[8,9,10] The first study reported no increased VTE risk for NGMN (Odds Ratio (OR) 0.9; 95% confidence interval (CI) = 0.5-5.6)[9] for non-fatal idiopathic cases. The second study initially reported a 60% increased VTE risk for cases identified by codes only and a twofold increased VTE risk for chart verified cases (OR 2.2; 95% CI – 1.3-3.8).[8] These studies were initially considered complementary, but quickly became two separate studies when results differed. The studies were designed to measure the relative incident risk of ATE [acute myocardial infarction (AMI) and stroke] and VTE [pulmonary embolism (PE) and deep vein thrombosis (DVT)] in NGMN users compared to users of a norgestimate product containing 35 μg of ethinyl estradiol (EE), an estrogen dose believed to be more comparable to the newly revised levels of estrogen exposure in the patch. Both studies included two-year extensions funded by the sponsor as part of their phase IV postmarketing commitment. One added two years of additional data collection to the initial study,[11] while the other re-did the analyses at two additional time periods to identify new cases and controls then pooled the results of all three analyses.[12,13]

Because one of these two postmarketing studies showed a twofold increased VTE risk, the label was amended in November 2005 with a boxed warning that women 15 to 44 years of age who choose to use the NGNM patch may be at increased VTE risk.

1.3 ETONOGESTREL

NuvaRing, referred to as ETON in this review, is a non-biodegradable, flexible, transparent, and colorless combination contraceptive vaginal ring containing two active components, the progestin etonogestrel (ETON) and EE. When placed in the vagina, each ring releases on average 0.120 mg/day of etonogestrel and 0.015 mg/day of ethinyl estradiol over a three-week period of use. Once inserted, the ring remains in place continuously for three weeks. It is removed for a one-week break, during which a withdrawal bleed usually occurs. A new ring is inserted one week after the last ring was removed.

ETON is indicated for the prevention of pregnancy in women who elect to use this product as a method of contraception. The label is a standard hormonal contraceptive label and warns prescribers and users of the potential increase in serious cardiovascular side effects from using this combination hormonal contraceptive particularly for older women over 35 years of age and for heavy smokers but no specific postmarketing safety studies were completed at the time the FDA/OSE study was initiated

Prescriptions for the ETON product were increasing[c] especially after concern with the transdermal patch surfaced after 2004. Both products were designed to provide

[c] *Source: SDI Vector One®: National, Years 2002-2010 Data Extracted September 2011*

continuous delivery. Questions were being raised at the same time whether continuous hormonal delivery placed women at greater risk for thrombotic and thromboembolic events. This product was included in the FDA/OSE study to assist in evaluating continuous hormonal exposure although the team realized that the study would most likely be underpowered to independently assess VTE and ATE risk for this product alone.

1.4 COMBINED HORMONAL CONTRACEPTIVE (CHC) STUDY RATIONALE

It was unknown in 2007-2008 whether risk differences observed for each product were the results of reporting and measurement artifacts, population or exposure definition differences, or differences in the progestin drug delivery and metabolism.

The objective of the FDA/OSE study then was to evaluate use of DRSP and the transdermal patch (along with another new continuous use product) compared to other commonly prescribed older oral contraceptive product(s) in populations of prevalent and new users (incident cohort). In addition, another objective was to assess the risk, the public health impact, patterns of use, and eventually, the behavioral and environmental factors that could be related to use that could place a woman at greater risk for thrombotic and thromboembolic event and/or death.

Since there had been reports of sudden deaths associated with DRSP and NGMN, and given that not all deaths can be identified with use of claims-based or electronic medical records (used by many postmarketing studies whether prospective or retrospective), access to linked vital statistics death records, identified in the feasibility study at Vanderbilt, Washington State and Kaiser Permanente provided FDA/OSE with a valuable opportunity to assess this important public health concern.

2 REVIEW METHODS AND MATERIALS

This review evaluates the final study results dated October 22, 2011[14] by Stephen Sidney, MD, MPH, the Lead Site Principal Investigator. The Final Report, titled *Combination Hormonal Contraceptives (CHCs) and the Risk of Cardiovascular Disease Endpoints* consists of the main report with five appendices (A through E).

- Appendix A: Endpoints, Exclusion, Covariates
- Appendix B: Supplemental Analyses
- Appendix C: Study CHC NDC codes
- Appendix D: NDC Codes of Prescription Drugs Used as Covariates
- Appendix E: CHC Data Collection Documents

The Final Report is evaluated for its consistency in adequately addressing the study concept submitted for funding on August 7, 2007 and addressing the study objectives stated in the report with respect to the selected study design specified.

Review of the study is supplemented with data from the

a) SDI, Vector One®: National (VONA) database which measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions (Appendix B in this review). Information on age and comorbidity was obtained from this database.

b) IMS Health, IMS Health Lifelink™ database which represents over 95 managed care plans and covers approximately 60 million commercially insured, de-identified patients. Claims are captured from doctor's offices (including outpatient clinics), retail and mail order pharmacies, patient visits to specialists, and hospitalizations. They include information about diagnoses, emergency room visits, office visits, home care, diagnostic tests, procedures and injections. These data represent approximately 11 percent of the U.S. commercially insured population during that time period (see Appendix B for more details).

For this review, data were obtained for all patients who had a pharmacy claim for one of the contraceptives of interest between Jan 1 2001 and Dec 31 2007.

c) SDI Physician Drug and Diagnosis Audit, Years 2001-2007. [d] The SDI, Physician Drug & Diagnosis Audit (PDDA) with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

The FDA-funded study is summarized first in Section 3. OSE/DEPI II comments and discussion are then presented in Section 4 and with Conclusions and Recommendations in Section 5.

3 FINAL STUDY REPORT

The final study included most of the information requested of the investigators by FDA with some differences either based on the investigators' recommendations or the unavailability of the information in the databases identified.

3.1 OBJECTIVE

The final study objectives were to

- Determine prevalence and incidence rates for venous and arterial thrombotic and thromboembolic events (VTE and ATE) and all-cause and cause-specific mortality in women exposed to the three newer study hormonal contraceptives compared to older frequently prescribed low estrogen hormonal contraceptives (Phase I - funded, completed and reviewed in this document).

[d] *Source: Extracted October 2011. File: PDDA 2010-PDDA_2011-1044_CHC_Study_Concm_Product_10-7-11(1).xls.*

- Identify medical, pharmacological, and behavioral characteristics from claims and medical records to assess predictors of increased risk for VTE, ATE, and death (to be completed at a later date if possible).

3.2 STUDY DESIGN

The FDA-funded study is a retrospective cohort study of current CHC use, using data from four geographically diverse health plans, to evaluate the risk of thrombotic and thromboembolic events and all-cause and cardiovascular mortality for three newer preparations compared to four older CHCs with varying progestin and low estrogen levels.

3.2.1 Data Source

The study investigators utilized computerized data files from four geographically diverse health plans: Kaiser Permanente Northern California (KPNC) the Lead Site, Kaiser Permanente Southern California (KPSC), and two state Medicaid programs: Tennessee State Medicaid (Vanderbilt University) and Washington State Medicaid (University of Washington). These sites have access to files that contain enrollment data, demographic information, ambulatory prescriptions from pharmacy records or claims, hospitalizations and outpatient visit data with diagnoses from health plan records or claims and death records obtained from state mortality files. All files were linked at each site to create the study cohorts.

3.2.2 Study Population and Time Period

Across the four sites, 835,826 women were identified who were between the ages 10 and 55 years and had at least one prescription filled for a study CHC between January 1, 2001 and December 31, 2007 that was preceded by at least 6 months of continuous membership (5 months plus 1 day for the Washington Medicaid study population).

Women were followed until the end of continuous membership, the end of a prescription period (days-supply + 42 days), date of a study event, first date of a pregnancy, reaching age 56 years, or end of study follow-up (12/31/2007).

3.2.3 Study Contraceptives and Comparators

The exposure contraceptives included the following products

- **DRSP:** 3.0 mg of drospirenone and 30 μg of ethinyl estradiol
- **NGMN:** 6.0 mg norelgestromin (NGMN) and 750 μg ethinyl estradiol (EE)
- **ETON:** 11.7 mg etonogestrel and 2700 μg ethinyl estradiol

And the comparators **(COMP)** were

- **LNG1:** 0.10 mg of levonorgestrel and 20 μg of ethinyl estradiol
- **LNG2:** 0.15 mg levonorgestrel and 30 μg ethinyl estradiol
- **NETA:** 1 mg norethindrone acetate and 20 μg ethinyl estradiol
- **NGM:** 0.18 – 0.25 mg of norgestimate and 35 μg of ethinyl estradiol

3.2.4 Exclusion Criteria

Women were excluded from the cohort if a serious or life threatening illness was documented during the pre-exposure eligibility period. These included sickle cell disease, cystic fibrosis, cerebral palsy, cancer, HIV, organ transplant, liver failure, severe congestive heart failure (CHF), renal failure, respiratory failure, or hospitalization for acute myocardial infarction, stroke, or venous thromboembolic disease.

Criteria for exclusion required that codes for these illnesses were based on having one [or for congestive heart failure (CHF), two] inpatient ICD-9 or procedure codes with the codes of interest appearing anywhere in the primary and secondary discharge diagnoses or two outpatient ICD-9 or procedure codes separated by at least 30 days.

3.2.5 Exposure

For assessing VTE, ATE, and mortality risks, three study CHCs [the transdermal patch referred to in the report as NGMN, the vaginal ring referred to as ETON, and the drospirenone product referred to as DRSP] were compared with four products with low estrogen content CHCs (20 μg – 35 μg ethinyl estradiol) regularly prescribed at the study sites. The four study CHCs comparators are referred to as COMP in the Final Report. The LNG2 product in COMP is a levonorgestrel contraceptive (0.15 mg levonorgestrel and 30 μg ethinyl estradiol) that was also used separately as a comparator in a secondary analysis to compare the results with the recently (2009 and 2011) published studies for DRSP.

Two separate exposure cohorts were included in this study. The first and largest included prevalent users (All Users) with cohort entry initiated at the first recorded prescription during the study period regardless of prior use for both study CHCs or other CHCs. Women were eligible for more than 1 exposure episode in the All User cohort provided they satisfied eligibility criteria. The other cohort, basically a sub-cohort, was an evaluation of New Users (incident) of study contraceptives with no history of ANY hormonal contraception during the 182 days prior to the first recorded study prescription fill. In the New User cohort, women were censored when their exposure period ended.

An exposure period to any one of the study CHC was defined as the prescription period use (dates that are covered by a prescription or series of prescriptions for a single study CHC) plus 42 days (the period of indeterminate use) and is referred to as current use. The rationale to extend the exposure period for 42 days after the end of the actual prescription period was primarily to account for biological effects such as increased coagulability that might persist after CHC use was stopped.

Periods of non-study CHC exposure were not included in the analysis dataset, but were considered in constructing the study CHC exposure data so that non-study CHC use could impact on the actual dates of study CHC exposure by adjusting either the stop date or start date of a study CHC prescription period.

3.2.6 Outcome

The primary study endpoints were hospitalization for acute myocardial infarction (AMI), ischemic stroke (IS), and venous thromboembolic events (VTE), as well as cardiovascular and total mortality.

All potential hospitalized cases were identified by the sites using the following primary discharge codes: AMI (410.x), stroke (430, 431, 432.0, 432.9, 433.x, 434.x, 436), and VTE (pulmonary embolism code 415.1 and DVT codes 451.1, 451.1x, 451.2, 451.8, 451.81, 451.82, 451.84, 451.89, 453.0, 453.1, 453.2, 453.3, 453.4, 453.8, 453.9).

Outpatient DVTs were identified by having an outpatient diagnosis of DVT followed by a first prescription for an anticoagulant (low-molecular weight heparin or warfarin) during the 30-day period subsequent to the diagnosis.

Arterial thrombotic events (ATE) included AMI and IS.

VTE included hospitalized deep venous thrombosis (DVT), hospitalized pulmonary embolism (PE) and DVT diagnosed as an outpatient.

Cardiovascular mortality included deaths resulting from an identified VTE and/or ATE event in the databases as well as deaths identified only by linking to the mortality files.

All hospitalized cases with available medical records were abstracted at the study sites using standardized criteria. Admission and discharge summaries, laboratory tests, and imaging study results were de-identified and sent to the lead site for adjudication. Four physicians adjudicated the cases blinded to the CHC. A cardiologist reviewed all acute myocardial infarctions (AMIs) and a neurologist reviewed most of the stroke cases with the principal investigator (PI) doing the remaining adjudications. Questionable cases were discussed with the principal investigator and a 10% sample of adjudicated cases was independently reviewed by another adjudicator blinded to the study contraceptives.

Outpatient DVTs identified from claims databases cannot be easily validated since they would require access to outpatient records and permission from all treating physicians. For this study, however, medical records of outpatient VTEs from only the lead site were obtained and adjudicated by the PI. Results show an 89.3% positive predictive value (PPV) with use of the outpatient DVT study definition.

Mortality was assessed by linking membership with state mortality files for all women in the study and for the entire study period. Cardiovascular mortality was defined by having an ICD-10 code of I01 to I99 as the underlying cause of death. Mortality from the main study CVD endpoints was also defined by the following ICD-10 codes as the underlying cause of death: acute myocardial infarction (I21.x – I23.x), ischemic stroke (I63.0 – I63.5, I65.x, I66.x), and VTE (I80.x, I81.x, I82.x).

3.2.7 Covariates and confounders

Covariates that were potential confounders or effect modifiers were ascertained from the electronic databases at each site. For this study (and many of the published studies), the covariates assessed as potential confounders in the statistical models were those identified from studies where CHC users were compared to nonusers. When comparing one contraceptive to another, however, the same covariates are not necessarily

confounders and, when included in the statistical models, none seem to change the risk estimate by 10% or more. Potential confounders evaluated included diabetes, hypertension, hyperlipidemia, surgery, ischemic heart disease, acne, thyroid disease. They also included use of other medications such as ACE inhibitors, hormonal replacement therapy, warfarin, platelet inhibitors, NSAIDS. Information on potentially important confounders such as body mass index (BMI), smoking, personal or family history of VTE cannot be reliably captured from claims-based or electronic medical records for all individuals and were not assessed in this phase of the study. A complete list is provided in tables 7a and b of the Final Report and by age group in Appendix A of the Final Report.

Assessment of covariates of interest began during the 6-months prior to a study CHC exposure period and continued to be assessed throughout the exposure period.

Given that a time-varying analysis was planned, the covariates were defined in one of three ways: fixed (chronic conditions), ever-never (only during the current exposure period) and current (mostly concurrent medications and exposures that were considered only during current exposure period (the days supply period).

3.2.8 Statistical Analyses

Cox proportional hazards (PH) regression was used to estimate the relative risk of study endpoints associated with current use of exposure CHCs relative to the comparator CHCs. The Cox proportional hazards model accommodates unequal length of follow-up due to varying duration of CHC exposure, termination of health plan membership, and end of study (i.e. right censoring). Time since cohort entry (i.e. first day of first exposure period during study period) was the time scale used in the Cox regression model. CHC exposure was considered as a 4-level time-varying covariate, capturing current use of the NGMN transdermal patch, ETON vaginal ring, DRSP pill, and the 4 comparator CHCs combined as one category (COMP). In the All Users models, the periods without CHC exposure were considered unobserved or window-censored given that events were not ascertained during these periods.

Cox models were stratified for age using 5-year age intervals, providing tight control for age and freeing the investigators from having to specify the form of the relationship between age and outcomes in the regression models. Additional control for potential residual confounding within age strata was achieved via inclusion of age as a continuous covariate in the regression model.

Age, site, calendar year of entry into study were included in all the Cox PH models. Established CVD risk factors (e.g., hypertension, hyperlipidemia, and diabetes mellitus) were included as fixed covariates in these Cox PH models that included ATE or CVD mortality as outcomes.

Each of the other potential covariates was tested individually in these base models with a decision to include it in further model testing if the estimate of relative risk associated with any of the exposure CHCs (vs. comparators) was changed by 10% or more. Like other published studies, none of the covariates met this criterion for any of the models so that none were included in final modeling. Because hypertension is in the causal

pathway between CHC use and AMI/stroke, the analyses ran models with and without hypertension. Hypertension was retained in the models for ATE because it minimally affected the risk estimates associated with the study CHCs.

Cox proportional hazards modeling was conducted to estimate the relative risks for both All Users and New Users. Modeling was conducted with all four of the comparator CHCs combined (LNG1, LNG2, NETA, and NGM) and with the four comparators kept separate in the model. While the main analyses were planned using the combined comparators, the separation of the comparators in the analyses enabled the estimation of the risks associated with DRSP relative to LNG2, since these preparations both contained exactly 30 μg of EE while two of the other comparators contained less than 30 μg of EE (LNG1 and NETA) and one contained more (NGM with 35 μg EE).

Associations of new use and of all use of CHCs with study endpoints were examined within age strata (10-35 years and 36-55 years) and within two site strata (KP and Medicaid sites).

The New User analyses were confined to the subset of women entering the cohort with exposure to any study CHC but with no previous use of any CHCs (study or non-study) during the prior 6 month cohort entry eligibility interval. In the New User analysis, follow-up ended for each woman at the end of the study CHC exposure period. Duration of use was examined only in the New User cohort.

Age-adjusted rates were calculated using direct adjustment using the age distribution of the entire study population at cohort entry as the standard (5-year age groups). Age- and site-adjusted incidence rate ratios were estimated using Poisson regression modeling.

3.3 STUDY RESULTS

The final All User cohort included 835,826 women with 898,251 person-years of exposure. The New User cohort included 573,680 women with 367,138 person years of observation. The New User cohort included 109,070 women with 80,171 person-years of exposure to DRSP, 62,316 women with 30,152 person-years of exposure to NGMN, 19,143 women with 8,784person-years of exposure to ETON, and 383,151 women with 248,013 person-years of exposure to COMP.

After adjudication, the cohort included 60 AMIs, 78 ischemic strokes, and 625 VTEs. In addition, there were 41 CVD deaths, and 267 total deaths during study CHC exposure periods.

The age-specific incidence rates (Tables 10 a to d in the Final Report and Appendix C in this review) per 10,000 person-years (PY) show an increasing VTE and ATE risk with age for exposure CHCs and comparators alike but for the older age groups (35+ years), the rates were lower for the comparator groups than the exposure CHCs.

Age- and site-adjusted VTE rates per 10,000 PY were higher for the exposure CHCs (DRSP - 10.2; NGMN – 9.8; and ETON - 11.9) than for COMP (6.0) or LNG2 (6.6)). Consequently VTE age- and site-adjusted incidence rate ratios were higher for exposure CHCs regardless of which comparator was used.

On the other hand, age-and site-adjusted ATE rates per 10,000 PY were slightly higher for COMP (1.4) and LNG2 (1.6) than DRSP (1.1) or NGMN (1.1) for All Users but not for New Users.

Similarly, age-and site-adjusted mortality rates per 10,000 PY were also slightly higher for COMP (3.5) and LNG2 (4.5) than DRSP (2.4) or NGMN (3.7) for All Users. For New Users, age-and site-adjusted mortality rates per 10,000 PY were higher for COMP (3.5) and LNG2 (5.4) than DRSP (2.6) and ETON (3.7) but not NGMN (6.3).

In adjusted (age, site, and year of entry into the study) analyses using Cox Proportional Hazard models, DRSP, NGMN, and ETON were associated with a higher risk of VTE relative to low-estrogen comparators (Table 1) in All Users even when only hospitalized VTEs were considered.

Table 1 Relative Hazard* of venous thromboembolic events (VTE) for exposure combined hormonal contraceptives (CHC) among All Users (prevalent use) and New Users (no prior CHC use), All Sites Combined 2001-2007 (Summarized from table 12 a in the Final Report 111022v2).

All VTE (inpatient and outpatient)

	All Users		New Users	
Exposure CHCs	**Relative Hazard**	**95% CI**	**Relative Hazard**	**95% CI**
DRSP	**1.7**	**1.4 - 2.1**	**1.8**	**1.3 - 2.4**
NGMN	**1.6**	**1.2 - 2.1**	1.4	0.9 - 2.0
ETON	**1.6**	**1.0 - 2.4**	1.1	0.6 - 2.2

Hospitalized VTE only

	Relative Hazard	**95% CI**	**Relative Hazard**	**95% CI**
DRSP	**1.8**	**1.4 - 2.3**	**2.1**	**1.5 - 3.0**
NGMN	**1.7**	**1.2 - 2.4**	1.4	0.9 - 2.4
ETON	**1.6**	**1.0 - 2.8**	0.9	0.3 - 2.5

**From Table 12 a in the Final Report. All models were adjusted for age, site, and year of entry into the study and compared to COMP (4 comparators combined)*

Hosp = hospitalized; CI = confidence interval; DRSP = drospirenone with 30 ug ethinyl estradiol; NGMN = norelgestromin transdermal patch; ETON =etonogestrel vaginal ring

Unlike the age-and site-specific and age-adjusted VTE incidence rates which were higher for New Users than All Users, the adjusted risk estimates (hazard ratios) were slightly lower for New Users except for DRSP where the relative hazard estimate was slightly higher than for All Users.

There was no increased risk observed for ATE in this study for any user except for new DRSP users. A relative ATE hazard and 95% confidence interval of 2.0 (1.1 – 3.8) was noted for this group.

Among New Users, duration-of-current use analysis showed a higher VTE risk during the first 3 months for all exposure CHCs but risk estimates for longer durations in these analyses appear to be sensitive to the comparator used in the model and show inconsistent variations.

In analyses the Cox PH analyses stratified by the age groups 10-34 and 35-55 years, the risk of VTE for all 3 exposure CHCs was higher in the younger than in the older age group for All Users and only for DRSP in New User group. There was also an increased risk of ATE associated with DRSP in New Users age 35 years and older. Interaction terms, that is non-additive modifiers of the effect for age, were significant for DRSP for both VTE and ATE ($p<0.001$). VTE risk estimates were also more likely to be statistically significant at the KP sites than in the Medicaid populations. Consequently, all models were adjusted for age, site, and year of entry into the study cohort. The increased VTE risk for younger CHC users has been noted elsewhere. [6,15]

Secondary analyses, using LNG2 alone as the comparator, were conducted since both DRSP and LNG2 products contain 30 μg of ethinyl estradiol. The findings with LNG2 as the comparator generally paralleled the findings for the combined comparators though not as many comparisons reached statistical significance.

The investigators concluded that the NGMN transdermal patch and DRSP were associated with higher risk of VTE relative to standard CHC pills, particularly in women younger than 35 years of age. DRSP was associated with higher risk of ATE in New Users overall with only this finding restricted to women 35-55 years of age. The finding of an increased VTE risk with the ETON vaginal ring relative to standard CHCs is new and raises concern but, due to the small numbers, needs to be replicated in other studies.

4 COMMENTS/DISCUSSION

OSE/DEPI II comments here on the effects of known confounders adjusted in the analysis, the possible influence of potential confounders for which covariates were incompletely captured by the study, and identify important but unmeasured confounders. This section also compares the incidence rates reported by this study with those of other DRSP and NGMN published and unpublished studies.

4.1 FDA-FUNDED STUDY RESULTS HIGHLIGHTS

As expected, age-specific incidence rates per 10,000 person-years (PY) show an increasing VTE and ATE risk with age for study contraceptives and comparators alike. The rate of increase in age-specific incidence rates, however, was lower for the comparator group than for the newer exposure CHCs: DRSP, NGMN, and ETON. Age-adjusted VTE incidence rate ratios were higher for study contraceptives regardless of which comparator was used.

Generally, VTE and ATE age-specific and age-and site-adjusted incidence rates were higher in New Users than All Users. This contrasts with the Cox Proportional Hazard Ratios (adjusted for age, site, and calendar time) which were slightly lower for New Users than All Users except for DRSP where risk estimates did not change (Table 2) but the differences are very small. The differences are likely due to the fact that the Cox PH model adjusted more tightly for age whereas the age-specific rates were presented in approximately 10-year age groups, and the age-and site-adjusted rates were standardized to the age distribution of the entire study population. The Cox PH models also adjusted for calendar time as well as being a time-varying analysis.

Table 2 Relative Hazard* of venous thromboembolic events (VTE) and arterial thrombotic events (ATE) for study combined hormonal contraceptives (CHC) among All Users (prevalent use) and New Users (no prior CHC use), All Sites Combined 2001-2007 (Summarized from Table 12a in the Final Report 111022v2).

Venous Thromboembolic Events (VTE). Includes inpatient and outpatient events				
Exposure CHCs	**All Users**		**New Users**	
vs. COMP	**Relative Hazard**	**95% CI**	**Relative Hazard**	**95% CI**
DRSP	**1.7**	**1.4 - 2.1**	**1.8**	**1.3 - 2.4**
NGMN	**1.6**	**1.2 - 2.1**	1.4	0.9 - 2.0
ETON	**1.6**	**1.0 - 2.4**	1.1	0.6 - 2.2
vs. LNG2 (30 µg EE)	**Relative Hazard**	**95% CI**	**Relative Hazard**	**95% CI**
DRSP	**1.5**	**1.2 - 1.8**	**1.6**	**1.1 - 2.2**
NGMN	**1.3**	**1.0 - 1.8**	1.2	0.8 - 1.9
ETON	1.3	0.8 - 2.0	1.0	0.5 - 2.0
Arterial Thrombotic Events (ATE)				
vs. COMP	**Relative Hazard**	**95% CI**	**Relative Hazard**	**95% CI**
DRSP	1.0	0.6 - 1.7	**2.0**	**1.1 - 3.8**
NGMN	1.3	0.6 - 2.7	1.1	0.4 - 3.2
ETON	1.7	0.6 - 4.8	1.7	0.4 - 7.1
vs. LNG2 (30 µg EE)	**Relative Hazard**	**95% CI**	**Relative Hazard**	**95% CI**
DRSP	0.8	0.5 - 1.4	1.6	0.8 - 3.4
NGMN	1.1	0.5 - 24.8	0.9	0.3 - 2.9
ETON	1.4	0.5 - 4.1	1.3	0.3 - 6.1

**All models were adjusted for age, site, and year of entry into the study*

CI = confidence interval; DRSP = drospirenone with 30 ug ethinyl estradiol; NGMN = norelgestromin transdermal patch; ETON =etonogestrel vaginal ring
COMP = 4 comparators combined

Table 3 shows that the lower bound of the confidence intervals for the VTE relative hazard was higher than 1.0 for all 3 exposure CHCs younger than in the older age group for All Users and only for DRSP in New User group. Again this is contrast with an increased ATE risk associated with DRSP in older New Users (age 35 years and older). Comparisons with LNG2 generally paralleled the findings for the combined comparator group although not as many comparisons reached statistical significance.

Table 3 Relative Hazard* of venous thromboembolic events (VTE) and arterial thrombotic events (ATE) for study combined hormonal contraceptives (CHC) among All Users (prevalent use) and New Users (no prior CHC use) by age groups, All Sites Combined 2001-2007 (Summarized from Table 14a, b andc in the Final Report 111022v2).

Venous Thromboembolic Events (VTE). Includes inpatient and outpatient events				
Age 10 to 34 Years	**All Users**		**New Users**	
vs. COMP	**Relative Hazard**	**95% CI**	**Relative Hazard**	**95% CI**
DRSP	**1.9**	**1.4 - 2.5**	**2.1**	**1.4 – 3.2**
NGMN	**1.6**	**1.1 - 2.3**	1.5	0.9 - 2.4
ETON	**2.1**	**1.3 - 3.4**	1.7	0.8 – 3.8
vs. LNG2 (30 µg EE)	**Relative Hazard**	**95% CI**	**Relative Hazard**	**95% CI**
DRSP	**1.7**	**1.2 - 2.3**	**2.2**	**1.3 – 3.5**
NGMN	1.4	0.9 - 2.1	1.4	0.8 – 2.6
ETON	**1.9**	**1.1 – 3.1**	1.7	0.7 – 4.1
Age 35+ years				
vs. COMP	**Relative Hazard**	**95% CI**	**Relative Hazard**	**95% CI**
DRSP	1.4	1.0 – 1.8	1.2	0.8 - 1.8
NGMN	1.4	0.9 - 2.3	1.3	0.7 – 2.5
ETON	0.7	0.3 – 1.9	0.6	0.1 – 2.3
vs. LNG2 (30 µg EE)	**Relative Hazard**	**95% CI**	**Relative Hazard**	**95% CI**
DRSP	1.2	0.8 - 1.7	1.1	0.7 – 1.7
NGMN	1.2	0.7 – 2.0	1.0	0.5 - 2.1
ETON	0.6	0.2 – 1.6	0.5	0.1 – 2.0

**All models were adjusted for age (5-year age groups), site, and year of entry into the study*

CI = confidence interval; DRSP = drospirenone with 30 ug ethinyl estradiol; NGMN = norelgestromin transdermal patch; ETON =etonogestrel vaginal ring

This study, like other retrospective observational studies published since market approval, shows an increased VTE risk for DRSP among All Users and New Users compared to older products (COMP and LNG2) and an increased ATE risk among New Users when compared to COMP but not to LNG2 (Table 2).

For NGMN, the study shows an increased VTE risk among All Users and, although not statistically significant, the risk is higher for New Users when compared to COMP but not when compared to LNG2. No increased ATE risk for this product was observed when compared to any study comparator.

Risk estimates comparing exposure CHCs to LNG2 are generally lower than when comparing to the entire COMP group. This might be explained by the smaller number of users in the LNG2 group. The confidence intervals, however, are not wider. The main difference between the two groups is that 30% of the COMP contraceptives (LNG1 and

NETA) contain lower estrogen levels (20 μg) than the exposure CHCs and may represent a different population of CHC users. Consequently, COMP represents a more heterogeneous mix of CHC users.

The study was carefully done, is comprehensive, and all hospitalized outcomes have been validated. In addition, one site validated outpatient DVTs. The study was able to link all records to state mortality files, evaluated two different exposure cohorts (All Users and New Users), and the contribution of known confounders in the two very different US populations.

Like other claims-based studies, however, this study is limited in that it captures only information available in the claims databases or in electronic medical records for the outcome cases. Limitations also include the absence of data on key covariates (obesity/BMI, smoking, personal and family history of VTE, lifetime previous use of hormonal contraceptives) and the inability to validate outpatient DVTs by chart review (except at only one site). The small number of ATEs limited the power for analyses of these outcomes, though the rates of these outcomes were consistent with published data.

The Final Report does not provide specific information on the number of VTE and ATE deaths identified only through linkage to the death files and whether the inclusion of at least the CVD deaths would modify the risk estimates reported. This was an important question for which the information is available but which was not provided in the report. This information which will be requested in future analyses.

The study achieved the objectives of the risk assessment phase of the study. The next sections will comment on potential patient and provider characteristics that could be indentified or surmised from this Final Report and others that could be explored. OSE/DEPI II will also comment on potential confounders that could not be addressed by this study.

A key question for the FDA was why some large epidemiology studies show a negative VTE risk for DRSP and NGMN whereas others show an increase VTE risk? The following sections will attempt to answer this question.

4.1.1 Exposure Definitions

Although the results of this study are consistent with other published studies that show an increased VTE risk for DRSP and NGMN when compared to other CHCs, the comparators and the exposure definitions vary across studies.

Comparators

Several earlier studies compared DRSP to LNG only.[4,15,16,17] Others, including the FDA funded study, also compared DRSP to a combined CHC group[8] and still others to non-users as well[18]. Another study compared DRSP to a combined CHC group only.[2]

Unlike the FDA-funded study which compared NGMN both with LNG and with a combined CHC group, other studies compared NGMN with only one other contraceptive type. Two sponsor-funded nested case-control studies and their updates compared NGMN with a norgestimate (NGM) contraceptive containing 35 ug EE[8,11,9,12,13] whereas

another study compared NGMN with LNG only[4]. All these studies used varying definitions of exposure.

Exposure Definitions

Unlike the EURAS study[1] which interviewed women about their lifetime exposures to hormonal contraceptives, studies using insurance claims and electronic medical records cannot capture information on lifetime CHC exposures and are limited to capturing this information in a pre-specified look-back period. Consequently many older women are survivors of previous exposures. Therefore, a definition of a new user usually includes women who are naïve users, switchers with or without a gap, and re-starters, each defined differently in many studies.

Exposure definitions in the published studies referenced in this review usually included a first new prescription fill for the exposure CHC during the study period, with only some studies imposing a new user or initiator design that included only a **study**-contraceptive-free period (or gap) during the specified look-back period allowing use of non-study CHCs.[2, 17] Only three studies required the look-back period to exclude study and non-study CHCs, two of these studies evaluated DRSP only,[15,17] the third was the FDA-funded study which evaluated both DRSP and NGMN. The FDA-funded study evaluated two exposure definitions; one definition basically not imposing any prior use requirement; the other, using a much stricter new user definition and excluded women with any prior CHC use in the prior six months not just the study CHCs. These two extreme exposure definitions using the same design for two different populations (HMO and Medicaid) in one study allows for a better assessment of different exposure definitions across analyses that evaluate risk in different population sources. The comparator group included several contraceptive products that contain either 20 μg, 30 μg or 35 μg of estrogen rather than limiting to one dose as originally proposed. This allows for secondary assessment of patient and provider characteristics although numbers of exposed users are much reduced in the subsets.

All studies, whether designed as cohort or case-control, evaluated current use of the CHCs although many also considered past use or duration of current use separately. The EURAS[1] and Dinger et al[16] studies were the only ones that could consider lifetime use because that information can only be obtained by personal interview.

The published cohort studies[1, 2] recruited first-ever users or switchers to any new study CHC product with one[2] of these studies also imposing no previous dispensing of the study CHCs in the previous 6 months. Lidegaard's 2009 study[18] identified a cohort of contraceptive users with exposure defined as current, previous, or never (included former) used. VTE risk among users was compared to no use. Lidegaard's reanalysis[17] also included a sub-analysis of new users having no CHC use in the previous 12 weeks. Most of these cohort studies evaluated risks for DRSP only. The only case-control study[16] showed no increased risk with DRSP. This study, however, also interviewed cases and community controls to obtain CHC exposure information (current, past, or never use) at the index date. Therefore, differences in VTE risk cannot likely be attributed to differences in study design (cohort versus case-control) but more dependent on study investigators and their ability to capture unmeasured confounders. However

unmeasured confounders can usually only be obtained with direct patient interviews (consenting users), possibly leading to a design that may be subject to selection bias.

All studies that evaluated the NGMN product were case-control studies said to be nested and required both cases and controls to be current users (± 30 days around the index date) of the study contraceptives.[8, 9] The FDA-funded study was the only cohort study that evaluated VTE, ATE, and mortality risks for both DRSP and NGMN. .

Variations in exposure definitions alone, whether it be utilizing a new user or initiator definition (whether study CHC only or all CHCs) or whether an exposure gap is imposed, does not seem to explain the differences seen in VTE risk estimates for DRSP and NGMN provided that study restrictions are applied equally to both exposure groups being compared in the same population source. This is clearly demonstrated in the FDA funded study where the increased risk between DRSP or NGMN and comparators is evident in All Users as well as New Users. The few exceptions may be seen in Lidegaard's DRSP reanalysis.[17] Based on requests from the European regulators, Lidegaard reanalyzed the information from the Danish database and applied the requested restrictions. Although the relative risk estimates, compared to non-users, differed based on the restrictions applied (the relative risk estimates ranged from 2.0 to 6.1 for LNG and from 5.6 to 10.0 for DRSP in the first year of exposure), the ratio of the relative risks for DRSP compared to LNG remained around 1.6 with 2 exceptions. The risk ratio increased to 2.2 and to 2.3 with the inclusion of only confirmed outcome events or the imposition of a CHC-free gap suggesting possible differences between users of the two treatments.

When comparing risk estimates across studies, differences observed may be the result of differences in population characteristics, exposure definitions, study design and/or comparators used. When comparing risk estimates within a study such as the FDA-funded study or Lidegaard's re-analysis, however, differences in risk estimates depend mostly on the selection and exclusion criteria applied. But when applied consistently, to all treatment groups, the resulting risk estimates differ but the relative ratios between a study contraceptive and its comparator should not differ unless the inclusion/exclusion criteria represents differences in treatment for the groups compared (channeling bias). Therefore, caution should be exercised when comparing rates and relative risks across studies.

4.2 KNOWN CONFOUNDERS ADJUSTED IN THE STUDY

Population characteristics that were available for evaluation and included in the statistical model for the control of confounding in the FDA-funded study include age, site, and calendar year of entry. Interaction for age terms (or treatment differences by age) were significant for DRSP both for VTE and ATE ($p<0.001$). For example, the interaction terms can explain if the effect is smaller or larger for younger women. The test for interaction by site in New Users was significant for DRSP only at the $p<0.001$ level in the VTE analysis with COMP. Close examination of these variables and their impact on risk provides some insight into possible population source and user differences among treatment groups.

4.2.1 Age and Age-Specific Incidence Rates

When comparing contraceptive products, investigators for most published studies have either adjusted or matched users on year of birth (exact year or five-year age groups) to control for this important confounder. As a result, CHC use by age cannot be independently examined. Investigators in the FDA-funded study chose not to pre-specify the age relationship. Instead, the Cox models were stratified by 5-year age intervals with the exact age included as a continuous covariate in the regression model to provide additional control for potential residual confounding within the age strata. This provided tight control for age, freed the investigators from having to pre-specify the nature of the relationship between age and outcomes in the regression models, but also allowed for the independent evaluation of the age effect. Several differences across study CHC groups are worth noting.

First, the age-specific VTE and ATE incidence rates increased with age for all contraceptive products examined in this study (Appendix 1). This was true for both New Users and All Users. The magnitude of the difference in the increase of incidence rates between the New User and All Users also increased with age suggesting that older New Users may be at greater risk than younger New Users. For users in the age-group 10 to 24 years, the difference between the DRSP incidence rate per 10,000 for New Users and All Users is only 1.4 whereas for women 35 to 44 years it is 2.6 and for women 45 to 55 years it is 13.6. For LNG2, the comparable differences are 0.0, 5.6, and 9.6 respectively. The increase in rate differences is also seen for COMP: 0.3, 7.3, and 6.3 respectively.

Secondly, as can be seen in Table 4 below, the mean age for women filling prescriptions for DRSP, NGMN and ETON at all sites combined is lower than the mean age for either COMP or LNG2. Only 38% of the COMP users at the KP sites but over 60% of the Medicaid users were younger than age 25 years. These slight differences in the mean age of study cohorts reveal more significant age differences in the groups being compared. The Medicaid sites had proportionally more (73%) women age 10 to 24 years prescribed NGMN compared to the KP sites but the proportion prescribed DRSP and ETON who were young was also high (66%) compared to KP sites.

Table 4: Mean age at first prescription of study contraceptive products (CHC) and proportion of users younger than 25 years by site (Summary of Table 4a1-3 Final Report 111022v2)

	All sites		KP Sites		Medicaid Sites	
CHC	**Mean age**	**Age: 10-24 (%)**	**Mean age**	**Age: 10-24 (%)**	**Mean age**	**Age: 10-24 (%)**
DRSP	25.9	50.0	26.3	47.7	22.9	65.6
NGMN	23.6	52.5	26.6	44.6	22.0	72.8
ETON	25.8	50.3	27.7	39.0	23.3	65.6
LNG2	27.9	42.1	28.7	38.2	23.8	62.1
COMP	27.7	44.7	29.2	37.8	22.8	67.6

Table 5 shows that the age distribution of users at the KP site, however, is more aligned with the age distribution of a nationally projected US population of CHC users identified from the SDI database (Appendix B). As noted previously in the FDA-funded study, the Medicaid user population was much younger than the KP users but that is likely due to the fact that Medicaid covers medical needs of a young population in general.[19] When information from the two sites is combined, the combined population, although slightly younger than the population represented by the nationally projected data, is more representative of users from the general US population.

Also of interest is the greater differences observed in the age distribution of the single CHC product types (see Table 5 or Appendix C in this review for all products) compared to the combined comparator products (COMP). For example, there is a higher proportion of older LNG2 users than NGMN users regardless of database used but that difference is more evident when comparing Medicaid users to KP users or to a nationally projected population of users. Although the differences observed only address age differences, age differences may be a proxy to other population differences as well. By matching DRSP initiators to other CHC initiators on propensity probability scores using insurance information from the 6 months prior to CHC initiation, Seeger[2] may have adjusted for these differences.

Consequently, conclusions reached about the safety of CHC products derived by comparing results across studies should be believed only after it is determined that the populations being treated are similar.

Table 5: Distribution of CHC Use by Age Group, FDA-funded Study (2001-2007 All Users) Compared to US Projected Total Prescriptions (SDI 2002-2007, Tables 4 a1 to a3, Final Report 111022v2).

	Age Group	SDI*	FDA-funded Study	KP**	Medicaid
NGMN	0-25 years	47.6	62.5	44.6	72.8
	26-34 years	34.5	29.2	39.9	23.2
	35+ years	17.5	8.3	15.6	4.1
DRSP_30	0-25 years	44.3	50.0	47.7	65.6
	26-34 years	31.0	34.7	35.9	26.8
	35+ years	24.5	15.2	16.5	7.6
COMP	0-25 years	41.4	44.7	37.8	67.6
	26-34 years	31.2	31.9	31.4	24.2
	35+ years	27.2	23.4	28.1	8.1
LNG2	0-25 years	28.8	42.1	38.2	62.1
	26-34 years	31.6	34.6	35.7	28.8
	35+ years	39.4	23.3	26.1	9.0

**Source: SDI Vector One®: National, Years 2002-2010 Data Extracted September 2011 (only years 2002-2007 shown).*
***KP = Kaiser Permanente*

4.2.2 Incidence Rate Comparisons

One objective of the FDA-funded study was to assess the incidence of ATE, VTE, and death among contraceptive users. For All Users, the overall incidence rate per 10,000 woman years was 6.96 for VTE; 0.67 for AMI, 0.87 for ischemic stroke, 0.46 for CVD mortality and 2.97 for all cause mortality. In this study, the incidence rates were higher for New Users (Appendix B in Final Report) compared to All Users.

The overall VTE incidence rate reported by Lidegaard[18] (4.00 per 10,000 person-years-) is lower than that reported in Table 9 of the FDA-funded study report (6.96 per 10,000). This is generally true for incidence rates reported by other investigators as well although some report age-specific rates only. [20] Other investigators only report product-specific incidence rates.[1,8,9,28] differences in what rate is reported makes direct comparisons challenging. To further complicate comparisons, some investigators report only crude incidence rates[1, 18] whereas others[2,8] also report adjusted rates such as was done for the FDA-funded Study. Variables included in the models for adjustment, however, vary across studies although most include age. The incidence rates for the FDA-funded Study were adjusted for age, site and calendar time.

Venous Thromboembolic Events (VTE)

When reported, age-specific rates increase with age but the rate of increase in some of the published studies is less than that observed in the FDA-funded Study. Lidegaard's[18] overall VTE unadjusted age specific incidence rates increase from 3.0 per 10,000 for women age 20 to 24 years up to 6.6 per 10,000 person-years for women age 40 to 44 years. In the FDA-funded Study, the DRSP age-specific incidence rates for the All User

comparator group increase from 3.4 per 10,000 for the 10 to 24 year age group to 27.4 per 10,000 for women 45 to 55 years. For NGMN, the age-specific incidence rates per 10,000 increase from 5.6 for users 10 to 24 years up to 62.0 for women 45 to 55 years. The age-specific VTE incidence rates per 10,000 among the All User in the FDA-funded study's comparator group are lower and range from 2.8 in women 10 to 24 years up to 16.1 in women age 45 to 55 years. These incidence rates are more comparable to those reported by van Hylckama Vlieg (3.7 per 10,000 in women < 30 years up to 13.3 per 10,000 in women age 40 to 50 years)[20].

Product-specific VTE incidence rates from published studies are similar to those for the FDA-funded study for some products and much lower for others. For DRSP (Table 6), Lidegaard[18] reported a crude incidence rate of 9.1 per 10,000 for DRSP, 8.0 for LNG and 5.2 for other contraceptives compared to the FDA-funded Study. The FDA-funded study reported age and site adjusted VTE rates per 10,000 for All Users of 10.2 for DRSP, 6.6 for LNG2, and 6.0 for all comparators (Table 10 b of the Final Report) although Seeger reported adjusted rates per 10,000 of 13.3 for DRSP and 14.0 per 10,000 for other contraceptives (rates for New Users are higher in the FDA-funded study). Rates reported by Seeger[2] were adjusted for age, calendar time, health plan, history of oral contraceptive use, health service consumption, and chronic medical conditions identified at baseline. In addition, the investigators note that these rates could include women with continuing preexisting conditions. Crude incidence rates among new users were also reported by Parkin[15] for the GPRD study which represents use in the United Kingdom and are much lower than other reported rates: 2.3 per 10,000 for DRSP and 0.9 per 10,000 for LNG with an adjusted risk ratio of 2.7 (1.5-4.7).

Table 6 Incidence rates per 10,000 person-years - DRSP

	All Users			New Users	
Contraceptive	**Lidegaard*[18]**	**Seeger**[2]**	**FDA****	**Parkin[15]**	**FDA**
DRSP	9.1	13.3	10.3	2.3	13.6
LNG	8.0	--	6.5	0.9	9.1
Other	5.2	14.0	5.9		8.4

DRSP = drospirenone with 30 ug EE; LNG = levonorgestrel
**Crude incidence rates*
*** Adjusted rates*

For NGMN (Table 7), however, published VTE incidence rates were lower than those reported in the FDA-funded study likely due to the differences in study design (case-control deemed nested compared to a cohort). Cole[8] reported an age-adjusted VTE incidence rate per 10,000 of 4.1 for NGMN and 1.8 for NGM. The comparable rates per 10,000 in the FDA-funded study were 9.8 for NGMN and 6.0 per 10,000 for the combined comparators which include NGM. Using the PharMetrics database, Jick[9] reported rates per 10,000 of 5.3 for NGMN and 4.2 for NGM. In another study[28] comparing NGMN with LNG, the PharMetrics incidence rates per 10,000 were 5.6 for NGMN and 3.8 for LNG. These rates differed with her use of MarketScan database: 2.5 per 10,000 for NGMN and 2.0 per 10,000 for LNG. For both Cole and Jick studies, incidence rates were only reported with the initial study report and not updated in the follow-up analyses.

Table 7 Incidence rates per 10,000 person-years - NGMN

	All Users			Jick[28]	
Contraceptive	**Cole*[8]**	**Jick[9]**	**FDA**	**PharMetrics**	**MarketScan**
NGMN	4.1	5.3	9.8	5.6	2.5
NGM	1.8	4.2	--	--	--
Other	--	--	6.0	--	--
LNG	--	--	6.6	3.8	2.0

NGMN – norelgestromin patch; NGM – norgestimate with 35 ug EE; LNG – levonorgestrel
** Adjusted rates*

It is noteworthy that incidence rates for all comparators are always lower than those for the newer products. Nonetheless, although differences in incidence rates could be attributed to differences in products used or differences in study design (cohort for DRSP and case-control for NGMN) and case selection, differences reported by Jick's analyses using a similar study design with two different populations (Pharmetrics and Marketscan) underscore the importance of considering differences in population sources selected for a given study. The FDA-funded study also emphasizes the importance of population source since the analyses showed an interaction by site. The KP site captures information from an HMO population compared to the Medicaid population at the other sites.

Arterial Thrombotic Events (ATE)

There are fewer published reports of ATE incidence rates and these are limited to the sponsor funded studies for both DRSP and NGMN. In the EURAS study, Dinger[1] reports crude ATE incidence rates per 10,000 of 0.7 for DRSP, 2.9 for LNG, and 1.7 for other contraceptives. This compares to age- and site-adjusted incidence rates per 10,000 in the FDA-funded study's of 1.1 for DRSP, 1.6 for LNG2, and 1.4 for other comparators. With the exception of other contraceptives, the CHC age-adjusted ATE incidence rates are generally higher than those reported in the EURAS study. As noted for VTE, the incidence rates for the i3 Ingenix[8] and Jick[9] studies were presented only in the initial report and not in the follow-up reports and the number of initial ATE events were too few to allow meaningful comparisons in the initial report. Although each study was extended for two years to obtain information on additional ATE events, risks estimates were reported as odds ratios in the updated reports but incidence rates were not updated with the additional data. This may be explained by the fact that the basic design of the NGMN studies was more of a case-control design although it was reported as a nested and obtaining incidence rates was mostly an after thought that could not be easily updated with the follow-up data.

Mortality

The EURAS study was the only published study reporting on all-cause mortality incidence. Dinger[1] reported a crude mortality incidence rate per 10,000 of 1.4 for DRSP, 2.5 for LNG, and 1.7 for other contraceptives. The FDA-funded Study reported an all-cause mortality rate per 10,000 of 2.4 for DRSP, 4.5 for LNG2, and 3.5 for other comparators.

For NGMN, the FDA-funded study is the only one reporting an incidence mortality rate. The NGMN age-adjusted mortality rate per 10,000 was 3.7 compared to 4.5 for LNG2 and 3.5 for the combined comparators.

The FDA-funded Study is also the only study reporting on adjusted CVD mortality incidence rates. The CVD mortality rate per 10,000 was 0.13 for DRSP, 0.07 for NGMN, 0.48 for LNG2 and 0.60 for all comparators.

The all-cause and CVD mortality rates in these studies are higher for the LNG and other comparator products than for DRSP or NGMN. Whether this is due to an inherent increase risk for LNG when using the product or whether it reflects channeling bias by medical providers who prescribe a perceived safer product to high risk women remains unknown.

Of significant interest both in the EURAS study[1] as well as the FDA-funded Study, incidence rates for ATE and mortality rates (all-cause and CVD deaths) were higher in the LNG/LNG2 group than for DRSP or NGMN. *Whether the higher incidence rates represent a truly higher risk of cardiovascular events and death among LNG/LNG2 users or whether prescribers channel the perceived safer LNG/LNG2 products to higher risk women remains to be evaluated.*

When comparing incidence rates (or any rates) across studies, it is important to note population and database differences as well as the evaluation methods used by the investigators (e.g. crude or adjusted rates). But even when comparing studies conducted by the same investigators, population differences can affect rates obtained. Jick's[28] evaluation of the incidence rates for NGMN and LNG in the PharMetrics compared to the MarketScan, databases is a good example.

4.2.3 Site or Population Source

The FDA-funded Study Medicaid users were on average 4.5 years younger than the KP users. In addition to the age differences, however, the number of users for study CHCs differed by site (Table 8). Medicaid women were more likely to use NGMN prescriptions (24%) than DRSP women (9%) and less likely to use LNG2 (15%) than KP women (27%). The trends were similar for All Users and New Users although New Users were more likely to use DRSP and NGMN than COMP. The differences in use across CHC types at both sites suggest that use of only one CHC type comparator, when evaluating VTE risk in multiple population sources, may be misleading. Type of CHC use varies by populations studied, as demonstrated in this study, and may be affected by differential prescribing, insurance formularies, and site-specific preferences. Several studies have evaluated prescribing patterns among European prescribers who, before prescribing, use indirect markers they consider relevant for differential diagnosis such as family history of venous thromboembolic disease (VTE), headache, smoking, age beyond 35 years, stability of the menstrual cycle, breast tenderness, body mass index, irregular bleeding and acne before prescribing. [21,22] . It is unknown whether there are similar prescribing analyses in U.S. populations.

Table 8. Number of women filling study CHC prescriptions by Site, 2001-2007 (From Tables 4a2 and 3, Final Report 111022v2)

All Users	Kaiser Permanente		Medicaid		Sites Combined	
	Number	Percent	Number	Percent	Number	Percent
Total	**617,943**		**217,883**		**835,826**	
DRSP	123,536	20.0	18,630	8.6	142,166	17.0
NGMN	30,092	4.9	52,845	24.3	82,937	9.9
COMP*	450,214	72.9	136,064	62.4	586,278	70.1
LNG2*	165,838	26.8	33,001	15.1	198,839	23.8
New Users						
Total	**415,654**		**158,026**		**573,680**	
DRSP	95,052	22.9	14,018	8.9	109,070	19.0
NGMN	22,091	5.3	40,225	25.5	62,316	10.9
COMP*	287,320	69.1	95,831	60.6	383,151	66.8
LNG2*	116,787	28.1	20,524	13.0	137,311	23.9

**All LNG2 users are included in COMP therefore percent total add to more than 100.0*

4.2.4 Exclusions

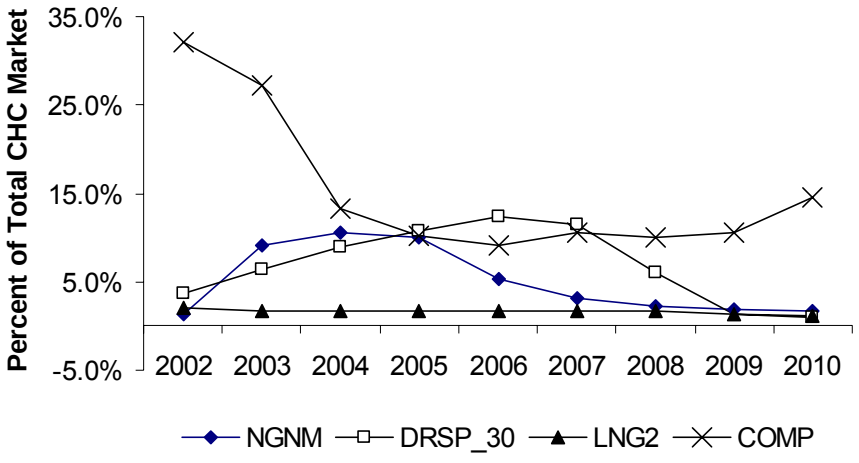
Published studies differed in which women were included in the study. The two DRSP sponsor-funded studies[1,2] did not exclude any women for any reason from the cohort. The only women excluded from the EURAS study were those that refused participation. The Seeger study matched each DRSP initiators to two other non-DRSP initiators using propensity probabilities. It should be noted that there were 428 (2%) of DRSP initiators that could not be matched and were therefore excluded from the cohort analysis. Other studies[18,20] including the FDA-funded study and studies reporting on NGMN[4,5,8], excluded prior to cohort assembly or case and control selection, users who were pregnant or had serious health conditions such as cancer, history of cardiovascular disease, and renal failure. Finally, other studies evaluated[8] or excluded [9,10,12,13,28] users who had any conditions associated with a high risk of VTE and considered only non-fatal, idiopathic VTE cases for analysis. Some of the exclusion or censoring criteria were also applied after cohort entry. These exclusions, if applied equally to each treatment group, do not necessarily bias the study results but may affect the interpretation when results are compared across studies if studies being compared apply different exclusion criteria. A good example is seen in the Lidegaard reanalysis.[17] With no exclusion, the risk estimates during the first year of use was 5.2 (95% CI - 2.2-12.6) for LNG and 8.5 (95% CI - 6.0-11.9) for DRSP. With exclusions implemented, the risk estimates increased to 6.1 (95% CI - 2.7-13.6) for LNG and 9.8 (95% CI - 7.1-13.5) for DRSP. Although the risk estimates increase when the exclusions are applied, the overall DRSP/LNG risk ratios for both are exactly 1.6. Therefore, if comparisons between studies rely solely on absolute risk estimates, than comparisons may be misleading. If comparisons are made using incidence or risk ratios, differences in estimates are less likely to be misleading if only exclusion criteria are considered.

4.2.5 Time Trends

Although the FDA-funded Study did not report on changes in use over time, the analyses did adjust for calendar year. The study report also presents information on length and duration of CHC current use.

Although the FDA-funded study report did not present use information on time trends, nationally projected information from SDI Vona (Figure 1) shows the total number of dispensed prescriptions nationwide for the study contraceptives by year beginning in 2002 through 2010. Dispensed prescriptions for DRSP were increasing during the study period (January 1, 2001 through December 31, 2007) whereas dispensed prescriptions for LNG2 remained relatively steady. The later decreases in dispensed prescriptions for DRSP that begins in 2007 may be related more to the introduction of other drospirenone contraceptives to the market than to adverse publicity. Papers questioning the safety of DRSP were first published in 2009. Dispensed prescriptions for NGMN were increasing until 2005 then decreased to the LNG2 levels by 2007, the decrease for this product was likely due to adverse publicity. Trends for the COMP prescriptions were higher than DRSP or NGMN mostly driven by prescriptions for NGM between 2002 and 2004 and for NETA beginning in 2009. Prescriptions for the study products combined, however, represent less than 25% of total CHC prescriptions. With the exception of COMP in the early years of the study, dispensed prescriptions for all study contraceptives did not exceed 20% of the total combined hormonal contraceptive market. Differences in use over time, at least in the US, mandates the importance that calendar time be considered in any analyses. Incidence rates and hazard ratio results in the FDA-funded study were all adjusted for age, site, and calendar time. Other studies considered the time effect mostly by matching on year of birth, index date, or time or enrollment in the clinical practice.

Figure 1: Total Prescriptions of FDA-funded Study Contraceptives by Year



Source: SDI Vector One®: National, Years 2002-2010 Data Extracted September 2011.

4.2.6 Duration of Use

Although DRSP and NGMN were both approved in 2001, persistency or average duration of use among women in this study is longer (268 days) for DRSP than for

NGMN (177 days) and comparable to COMP (236 days) and LNG2 (259 days). Persistency for the products included in COMP also varies and range from 184 days to 259 days. DRSP had the largest proportion (21.7%) of New Users continuing use for more than 365 days. Consequently, comparison of ATE, VTE, and mortality risks by duration of use between NGMN and COMP or LNG2 may be unreliable for any time period longer than 180 days (6 months). Questions on whether the low NGMN persistency in this study is the result of adverse publicity, problems (such as adverse events and acceptability) with the product, or whether it is an enrollment artifact remains unresolved (continuous enrollment in Medicaid may be of short duration due to the nature of the benefit design and eligibility criteria). Low persistency for NGMN product, however, has been reported elsewhere.[23,24]

Table 9: Mean Number of Days and Proportion of New Use by Study Combined Hormonal Contraceptives (CHC), All Sites 2001-2007 (Adapted from Table 5, Final Report 111022v3)

CHC	Mean (days)	% < 90 days	% >365 days
DRSP	268.3	18.6	21.7
NGMN	176.6	37.3	11.4
ETON	167.4	34.9	9.8
LNG2	*258.6*	*18.6*	*19.9*
COMP	*236.3*	*21.4*	*17.2*

4.2.7 Duration of Use: Comparison of VTE Risk

When comparing DRSP to COMP, the hazard ratios for VTE among New Users show an statistically significant increased risk for DRSP for use less than 3 months among (HR 1.9; 95% CI - 1.2-3.0) and a non-statistically significant but elevated risk for NGMN (HR - 1.6; 95% CI - 0.9-2.8) during the same period of use. Statistical significance is reversed, however, when using LNG2 as comparator (DRSP = HR 1.6; 95% CI - 0.9-2.7; NGMN = HR - 2.5; 95% CI - 1.4-4.5).

The risks are lower for use between 3 to 6 months for all study products but only for DRSP when compared to COMP. Risk estimates for duration of use for 12 months or longer are unreliable due to the decrease in number of exposure episodes lasting this long among New Users of DRSP, NGMN, COMP and LNG2. Although the risk estimates do not necessarily change direction, whether one interprets the results as a statistically significant different or not, the results are heavily dependent on the comparator used as well as changes in use over time for each product.

4.3 OTHER POTENTIAL CONFOUNDERS AND PRESCRIBING PATTERNS

All approved CHCs are effective in preventing pregnancy. Therefore which CHC formulation is prescribed may depend on patient preferences, existing health conditions, prescriber knowledge and preferences, and economic factors that include reimbursable products and insurance formulary restrictions. The current study captures some but not all of these potential confounders, some of which may influence the results observed in

the FDA-funded and all other studies. Although not always measured, these potential confounders and their potential impact on observed risk estimates cannot be ignored.

4.3.1 Measured Covariates

Although the investigators for the FDA-funded study included some known cardiovascular risk factors in the ATE analytic models, other covariates, known to predict VTE risk in users compared to non-users, were tested individually for possible inclusion in the VTE analytical models. Because none of these covariates changed the risk estimate by 10% or more, none were included in the final analysis. The same observation was reported by investigators for the i3 Ingenix DRSP and NGMN studies. Nonetheless, the CHC Final Report provides a summary of these covariates in tables 7a (New Users) and 7b (All Users). The same information is also provided in Appendix B for New Users separately by age group 10-34 years, 35-55 years (Table 10). Although none of the covariates contributed to a 10% change in the analytical models for the entire study cohort, some covariates such as acne, premenstrual tension, and potassium sparing diuretics were present more frequently in DRSP users and particularly in New Users younger than 35 years of age, the group with the higher VTE risk in this study. No covariate was present as prominently for NGMN although there was a tendency to have more New Users with codes for heart disease, coagulopathy, migraine, and drug dependency among younger users (< 35 years of age) suggesting possible prescribing differences and channeling.

Table 10: Proportion of Study CHC Users with Select Covariates by Age Groups and Study Contraceptives, All Sites 2001-2007.

Covariates		All ages		Age 10-34	Age 35-55
		New Users	All Users	New Users	New Users
Acne	DRSP	4.2	4.3	4.6	1.9
	NGMN	0.7	0.9	0.7	0.4
	COMP	2.1	2.5	2.5	0.8
Premenstrual Tension	DRSP	0.2	0.2	0.1	0.7
	NGMN	0.0	0.1	0.0	0.0
	COMP	0.1	0.1	0.1	0.3
Diuretic K sparing	DRSP	0.9	1.2	0.7	2.0
	NGMN	0.4	0.6	0.3	1.7
	COMP	0.8	1.2	0.4	2.2
Polycystic ovarian syndrome (PCOS)	DRSP	0.0	0.0	0.0	0.0
	NGMN	0.0	0.0	0.0	0.1
	COMP	0.0	0.0	0.0	0.0

Although not captured in the FDA-funded study, other gynecological disorders besides menstrual disorders may also be responsible for an increase VTE risk. The NGMN extension study completed by i3 Ingenix report a lower VTE risk when adjusting for gynecological disorders (OR 1.5; 95% CI 0.7-3.6)[25] for the extension year 2005-2006 compared to the unadjusted VTE risk (OR 2.1; 95% CI 1.2-3.6) for the same extension

year 2001-2006 and a five-adjusted VTE risk (OR of 2.1; 95% CI 1.2-3.3) which accounts for matching and initiator status[26] Although it could be argued that comparing risk estimates from different years is misleading, the interim report[27] does provide the VTE risk estimates for only the 2005-2006 year (OR 2.1; 95% CI 1.2-3.6). This risk estimate is similar to that reported for the whole study.

The BCDSP investigators, in their 2010 manuscript,[28] provided univariate risk estimates for the covariates selected for analysis. When comparing currently exposed (NGMN and LNG) cases and controls, gynecological disorders (menstrual disorders, endometriosis, uterine fibroids) showed a twofold increased risk of VTE in the MarketScan database (OR 2.0; 95% CI 1.2-3.5) although this was not seen in the PharMetrics database (OR 1.2; 95% CI 0.5-3.2).

4.3.2 Prescribing Patterns

The Society of Obstetrics and Gynecology of Canada (SOGC) Clinical Practice Gynecology Committee (whose guidelines were approved by the Executive and Council of the SGOC)[29] suggest that because newer products tend to be prescribed to women who already have VTE and ATE risk factors, occurrence of outcomes may be selectively biased towards certain products, giving a misleading impression of risk. If this statement is true for many CHC prescribers, any resulting epidemiologic analyses should seriously consider and adjust for potential channeling bias. This statement is also consistent with the observation that the newer (at study initiation) products, at least in the more recent published studies and the FDA-funded study, are nearly always associated with an increased risk of thrombotic and thromboembolic events when compared to older products. The FDA-funded Study was initiated to begin a deeper examination of these concerns.

The literature assessing prescribing patterns, however, is overwhelmingly European and describes prescribing patterns of European clinicians who may have different prescribing patterns than US clinicians. Nonetheless, the findings by Bitzer and colleagues[21] are worth considering. The authors note that Swiss gynecologists and general practitioners use indirect markers for differential prescribing. The most relevant criteria were family history of VTE, headache, smoking, stability of the menstrual cycle, breast tenderness, body mass index, irregular bleeding, age beyond 35 years and acne. The 20 μg EE dosage was preferred for women older than 35 years, those smoking more than 15 cigarettes per day, those with a family history of VTE, and those complaining of breast tenderness or headache. The 30 μg EE dosage was preferred for patients with a history of irregular bleeding, a family history of osteoporosis, expected poor compliance and acne.

With the exception of the Dinger and the Vlieg studies where investigators were able to interview the women, all other studies (including the FDA-funded study) rely on information captured in claims or electronic databases. Therefore information on family history of VTE, headache, smoking, stability of the menstrual cycle, breast tenderness, body mass index, irregular bleeding is not readily available or available only for hospitalized cases. Information on irregular bleeding, poor compliance, acne and other diagnosed conditions may be available but are frequently not captured.

4.3.3 Unmeasured Covariates

As suggested in the previous section, serious consideration needs to be given to the possibility for channeling bias when comparing progestin types. Both the 2004 European Society of Human Reproduction and Embryology (ESHRE) Workgroup[30] and the 2010 American College of Obstetricians and Gynecologists Guidelines[31] address the non-contraceptive benefits of hormonal contraceptive use, summarize scientific studies that support these benefits, and provide prescribing recommendations. The potential benefits of interest that may influence the results of this and other epidemiologic studies include use of hormonal contraceptives to treat menorrhagia (heavy menstrual bleeding), dysmenorrhea (painful menses), premenstrual syndrome, acne or hirsutism, bleeding due to leiomyomas, pelvic pain due to endometriosis, and menstrual cycle regulation. Some CHCs are approved for treatment of acne (DRSP and NGM) and PMDD (DRSP) although approval of DRSP for treating these conditions (in addition to contraception) is very recent (2006-2007). ESHRE and ACOG Guidelines[30,31] and other published reports mention the anti-androgenic benefits of DRSP and desogestrel for treating these conditions which could possibly lead to channeling bias. The FDA-funded Study did not capture information on many of these conditions during the risk assessment phase other than acne, polycystic ovary syndrome, migraines, dysmenorrhea, and premenstrual tension. The presence of these health conditions by themselves does not necessarily bias the results of the study even if present disproportionally across treatments being compared unless they also increase the woman's risk of having a thrombotic or a thromboembolic event. Information on the VTE risk for these women, however, is scant.

The FDA-funded Study (and most postmarketing studies) however, identified users of study CHCs from claims databases or electronic medical records. Therefore, they very likely would capture the experience of <u>all</u> CHC users, not just that of women who use CHCs mostly for contraception. If women using CHCs mostly for the non-contraceptive benefits of CHCs are at increased risk of VTE by nature of their condition, and if specific CHC products are preferred in treating those conditions (channeling), then differences in risk estimates observed between the CHC products may be attributed to a specific product but would likely be the result of the health condition.

Acne, hirsutism, alopecia and PCOS: There is no reason to believe, based on the available literature, that the presence of acne by itself places a woman at greater risk for VTE. Acne, however, is thought to be present in about 10 to 34% of women with polycystic ovary syndrome (PCOS)[32] and is one of the symptoms, in addition to hirsutism and alopecia (conditions not captured in the FDA-funded Study) frequently associated with PCOS. PCOS women tend to be overweight and possibly at increased risk of experiencing a VTE (1.8; 95% CI 1.1-2.9) when compared to women without PCOS[33]. Based on the results of the Chuan study, it remains unclear whether this increase in risk was solely a treatment effect, due to the disease, or an effect of both disease and treatment. Spironolactone is one product used for treating acne in these women and hormonal contraceptive use is recommended while on spironolactone treatment[32]. Although there were very few women with a diagnosis of PCOS in the FDA-funded Study (Table 10), given that the drospirenone in DRSP is known to have anti-androgenic activity and that DRSP is also a hormonal contraceptive, it is highly likely that this product would be preferentially prescribed to women whose acne, as determined by their

health care providers, might be a marker for developing PCOS. Whether women with PCOS are at increased risk of VTE is not clear. The 2010 Guidelines[31] summarize two small randomized clinical trials (RCT) that demonstrated DRSP and the third generation desogestrel benefits in treating acne and hirsutism were as effective as other CHC products compared.

In the FDA-funded Study, acne was present twice as frequently among DRSP users than COMP users despite the fact that COMP also included an NGM product approved for the treatment of acne. What proportion of women with acne using DRSP in the FDA-funded study that also had hirsutism and/or alopecia is unknown at this time.

Menorrhagia and Bleeding

The ESHRE guidelines[30] note that approximately 10 % of fertile women suffer from menorrhagia and menstrual blood loss. Anemia could be present if the blood loss is severe. Treatment benefits with use of CHCs containing 30 to 35 ug EE have been reported to reduce bleeding by as much as 50%. Very few studies, however, have evaluated the risk of VTE among menorrhagic women. In a case-control study, Sundström[34] noted an association between an increased VTE risk and recent diagnosis of anemia or hemoglobin values less than 11.5 g/dl (odds ratio 2.2; 95% confidence interval 1.0-4.9). The results suggested that a diagnosis of anemia or having low hemoglobin levels during 14 days before or after a record of menorrhagia could be a predictor of disease severity as well as susceptibility to VTE. Other confounders, however, were also observed in this study since cases also had a high BMI and were likely to be smokers. The Guidelines[31,30] note that all CHCs (LNG, desogestrel) may provide short term benefits in reducing bleeding but that continuous or extended use CHCs may be most beneficial. The FDA-funded Study did not capture information on menorrhagia.

Migraines

According to the SOGC 2010 Guidelines[31], menstrual migraines (with no aura) occur in 8% to 14% of reproductive age women. These migraines are experienced exclusively at the time of menstruation with very few also occurring at ovulation. The Guidelines summarize studies that show the benefit of extended cycle or continuous hormonal contraceptives. The Guidelines and others[35], however, caution about use of combined hormonal contraceptives for migraines due to the possible increase risk for a experiencing a cerebrovascular stroke.

The FDA-funded Study shows a higher proportion of younger women with a code for migraine with NGMN (2.1%) and ETON (2.5%) than COMP (1.9%) or DRSP (1.9).

IMS Pharmetrics –Non-contraceptive Diagnoses

It is unclear what proportion of CHC users is prescribed CHCs for non-contraceptive benefits in addition to their contraceptive benefit. Information from the FDA-funded study captured only some of these associated diagnoses and it is also not representative of the US population. To obtain a better understanding on whether use of CHCs for related non-contraceptive indications could be an important confounder in a larger US

population (PharMetrics[e]), we examined recorded diagnoses within 30 days of a first CHC prescription close to the same time period (2002 and 2007) as the FDA-funded study. The same new user exposure definition was applied to the selected cohort and the same CHC products were selected using the FDA-funded study's NDC numbers.

In reviewing information from this US database, 252,943 unique patients were identified that filled a prescription from any CHC drug class. After selecting CHCs with the same NDC number in the FDA-funded study, and selecting only women who were incident users (no CHCs in the prior six months), 38,872 (15.4%) users were selected for evaluation. Diagnoses of interest, representing possible non-contraceptive indications for use, were examined. Only the first diagnosis of interest that occurred within 30 days of the first CHC prescription drug claim was identified. Among the incident cohort, NGM was used more frequently (32%) followed by DRSP (19%), NGMN (15%), and LNG1 (13%).

In this population, there were 4,946 diagnoses of interest temporally associated with first new use of the study CHC. Although all study CHCs had temporally associated diagnoses of interest, DRSP and NGM were dispensed more frequently to women with codes for all conditions except menorrhagia (heavy bleeding). Women with codes for PCOS, PMTS, and hirsutism were more frequently taking DRSP (Table 11).

Table 12 shows the distribution of codes for the selected conditions among women dispensed each CHC. Again, all CHCs were associated temporally with all selected conditions although DRSP was more frequently temporally associated with PCOS, PMTS, and hirsutism. The older CHCs, on the other hand, were temporally associated more with dysmenorrhea (pain) and menorrhagia (heavy bleeding) although DRSP was dispensed just as frequently with codes for dysmenorrhea. The study CHCs were more frequently associated temporally with PCOS, dysmenorrhea, hirsutism, and acne in users younger than 35 years of age than older users. Although these diagnoses have not been validated (e.g. medical charts obtained to determine that these women indeed meet a case definition for these disorders), these data are suggestive of differential prescribing of contraceptives to women with and without these conditions, particularly for younger women.

In the FDA-funded study, more women dispensed DRSP had codes for acne (4.3%) and PMTS (0.2) compared to COMP (2.5% acne and 0.1% PMTS) whereas more women dispensed NGMN had codes for PCOS (0.04%) than COMP (0.01%). Hirsutism was not captured. These proportions are lower than those observed in PharMetrics (Table 12).

[e] *IMS Health, IMS Health Lifelink™, 1/1/2002 to 12/31/2007.*

Table 11. Distribution of study CHCs (%) for Selected Health Conditions, 2002-2007

	PCOS	Pain*	PMTS**	Bleeding*	Hirsutism	Acne
	100.0	100.0	100.0	100.0	100.0	100.0
DRSP	47.6	18.6	33.2	16.7	47.4	24.4
NGM	22.9	29.0	17.3	14.5	26.6	49.3
NGMN	5.9	14.1	7.3	8.3	8.4	6.5
ETON	3.1	3.0	5.9	5.2	2.0	3.6
NETA	6.1	10.8	10.7	18.8	2.6	3.8
LGN2	3.8	8.3	8.0	7.3	3.3	4.0
LGN1	10.7	16.3	17.7	29.2	9.7	8.5

Source: IMS Health, IMS Health Lifelink™, 1/1/2002 to 12/31/2007
CHC – all-time use of study combined hormonal contraceptive;
Dx – diagnosis occurring within 30-days of first CHC prescription date (index date);
PCOS – polycyctic ovarian syndrome;
** pain - dysmenorrhia; bleeding - menorrhagia*
*** PMTS – premenstrual tension syndrome*

Table 12. Distribution (%) of Selected Health Conditions among study CHCs, 2002-2007

	PCOS	Pain*	PMTS**	Bleeding*	Hirsutism	Acne
DRSP	4.4	11.2	2.3	0.4	1.7	8.2
NGM	1.0	8.8	0.6	0.2	0.5	8.2
NGMN	0.6	8.9	0.5	0.2	0.3	2.2
ETON	0.8	4.6	1.1	0.3	0.2	3.2
NETA	1.1	12.3	1.4	0.8	0.2	2.5
LGN2	0.8	11.5	1.2	0.4	0.3	3.1
LGN1	1.1	11.0	1.4	0.8	0.4	3.3

Source: IMS Health, IMS Health Lifelink™, 1/1/2002 to 12/31/2007
CHC – all-time use of study combined hormonal contraceptive;
PCOS – polycyctic ovarian syndrome;
** pain - dysmenorrhia; bleeding - menorrhagia*
*** PMTS – premenstrual tension syndrome*

In conclusion, the IMS data show possible prescribing preferences or channeling for non-contraceptive benefits may exist in the U.S. Whether channeling effects are seen in other study populations remains to be evaluated.

4.4 UNMEASURED BUT SUSPECTED CONFOUNDERS

Information on age, duration of current product use, and selected covariates (dysmenorrheal, acne, migraines, and premenstrual tension) were available for evaluation in the FDA-funded study and provided in the Final Report. Information on other concomitant diagnoses such as anemia, menorrhagia, endometriosis, and hirsutism might be available but was not collected. Unfortunately, other likely important variables, noted in the previous sections, such as body mass index (BMI), smoking, lifetime contraception use, and family and personal history of VTE were unavailable for this analysis. Those

potential important confounders were also not available for most of the DRSP published postmarketing studies and all the published NGMN studies and remain a concern.

There were two postmarketing studies required by the FDA or European regulatory agencies that reported no increase VTE risk between DRSP and LNG or other progestins. The studies were able to obtain information or address the important confounders not available in claims databases or electronic medical records either by direct interview with the women[1] or by matching on the probability of having similar baseline characteristics to the DRSP initiator using the information available at the time of initial use.[2] Although other methodological differences exist between these early studies and those conducted later, having the ability to capture or match on important VTE confounders may be the most important difference.

At the time this FDA-funded Study was conceptualized, two phases were considered. The first would include a risk assessment component that would also obtain sufficient patient and prescribing characteristics allowed with the use of claims data and hospitalized records. If an increased risk was observed, however, a second phase would be considered. The second phase would include more extensive medical record review and possible physician and patient interviews to obtain the information on the important but missing confounders. Whether this second phase is completed depends on its feasibility at this time and the availability of funds.

5 CONCLUSIONS AND RECOMMENDATIONS

The results of the FDA-funded study are consistent with the published studies demonstrating an increase VTE risk among current users of DRSP and NGMN particularly among women younger than 35 years of age. This study is also the first to report an increase ATE risk among older DRSP users. Linkage to state mortality files did not reveal any large discrepancy in missed ATE and VTE case identification. The increase VTE risk for ETON needs further evaluation.

The FDA-study showed that incidence rates increase with age both in all users and new users. Age-specific incidence rates were higher for new users than for all users but not for the adjusted rates. This study also demonstrated the importance of considering differences in population sources, population characteristics, and comparators when comparing product types including the possible channeling by prescribers for non-contraception benefits provided by these products.

The study was carefully done, is comprehensive, and all hospitalized outcome have been validated with medical records. One site also validated outpatient DVTs. In addition, the study was able to link records to state mortality files, evaluated two different exposure cohorts (All Users and New Users), and the contribution of known confounders in the two very different US populations (Medicaid and a large HMO).

Like other claims-based studies, however, the study is limited in that it captures only information available in the claims databases or in electronic medical records for cases only. Limitations also include the absence of data on key covariates (obesity/BMI, smoking, personal and family history of VTE, lifetime use of hormonal contraceptives) and the inability to validate outpatient DVTs by chart review (except at only one site).

The small number of ATEs limited power for analyses of these outcomes, though the rates of these outcomes were consistent with published data.

The FDA-funded study as well as most postmarketing studies, however, identified all users of study CHCs from claims databases or electronic medical records. Therefore, the studies very likely would capture the experience of all CHC users, not just the experience of women who use CHCs mostly for contraception. And even though some studies excluded women with known risk factors for experiencing VTEs, none have assessed whether channeling by prescribers and potential risk associated with CHC use for non-contraceptive benefits. If women using CHCs mostly for the non-contraceptive benefits of CHCs are at increased risk of VTE by nature of their condition, and if specific CHC products are preferred over other CHCs in treating those conditions (channeling), then differences in risk estimates observed between the CHC products may be attributed to a specific product but would more likely be the result of the health condition.

None of the studies to date provides a definitive answer as to the safety of DRSP and NGMN with regard to thrombotic and thromboembolic events (TTE). The entire body of studies provides conflicting evidence that cannot be easily reconciled by any single difference among studies. Most of these studies have unique strengths and limitations, but the challenge lies in trying to reconcile multiple methodological differences among studies conducted in very different populations, often using different comparators and different exposure definitions. There is a history that newer contraceptive products being observed often have associations with increased risk for thrombotic and thromboembolic events and the Agency would like to better understand whether channeling of newer products to patients already at higher risk for these events may play a role. The FDA-funded study was originally designed to be the first phase in a multi-phase study designed to address many of the unresolved questions perceived by the Agency to possibly provide alternative explanations for the risks seen, other than the individual drugs themselves.

Since FDA cannot at this time determine whether or not the increased risk seen for thrombotic and thromboembolic events in some of the epidemiologic studies is actually due to use of the DRSP and NGMN products, we believe that, because of the consistency in recent reports for an increased risk, product labeling should reflect that very real possibility. However, the Agency advocates further study of this issue, as part of a larger effort to better understand the risk for thrombotic and thromboembolic events associated with all newer contraceptive agents. Such studies should assure the comparability of population sources, study design, exposure definitions, and adequate capture and adjustment of age, non-contraceptive co-indications, other co-morbid diseases (e.g. ob/gynecological conditions), and known confounders such as BMI, smoking, and personal and family history of thrombotic and thromboembolic events.

For contractual purposes, the Final Report, presenting results from the risk assessment phase of this study achieved its objectives.

6 REFERENCES

[1] Dinger JC, Heinemann LAJ, Kühl-Habich D. 2007. *The Safety of a drospirenone-containing oral contraceptive: final results from the European Active Surveillance study on oral contraceptives based on 142,475 women-years of observation.* Contraception, 75:344-354.

[2] Seeger JD, Loughlin J, Eng PM, Clifford CR, Cutone J, and Walder AM. 2007. *Risk of thromboembolism in women taking ethinylestradiol/drospirenone and other oral contraceptives.* Obstetrics and Gynecology; 110(3):587-593.

[3] Eng PM, Seeger JD, Loughlin J, Clifford CR, Mentor S, and Walker AM. 2008. *Supplementary data collection with case-cohort analysis to address potential confounding in a cohort study of thromboembolism in oral contraceptive initiators matched on claims-base propensity scores.* Pharmacoepidemiology and Drug Safety, 17:297-305.

[4] Jick SS, Hernandez RK. 2011. *Risk of non-fatal venous thromboembolism in women using oral contraceptives containing drospirenone compared with women using oral contraceptives containing levonorgestrel: case-control study using United States claims data*. BMJ 2011;340:d2151 doi:10.1136/bmj.d2151.

[5] Parkin L, Sharples K, Hernandez RK, Jick SS. 2011. *Risk of venous thromboembolism in users of oral contraceptives containing drospirenone or levonorgestrel: nested case-control study based on UK General Practice Research Database*. BMJ 2011;340:d2139 doi:10.1136/bmj.d2139

[6] Lidegaard Ø, Løkkegaard E, Svendsen AL, and Agger C. 2009. *Hormonal contraception and risk of venous thromboembolism: national follow-up study*. BMJ 2009;339:b2890 doi:10.1136/bmj.b2890

[7] van Hylckama Vlieg A, Helmerhorst FM, Vandenbroucke JP, Doggen CJM, Rosendaal FR. 2009. The venous thrombotic risk of oral contraceptives, effects of oestrogen dose and progestogen type: results of the MEGA case-control study. BMJ 2009;339:b2921 doi:10.1136/bmj.b2921

[8] Cole JA, Norman H, Doherty M, and Walker AM. 2008 *Venous Thromboembolism, Myocardial Infarction, and Stroke among Transdermal Contraceptive System Users*. Obstetrics & Gynecology 2007; 109(2): 339-346. Erratum 2008: 111(6):1449.

[9] Jick SS, Kaye JA, Russmann S, and Jick H. 2006. *Risk of nonfatal venous thromboembolism in women using a contraceptive transdermal patch and oral contraceptives containing norgestimate and 35 μg of ethinyl estradiol*. Contraception; 73:223-228.

[10] Jick SS and Jick H. 2007. *The Contraceptive Patch in Relation to Ischemic Stroke and Acute Myocardial Infarction.* Brief Reports. Pharmacotherapy; 27:218-220.

[11] Dore DD, Norman H, Loughlin J, Seeger JD. 2010. *Extended case-control study results on thromboembolic outcomes among transdermal contraceptive users.* Contraception; 81:408-413.

[12] Jick S, Kaye JA, Li L and Jick H. 2007. *Further results on the risk of nonfatal venous thromboembolism in users of the contraceptive transdermal patch compared to users of oral contraceptives containing norgestimate and 35 μg of ethinyl estradiol.* Contraception 2007; 76:4-7.

[13] Jick SS, Hagberg KW, Kaye JA. 2010. *Ortho Evra and Venous Thromboembolism: An Update*. Letter to the Editor. Contraception; 81:452-453.

[14] FDA Office of Surveillance and Epidemiology. 2011. *Combined hormonal contraceptives (CHCs) and the risk of cardiovascular disease endpoints*. October 22, 2011 http://www.fda.gov/downloads/Drugs/DrugSafety/UCM277384.pdf

[15] Parkin L, Sharples K, Hernandez RK, Jick SS. 2011. *Risk of venous thromboembolism in users of oral contraceptives containing drospirenone or levonorgestrel: nested case-control study based on UK General Practice Research Database*. BMJ 2011;340:d2139 doi:10.1136/bmj.d2139

[16] Dinger J, Assmann A, Mőhner S, and Minh TD. 2010. *Risk of venous thromboembolism and the use of dienogest- and drospirenone-containing oral contraceptives: results from a German case-control study*. *J Fam Plann Reprod Health Care*; 36(3): 123–129.

[17] Ouellet-Hellstrom R. 2011. *Review of Lidegaard's Reanalysis*. September 3, 2011. RCM 2011-1764.

[18] Lidegaard Ø, Løkkegaard E, Svendsen AL, and Agger C. 2009. *Hormonal contraception and risk of venous thromboembolism: national follow-up study*. BMJ 2009;339:b2890 doi:10.1136/bmj.b2890

[19] U,S,DHHS Health Care Financing Administration. 2000. *A Profile of Medicaid*, Chart Book. September 2000.

[20] van Hylckama Vlieg A, Helmerhorst FM, Vandenbroucke JP, Doggen CJM, Rosendaal FR. 2009. *The venous thrombotic risk of oral contraceptives, effects of oestrogen dose and progestogen type: results of the MEGA case-control study.* BMJ 2009;339:b2921 doi:10.1136/bmj.b2921

[21] Bitzer J, Frey B, von Schönau M, Sabler N, and Tschudin S. 2009. *Twenty or thirty microgram ethinyloestradiol in an oral contraceptive: Does itmakea difference in the mind and the daily practise of gynaecologists and general practitioners?* The European Journal of Contraception and Reproductive Health Care; 14(4):258–267

[22] Sannisto T and Kosunen E. 2010. *Provision of contraception: a survey among primary care physicians in Finland*. Acta Obstetricia et Gynecologica; 89: 636–645.

[23] Nelson AL, W C, and Schnare SM. 20087. *Real-World Patterns of Prescription Refills for Branded Hormonal Contraceptives. A Reflection of Contraceptive Discontinuation*; Obstetrics & Gynecology, 112(4): 782-787.

[24] Murphy PA and Bixner D. 2008. *Hormonal contraceptive discontinuation patterns according to formulation: investigation of associations in an administrative claims database*. Contraception; 77: 257-263.

[25] i3 Ingenix. 2008. *The Risk of Venous Thromboembolism, Myocardial Infarction, and Ischemic Stroke Among Women Using the Transdermal Contraceptive System Compared to Women Using Norgestimate-Containing Oral Contraceptives With 35 μg Ethinyl Estradiol Nested Case-Control Extension 2005-2006*. Interim Report. June 18 2008

[26] i3 Ingenix. 2009. *The Risk of Venous Thromboembolism, Myocardial Infarction, and Ischemic Stroke Among Women Using the Transdermal Contraceptive System Compared to Women Using Norgestimate-Containing Oral Contraceptives With 35 μg Ethinyl Estradiol Nested Case-Control Study*. Final Report. June 29, 2009.

[27] i3 Ingenix. 2008. *The Risk of Venous Thromboembolism, Myocardial Infarction, and Ischemic Stroke Among Women Using the Transdermal Contraceptive System Compared to Women Using Norgestimate-Containing Oral Contraceptives With 35 μg Ethinyl Estradiol Nested Case-Control Study Extension 2005-2006 Interim Report June 18, 2008.* Prepared for Johnson & Johnson PRD Confidential

[28] Jick SS, Hagberg KW, Hernandez R, and Kaye JA. 2010. *Postmarketing study of OrthoEvra® and levonorgestrel oral contraceptives containing hormonal contraceptives with 30 mcg of ethinyl estradiol in relation to nonfatal venous thromboembolism.* Contraception 81:16-21.

[29] SOGC Clinical Practice Guidelines. 2011. *Oral contraceptives and the risk of venous thromboembolism: An update No. 252, December 2010.* International Journal of Gynecology and Obstetrics 112 (2011) 252–256.

[30] The ESHRE Capri Wrokshop Group. 2005. *Noncontraceptive health benefits of combined oral contraception.* Human Reproduction Update; 11(5): 513-525.

[31] The American College of Obstetricians and Gynecologists. 2010. *Noncontraceptive Uses of Hormonal Contraceptives Clinical Management Guidelines for Obstetrician-Gynecologists, Number 110, Janu ary 2010.* OBSTETRICS & GYNECOLOGY, 115(1): 206-218.

[32] Chuan SS and Chang RJ. 2010. *Polycystic Ovary Syndrome and Acne*. Skin Therapy Lett; 15(10):1-4.

[33] Seaman HE, de Vries CS, and Farmer RDT. 2004. *Venous thromboembolism associated with cyproterone acetate in combination with ethinyloestradiol*

(Dianette1): observational studies using the UK General Practice Research Database. PDS 13:427-436.

[34] Sundström A, Seaman H, Kieler H, Alfredsson L. 2009. *The risk of venous thromboembolism associated with the use of tranexamic acid and other drugs used to treat menorrhagia: a case-control study using the General Practice Research Database*. BJOG.;116(1):91-7. Epub 2008 Nov 11

[35] Moschiano F, D'Amico D, Ciusani E, Erba N, Rigamonti A, Schieroni F, Bussone G. 2004. *Coagulation abnormalities in migraine and ischaemic cerebrovascular disease: a link between migraine and ischaemic stroke?* Neurol Sci (2004) 25:S126–S128 DOI 10.1007/s10072-004-0269-5.

7 APPENDIX A

Table 1A: Age-Specific VTE Incidence Rates per 10,000 person-years (PY) for New and All Users by Selected Study Hormonal Contraceptive, 2001-2007 (From Table 10b, Final Report 111022v2)

	New Users			All Users		
DRSP	**PY**	**Events**	**Rate/10k**	**PY**	**Events**	**Rate/10k**
10 to 24	39,452	19	4.8	79,590	27	3.4
25 to 34	27,362	26	9.5	72,346	54	7.5
35 to 44	10,672	18	16.9	29,968	43	14.3
45 to 55	2,684	11	41.0	7,306	20	27.4
NGMN						
10 to 24	17,680	11	6.2	37,602	21	5.6
25 to 34	9,424	12	12.7	22,781	26	11.4
35 to 44	2,651	8	30.2	6,515	14	21.5
45 to 55	397	2	50.4	967	6	62.0
LNG2						
10 to 24	39,977	10	2.5	80,454	20	2.5
25 to 34	33,843	15	4.4	89,057	33	3.7
35 to 44	17,544	33	18.8	54,546	72	13.2
45 to 55	5,896	16	27.1	20,550	36	17.5
COMP						
10 to 24	103,683	32	3.1	218,616	62	2.8
25 to 34	77,191	39	5.1	207,964	80	3.9
35 to 44	42,631	79	18.5	121,685	136	11.2
45 to 55	24,526	55	22.4	69,000	111	16.1

Age-adjusted VTE rates per 10,000 person-years (PY) and Incidence Rate Ratios (IRR)

ALL USERS

EXPOSURE	**Age-adjusted rate**	**Incidence Rate Ratio**	**95% CI**	**Incidence Rate Ratio**	**95% CI**
DRSP	10.2	1.7	1.4 – 2.1	1.5	1.2 – 1.9
NGMN	9.8	1.5	1.2 – 2.0	1.3	0.9 – 1.7
LNG2	6.6			Reference	--
COMP	6.0	Reference	--		

NEW USERS

EXPOSURE	**Age-adjusted rate**	**Incidence Rate Ratio**	**95% CI**	**Incidence Rate Ratio**	**95% CI**
DRSP	13.7	1.6	1.2 – 2.1	1.5	1.1 – 2.1
NGMN	12.3	1.3	0.9 – 1.9	1.1	0.7-1.7
LNG2	9.2			Reference	--
COMP	8.2	Reference	--		

Table 2A: Age-Specific ATE Incidence Rates per 10,000 person-years (PY) for New and All Users by Study Hormonal Contraceptive, 2001-2007 (From Table 10a Final Report 111022v2)

	New Users			All Users		
DRSP	**PY**	**Events**	**Rate/10k**	**PY**	**Events**	**Rate/10k**
10 to 24	39,452	-	-	79,590	-	-
25 to 34	27,362	3	1.1	72,346	3	0.4
35 to 44	10,672	5	4.7	29,968	8	2.7
45 to 55	2,684	6	22.4	7,306	6	8.2
NGMN						
10 to 24	17,680	1	0.6	37,602	2	0.5
25 to 34	9,424	2	2.1	22,781	6	2.6
35 to 44	2,651	1	3.8	6,515	1	1.5
45 to 55	397	-	-	967	-	-
LNG2						
10 to 24	39,977	2	0.5	80,454	7	0.9
25 to 34	33,843	4	1.2	89,057	6	0.7
35 to 44	17,544	3	1.7	54,546	12	2.2
45 to 55	5,896	8	13.6	20,550	19	9.3
COMP						
10 to 24	103,683	5	0.5	218,616	12	0.6
25 to 34	77,191	9	1.2	207,964	19	0.9
35 to 44	42,631	13	3.1	121,685	29	2.4
45 to 55	24,526	18	7.3	69,000	48	7.0

Age-adjusted ATE rates per 10,000 person-years (PY) and Incidence Rate Ratios (IRR)

ALL USERS

EXPOSURE	**Age-adjusted rate**	**Incidence Rate Ratio**	**95% CI**	**Incidence Rate Ratio**	**95% CI**
DRSP	1.1	0.8	0.9 – 3.1	1.4	0.7 – 2.8
NGMN	1.1	1.1	0.3 – 2.5	0.7	0.2 – 2.2
LNG2	1.6			Reference	--
COMP	1.4	Reference	--		

NEW USERS

EXPOSURE	**Age-adjusted rate**	**Incidence Rate Ratio**	**95% CI**	**Incidence Rate Ratio**	**95% CI**
DRSP	2.6	1.7	0.9 – 3.1	1.4	0.7 – 2.8
NGMN	1.8	0.9	0.3 – 2.5	0.7	0.2 – 2.2
LNG2	2.3			Reference	
COMP	1.8	Reference			

8 APPENDIX B

SDI, Vector One®: National (VONA)

The SDI, Vector One®: National (VONA) database measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 1.4 billion prescription claims per year, representing over 120 million unique patients. Since 2002 Vector One® has captured information on over 8 billion prescriptions representing over 200 million unique patients.

Prescriptions are captured from a sample from the universe of approximately 59,000 pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. SDI receives all prescriptions from approximately one-third of stores and a significant sample of prescriptions from many of the remaining stores.

IMS Health, IMS Health Lifelink™ database

The IMS Health, IMS Health Lifelink™ database was used to evaluate the utilization of oral contraceptives, Ortho Evra, and NuvaRing from 1/1/2002 – 12/31/2007. The IMS Health Plan Claims Database represents over 95 managed care plans and covers approximately 60 million commercially insured, de-identified patients. Claims are captured from doctor's offices (including outpatient clinics), retail and mail order pharmacies, patient visits to specialists, and hospitalizations. They include information about diagnoses, emergency room visits, office visits, home care, diagnostic tests, procedures and injections. These data represent approximately 11 percent of the U.S. commercially insured population during that time period. Claims for these products are primarily submitted for insurance payment by dispensing pharmacies.

However, since pharmacists typically do not have access to the patient's medical record, pharmacy claims are submitted without supporting ICD-9 diagnostic codes. To assess the indication for use of the contraceptive products, medical claims filed closest (within 30 days before and after the patient's first contraceptive prescription to the claim date for the contraceptive prescription) were examined. Medical claims are required to be submitted with at least one, and up to four supporting diagnosis ICD-9 codes. When several ICD-9 codes of interest were supplied, he code appearing first was used. Patients were eligible for inclusion if there was a prescription claim for a contraceptive between January 1, 2002 and December 31, 2011 and no previous claim for an oral contraceptive in the preceding 180 days prior to their first claim with insurance eligibility during that 6 month look-back period. Since this analysis was concerned with a patient's first medical claim during the study period, continuous eligibility throughout the study period was not required. The diagnoses selected are listed below

Code Description
706.1 ACNE NEC
704.1 HIRSUTISM
256.4 POLYCYSTIC OVARIES
625.4 PREMENSTRUAL TENSION
625.3 DYSMENORRHEA
627.0 PREMENOPAUSE MENORRHAGIA
346.4 MENSTRUAL MIGRAINE
346.42 MENSTRUAL MIGRAINE W/O INTRA
346.43 MENSTRUAL MIGRAINE INTRACT
346.41 MENSTL MGRN W NTRC WO ST
346.40 MENSTRUAL MIGRAINE W/O INTRA

SDI, Physician Drug & Diagnosis Audit (PDDA) with Pain Panel

The SDI, Physician Drug & Diagnosis Audit (PDDA) with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

9 APPENDIX C

Table 13B: Distribution of CHC Use by Age Group, FDA-funded Study (2001-2007 All Users) Compared to US Projected Total Prescriptions (SDI 2002-2007).

	Age Group	SDI*	FDA-funded Study	KP**	Medicaid
NGMN	0-25 years	47.6	62.5	47.7	72.8
	26-34 years	34.5	29.2	39.9	23.2
	35+ years	17.5	8.3	15.6	4.1
DRSP_30	0-25 years	44.3	50.0	47.7	65.6
	26-34 years	31.0	34.7	35.9	26.8
	35+ years	24.5	15.2	16.5	7.6
ETON	0-25 years	40.6	50.3	39.0	65.6
	26-34 years	37.4	37.2	43.1	29.3
	35+ years	21.9	12.5	17.8	5.2
COMP	0-25 years	41.4	44.7	37.8	67.6
	26-34 years	31.2	31.9	31.4	24.2
	35+ years	27.2	23.4	28.1	8.1
LNG2	0-25 years	28.8	42.1	38.2	62.1
	26-34 years	31.6	34.6	35.7	28.8
	35+ years	39.4	23.3	26.1	9.0
LNG1	0-25 years	35.4	60.4	34.3	65.9
	26-34 years	27.3	25.7	38.1	23.1
	35+ years	37.1	13.8	27.6	10.9
NGM	0-25 years	48.4	56.5	49.7	73.3
	26-34 years	34.0	33.8	38.6	22.0
	35+ years	17.5	9.6	11.6	4.7
NETA	0-25 years	21.6	26.0	23.9	56.3
	26-34 years	22.6	26.7	26.8	26.5
	35+ years	55.8	47.2	49.3	17.2

**Source: SDI Vector One®: National, Years 2002-2010 Data Extracted September 2011 (only years 2002-2007 shown) and Tables 4a1-3, Final Report 111022v2).*

*** KP = Kaiser Permanente*

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/s/

RITA P OUELLET-HELLSTROM
11/04/2011

GERALD J DALPAN
11/04/2011

Appendix C

FDA Review of Drug Utilization Patterns for Ortho Evra and Other Combined Hormonal Contraceptive Products

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Drug Use Review

Date:	November 9, 2011
Reviewer(s):	Patty Greene, Pharm.D., Drug Use Data Analyst Division of Epidemiology II (DEPI II)
Team Leader (Acting):	Grace Chai, Pharm.D. Division of Epidemiology II (DEPI II)
Director:	Judy A. Staffa, Ph.D., R.Ph. Division of Epidemiology II (DEPI II)
Drug Name(s):	Ortho Evra® (norelgestromin and ethinyl estradiol)
Application Type/Number:	NDA 21-180
Applicant/sponsor:	Ortho-McNeil-Janssen Pharmaceuticals, Inc.
OSE RCM #:	RCM 2011-1044

This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.

CONTENTS

EXECUTIVE SUMMARY

This review examines drug utilization patterns in women (0-25, 26-34, 35+ years) for Ortho Evra® (norelgestromin and ethinyl estradiol) contraceptive patch and other combined hormonal contraceptive (CHC) products (USC class 33230, 33390) in the U.S. outpatient retail pharmacy setting for year 2002 through 2010.

- In year 2010, approximately 83.7 million prescriptions were dispensed in the total contraceptive market, a net decrease of 10% since year 2002.
- The projected number of prescriptions dispensed for Ortho Evra® decreased from a peak in use of nearly 10 million prescriptions in year 2004 (10.5% of the CHC market) to 1.3 million prescriptions in year 2010 (2% of the CHC market). The projected number of patients who received dispensed prescriptions of Ortho Evra® also decreased from about 2.4 million patients in year 2004 (14% of CHC patients) to 345,000 patients in year 2010 (2% of CHC patients). A similar decrease was noted when the prescription data were adjusted for population growth.
- Women aged 0-25 years accounted for a larger proportion of Ortho Evra® prescriptions (45%-50% of the annual prescription share), followed by women aged 26-34 years (32%-36%) and women aged 35 years or older (14%-22%).
    - For all other CHCs, women aged 0-25 years accounted for 32%-42% of prescriptions followed by women aged 26-34 years and 35 years or older, each accounting for 29%-34% of the annual prescription share.
- For Ortho Evra users, there appeared to be a slightly higher proportion of patients with BMIs 25+ (overweight and obese) than among users of other products but only in the younger (0-25yrs) and older (35+years) age groups. However, the BMI was unknown in a large proportion of drug occurrences, so these findings should be viewed with caution.
- Across all age groups, a smaller proportion of Ortho Evra users had one or more diagnoses for Acne (ICD-9 706.1), Hirsutism (ICD-9 704.1), and/or Premenstrual Tension or PMDD (ICD-9 625.4) than for any other CHC user group.

1 BACKGROUND

On December 9, 2011, the Advisory Committee for Reproductive Health Drugs and the Drug Safety and Risk Management Advisory Committee will meet to discuss the risks and benefits of combined hormonal contraceptive (CHC) products containing norelgestromin and ethinyl estradiol. In the literature, there are several published studies which examined the association between oral contraceptives and the risk of venous thromboembolism (VTE). A case-control study from Dore et al. reported a 2-fold increase in the risk of venous thromboembolism (VTE) among users of contraceptives with norelgestromin compared to norgestimate.[1] Other studies show no association. The Division of Epidemiology II (DEPI II) will present findings from an FDA-funded study which found an increased risk of (VTE) associated with Ortho Evra® compared to CHC products containing ethinyl estradiol and the progestin norgestimate. The

[1] Dore D (2010). Extended case-control study results on thromboembolic outcomes among transdermal contraceptive users. *Contraception*. 81 (1), 408-413.

purpose of the FDA-funded study was to assess cardiovascular risks, including the risk of thrombotic and thromboembolic events and death across multiple CHC product groups containing the progestins levonorgestrel, norethindrone, or norgestimate combined with 0.02 mg to 0.035 mg of ethinyl estradiol.

FDA has concerns about whether there may be sources of unmeasured confounding in studies of norelgestromin-containing products and risk for thrombotic and thromboembolic events. Some of these unmeasured confounders may relate to co-morbid conditions of the women prescribed these products that may or may not be related to the physician's decision to prescribe a norelgestromin-containing product. The decision was made to explore some of the drug utilization data available to the Agency to both better understand the overall utilization of contraceptive products, as well as to explore for sources of potential confounding.

In support of the Advisory Committee meeting, this review will provide national patterns of drug utilization data for Ortho Evra® by patient age (0-25, 26-34, 35+ years) for 2002-2010, as well as for other CHC products included in the FDA study (referred to as Study CHC products) for years 2001 through 2007. We examined medical diagnoses and body mass index (BMI) codes associated with the mention of each of these products during visits to office-based physicians. In addition, we used a large claims database to compare women treated with Ortho Evra® and study CHCs to examine the frequency of women with one or more diagnosis codes for Acne (ICD-9 706.1) and Hirsutism (ICD-9 704.1), and/or Premenstrual Tension or PMDD (ICD-9 625.4) in their recent claims history.

2 METHODS AND MATERIALS

2.1 DETERMINING SETTINGS OF CARE

The IMS Health, IMS National Sales Perspectives™ was used to determine the various retail and non-retail channels of distribution for Ortho Evra®. Sales data for Ortho Evra® indicated that 72% of patches (Eaches) for Ortho Evra ® were distributed to outpatient retail pharmacies; 21% were to non-retail settings; and 6% were to mail order pharmacies during year 2010.[2] As a result, outpatient retail pharmacy utilization patterns were examined. Non-retail and mail order settings were not included in this analysis.

2.2 DATA SOURCES USED

Proprietary drug use databases licensed by the Agency were used to conduct this analysis (See Appendix 2 for full database descriptions).

IMS Health, IMS National Sales Perspectives™ was used to obtain the sales data for Ortho Evra® by the number of eaches (boxes, packages, etc.) sold from manufacturers to retail (including mail order) and non-retail channels of distribution for years 2006 through 2010.

SDI, Vector One®: National (VONA) was used to obtain estimates of the nationally projected number of outpatient dispensed prescriptions for Ortho Evra® and the combined hormonal contraceptive (CHC) market, stratified by age (0-25, 26-34, 35+ years), in the outpatient retail pharmacy setting for years 2002 through 2010; we also examined the nationally projected

[2] IMS Health, IMS National Sales Perspectives™. September 2010-August 2011. Data extracted October 2011. File: NSPC 2011-1044 Ortho Evra sales by channel 10-1-11.xls

number of outpatient dispensed prescriptions for study CHC products for years 2002-2007 (See Appendix 3 for Study CHCs Product Groups).

U.S. Census data were obtained to account for population growth over time for years 2002 through 2010.[3,4] The utilization of prescriptions dispensed per 100,000 U.S. women was calculated by dividing the number of prescriptions dispensed by U.S. Census population estimates of women aged 5-64 years, multiplied by 100,000. Prescription data was adjusted for females of child-bearing potential by combining U.S. census age groups (ages 5-13 years, 14-17 years, and 18-64 years) to account for population growth in the population of interest.

SDI, Vector One®: Total Patient Tracker (TPT) was used to obtain estimates of the nationally projected number of patients receiving a dispensed prescription for Ortho Evra® and the combined hormonal contraceptive (CHC) market, stratified by age (0-25, 26-34, 35+ years), in the outpatient retail pharmacy setting for years 2002 through 2010.

Selected diagnoses associated with the use of Ortho Evra® and study CHC products (See Appendix 4 for ICD-9 Diagnosis Codes), stratified by age (0-25, 26-34, 35+ years), were obtained from the SDI, Physician Drug and Diagnosis Audit™ (PDDA) for years 2001 through 2007 (See Appendix 3 for study CHCs product groups-Note: Only study CHC products with data available in PDDA were included in this analysis).

Wolters Kluwer Health's Source® Lx database was used to compare treatment with Ortho Evra® and study CHC products in women with one or more diagnosis codes for Acne (ICD-9 706.1) and Hirsutism (ICD-9 704.1), and/or Premenstrual Tension or PMDD (ICD-9 625.4). We obtained the nationally projected number of unique patients with a prescription claim for Ortho Evra® and study CHC products, stratified by age (0-25, 26-34, 35+ years), in the outpatient retail pharmacy setting for years 2007 through 2010, cumulative. Patients' histories with a prescription claim for Ortho Evra® and study CHC products were searched using the national drug code (NDC) and ICD-9 diagnosis codes within 60 days of the prescription claim (see Appendix 3 for full list of NDCs and Appendix 4 for ICD-9 diagnosis codes).

2.3 PRODUCTS INCLUDED[5]

Indication and Usage

Ortho Evra® is a combined hormonal contraceptive approved for the prevention of pregnancy in women who elect to use a transdermal patch as a method of contraception.

Dosage and Administration

Ortho Evra® is a transdermal patch that contains 6.0 mg norelgestromin (NGMN) and 0.75 mg ethinyl estradiol (EE) and is available in the following package size:

• Packages: (NDC 0062-1920-15; NDC 50458-192-15 NDC 0062-1920-24; NDC 50458-192-24; NDC 0062-1920-01 or NDC 50458-192-01)

Study Combined Hormonal Contraceptive (CHCs)

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[3] Annual Estimates of the Resident Population by Sex and Selected Age Groups for the United States: April 1, 2002 to July 1, 2009. U.S. Census Bureau, Population Division, U.S. Dept of Commerce. September 2011.

[4] Projections of the Population by Selected Age Groups and Sex for the United States: 2010 to 2050 U.S. Census Bureau, Population Division, U.S. Dept of Commerce. September 2011.

[5] Ortho Evra® Patient Label (http://www.orthoevra.com/)

Study combined hormonal contraceptives include drospirenone/ethinyl estradiol, etonogestrel/ethinyl estradiol and norelgestromin/ethinyl estradiol. Comparators include levonorgesetrel/ethinyl estradiol, norethindrone/ethinyl estradiol and norgestimate/ethinyl estradiol products. For the purpose of the prescription, patient, and indication analyses, we examined norelgestromin/ethinyl estradiol and comparator products only.

Study CHC: 3.0 mg Drospirenone and 30 µg of Ethinyl Estradiol (DRSP): **Yasmin®**

Study CHC: 11.7 mg Etonogestrel and 2700 µg Ethinyl Estradiol (ETON): **Nuvaring®**

Study CHC: 6.0 mg Norelgestromin and 750 µg Ethinyl Estradiol (NGNM): **Ortho Evra Patch®**

Comparator CHC: 0.10 mg of Levonorgesetrel and 20 µg of Ethinyl Estradiol **(LNG 1)**

Comparator CHC: 0.15 mg of Levonorgesetrel and 30 µg of Ethinyl Estradiol **(LNG 2)**

Comparator CHC: 1 mg Norethindrone Acetate and 20 µg of Ethinyl Estradiol **(NETA)**

Comparator CHC: 0.18-0.25 mg of Norgestimate and 35 µg of Ethinyl Estradiol **(NGM)**

Data for Yaz® (3.0 mg Drospirenone and 20 µg Ethinyl Estradiol) from approval in March 2006 to December 2007 were also analyzed with the Study CHC products.

(see Appendix 3 for Study CHCs Product Group and NDC Code)

3 RESULTS

3.1 ORTHO EVRA® SALES DATA, Y2006-2010

Figure 1 shows the sales data for Ortho Evra® by the number of eaches (packages, boxes, etc.) sold from manufacturers to retail (including mail order) and non-retail channels of distribution for years 2006 through 2010. In year 2010, there were 2.2 million packages of Ortho Evra® distributed, about a 64% decrease in sales since year 2006 (6.2 million packages).

3.2 PROJECTED NUMBER OF DISPENSED PRESCRIPTIONS FOR THE CONTRACEPTIVE MARKET, Y2002-2010

Table 1 displays the projected number of dispensed prescriptions for the hormonal contraceptive market by Uniform System of Classification code (USC code) in U.S. outpatient retail pharmacies for years 2002 through 2010. From year 2002 to 2004, there was a 6% increase in the projected number of dispensed prescriptions (from 92.8 million to 98.5 million prescriptions) primarily due to market growth in other contraceptives (USC 33390). The other contraceptive drug class includes combined hormonal contraceptives available in **non-oral** dosage form [(e.g. patch (Ortho Evra®) or vaginal ring (Nuvaring®)]. Between years 2005 to 2007, the total projected number of dispensed prescriptions for all contraceptives decreased by 11% (from 97.5 million to 87.2 million prescriptions). In year 2010, approximately 83.7 million prescriptions were dispensed in the hormonal contraceptive market, a net decrease of 10% since year 2002. Throughout the review period, the combined hormonal contraceptives class (USC 33230) and the other contraceptives class (USC 33390) accounted for 96%-97% of the annual prescription share combined. All other contraceptives accounted for 3%-4% of the annual prescription share combined.

3.3 PROJECTED NUMBER OF DISPENSED PRESCRIPTIONS FOR ORTHO EVRA®, Y2002-2010

Table 2 shows the projected number of dispensed prescriptions for Ortho Evra® by patient age in U.S. outpatient retail pharmacies. In year 2002, Ortho Evra® accounted for 1% of the combined hormonal contraceptive (CHC) market (USC 33230 and USC 33390). The projected number of dispensed prescriptions of Ortho Evra® increased nearly 8-fold from 1.3 million prescriptions in year 2002 to a peak in use of nearly 10 million prescriptions in year 2004 (10.5% of the CHC study market in year 2004). However from year 2004 to year 2010, dispensed prescriptions of Ortho Evra® decreased by 87% to account for approximately 2% of the CHC market (1.3 million prescriptions) in year 2010.

For Ortho Evra®, women aged 0-25 years accounted for a larger proportion of the prescription share at 45%-50% followed by women aged 26-34 years at 32%-36% of the annual prescription share. Women aged 35 years or older accounted for 14%-22% of the annual prescription share. For all other CHCs, women aged 0-25 years accounted for 32%-42% of prescriptions followed by women aged 26-34 years and 35 years or older, each accounting for 29%-34% of the annual prescription share.

Figure 2 shows the projected number of prescriptions for Ortho Evra® dispensed to U.S. women (prescriptions/100,000 women) from outpatient retail pharmacies for years 2002 through 2010. In year 2010, there were 1,056 Ortho Evra® prescriptions per 100,000 US women, an 87% decrease in prescription volume since its peak in year 2004.

3.4 PROJECTED NUMBER OF PATIENTS FOR ORTHO EVRA®, Y2002-2010

Table 3 shows the projected number of patients for Ortho Evra® by patient age in U.S. outpatient retail pharmacies. In year 2002, Ortho Evra® accounted for 3% of patients in the combined hormonal contraceptive (CHC) market (USC 33230 and USC 33390). The projected number of patients who received a dispensed prescription of Ortho Evra® increased from 594,000 patients in year 2002 to 2.4 million patients in year 2004. By year 2010, patients dispensed Ortho Evra® accounted for approximately 2% of the CHC market (345,000 patients); a net decrease of 42% for patients dispensed Ortho Evra® since year 2002.

Similar to prescription data for Ortho Evra®, women aged 0-25 years accounted for a larger proportion of the patient share at 52%-55% followed by women aged 26-34 years at 32%-33% of the annual patient share. For all other CHCs, women aged 0-25 years accounted for 38%-46% of patients followed by women aged 26-34 years at 31%-34% of patients and 35 years or older at 26%-30% of patients.

3.5 PROJECTED NUMBER OF DISPENSED PRESCRIPTIONS FOR ORTHO EVRA® AND STUDY COMBINED HORMONAL CONTRACEPTIVES (CHCS), Y2002-2007

Table 4 provides the projected number of dispensed prescriptions for the selected combined hormonal contraceptives (CHCs) products included in the FDA-funded study, by product group and patient age in U.S. outpatient retail pharmacies from years 2002 to 2007.(See Appendix 3 for full list of products) The projected number of dispensed prescriptions for all study and comparator CHC products ranged from 40.2 million to 49.2 million prescriptions, annually. Ortho Evra® ranged from 16%-55% of the prescription share in the study CHCs group and norgestimate (NGM) accounted for the majority of the prescription share in the comparator CHCs (45% to 60%) for the study period.

For NGM, the age distribution was similar to Ortho Evra® with women aged 0-25 years accounting for a larger proportion of the prescription share at 46%-50% followed by women aged 26-34 years at 34%-35% of the prescription share. Women 35 years or older accounted for

16%-19% of the NGM prescription share. In other comparator CHCs, women 35 years or older accounted for a larger proportion of the prescription share for norethindrone acetate (NETA) at 42%-64% and levonorgestrel (LNG 2) products at 38%-42% of prescriptions. For levonorgesetrel (LNG 1), women aged 0-25 years and 35 years or older accounted for a slightly proportion of the prescription share followed by women aged 26-34 years.

3.6 Selected Diagnoses Associated with the Use of Ortho Evra® and Study Combined Hormonal Contraceptives (CHCs), Y2001-2007

We also examined selected diagnoses associated with the use of Ortho Evra® and the study CHCs by patient age for years 2001 through 2007, cumulative. Although Yaz® was not included in the FDA-funded study, data for Yaz® from approval to December 2007 were also presented in this analysis. According to office-based physician practices in the U.S., the most common diagnosis codes associated with the use of study CHC products for all age groups were "Contraceptive Mgmt-Counsel" (ICD-9 V25.0) or "Contraceptive Surveillance" (ICD-9 V25.4) at a combined 84%-97% of drug mentions followed by "Dysmenorrhea" (ICD-9 625.3) at 2%-8% of drug mentions. For norgestimate (NGM), "Acne" (ICD-706.1) accounted for 5% of drug mentions in women aged 0-25 years and 2% of drug mentions in women aged 26-34 years (***Table 5***).

3.7 Ortho Evra® and Study Combined Hormonal Contraceptives (CHCs) by BMI, Y2001-2007

Table 6 and Figure 3 show the proportion of drug occurrences for Ortho Evra® and study CHC products by body mass index (BMI) in women aged 0-25 years as reported by U.S. office-based physician practices for years 2001 through 2007, cumulative. For the study period, 30% of drug occurrences for Ortho Evra® were in women aged 0-25 years with a BMI of 25 or greater; this same was true for drug occurrences relating to NuvaRing (ETON). The frequency of women with a BMI of 25 or greater among the other products ranged from 22-27%. Among the study CHC products, women with a BMI of 0-18 (underweight) ranged from 2%-5% of drug occurrences and BMI of 19-24 (normal weight) ranged from 42%-58%. BMI was unknown for approximately 14-35% of drug occurrences in women aged 0-25 years, so these results should be interpreted with caution.

Table 6 and Figure 4 show the proportion of drug occurrences for Ortho Evra® and study CHC products by body mass index (BMI) in women aged 26-34 years as reported by U.S. office-based physician practices for years 2001 through 2007, cumulative. For the study period, 35% of drug occurrences for Ortho Evra® were in women aged 26-34 years with a BMI of 25 or greater. The percentage for other CHCs was similar and varied from 33-37%. Among the study CHC products, women with a BMI of 0-18 (underweight) ranged from 1%-2% of drug occurrences and BMI of 19-24 (normal weight) ranged from 33%-55%. Again, BMI was unknown for approximately 11-33% of drug occurrences in women aged 26-34 years.

Table 6 and Figure 5 show the proportion of drug occurrences for Ortho Evra® and study CHC products by body mass index (BMI) in women aged 35+ years as reported by U.S. office-based physician practices for years 2001 through 2007, cumulative. For the study period, 50% of drug occurrences for Ortho Evra® were in women aged 35+ years with a BMI of 25 or greater. This was a bit higher than most other CHCs (which varied between 31-42%) except for LNG-1 which was approximately 47%. Among the study CHC products, women with a BMI of 0-18 (underweight) ranged from 1%-3.5% of drug occurrences and BMI of 19-24 (normal weight) ranged from 31%-45%. Again, BMI was unknown for approximately 13-29.5% of drug occurrences in women aged 35+ years.

3.8 ORTHO EVRA® AND STUDY COMBINED HORMONAL CONTRACEPTIVES (CHCS) FOR ONE OR MORE SELECTED DIAGNOSES, Y2007-2010

We also examined the projected number of patients (0-25, 26-34, 35+ years) with a prescription claim for a study CHC product either preceded or followed by a medical claim with one or more diagnosis codes for Acne (ICD-9 706.1), Hirsutism (ICD-9 704.1), and/or Premenstrual Tension or PMDD (ICD-9 625.4) for years 2007 to 2010. Of patients aged 0-25 years, only 0.4% of patients with a prescription claim for Ortho Evra® had one or more diagnoses for Acne (ICD-9 706.1), Hirsutism (ICD-9 704.1), and/or Premenstrual Tension or PMDD (ICD-9 625.4), compared to Yaz® (2.3% of Yaz® patients) and Yasmin® (2.0% of Yasmin® patients) the CHC products with the highest proportion of diagnoses claims.(**Figure 6**) Of patients aged 26-34 years, only 0.3% of patients with a prescription claim for Ortho Evra® had one or more diagnoses for Acne (ICD-9 706.1), Hirsutism (ICD-9 704.1), and/or Premenstrual Tension or PMDD (ICD-9 625.4), compared to Yaz® (1.4% of Yaz® patients) and Yasmin® (1.2% of Yasmin® patients). (**Figure 7**) Ortho Evra® accounted for 0.4% of patients compared to Yaz® (1.4% of patients) and Yasmin® (1% of patients), respectively for Acne, Hirsutism and/or PMDD in women 35 years or older. (**Figure 8**)

4 DISCUSSION

Ortho Evra® accounted for approximately 2% of the combined hormonal contraceptive market in year 2010, a decrease from 10.5% of the CHC market share in year 2004. Despite the decline in market share, there were 1.3 million dispensed prescriptions for Ortho Evra® to approximately 345,000 women in year 2010. Our findings show that Ortho Evra® users were similar to norgestimate (NGM) in relation to age, with the largest proportion occurring in women aged 0-25 years. The data suggest that Ortho Evra users may have somewhat higher BMI than users of many other CHCs, particularly in women 0-25 years and 35 years+ for the study period. However, the BMI data was unknown in a large proportion of drug occurrences and so these findings should be viewed with caution. Among patients taking Ortho Evra,® approximately 0.4% had diagnoses for Acne, Hirsutism and/or PMDD in women 35 years or older. This was less than users of Yaz® (1.4% of patients) and Yasmin (1% of patients), respectively, as well as less than that seen in users of other CHC products. However, the frequencies of these selected diagnoses across all drug groups were extremely low.

We speculated whether there might have been more dramatic differences between users of Ortho Evra and users of other products in its early years of marketing, before the decline in use (presumably due to widely publicized safety concerns). We re-examined the frequency of diagnoses among Ortho Evra users for the years 2003-2005, but our findings did not change.

These findings should be interpreted in the context of the limitations of the drug utilization data sources used to generate them. The sales analysis for Ortho Evra® was provided as the number of packages sold from the IMS Health, IMS National Sales Perspectives™. The sales estimates provided are national estimates, but no statistical tests were performed to determine statistically significant changes over time or between products. Therefore, all changes over time should be considered approximate, and may be due to random error. Furthermore, these data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution. The amount of product purchased by these channels of distribution may be a possible surrogate for use, if we assume the facilities purchase drugs in quantities reflective of actual patient use.

The data analyses for study CHCs by diagnosis and body mass index (BMI) were examined using office-based physician survey data. Analyses of data obtained from physician survey data should be interpreted with caution as sample sizes below 100,000 drug use mentions or drug occurrences are very small with correspondingly large confidence intervals. It is important to note that several study CHC products were not captured in the PDDA database. SDI uses the term "drug uses" to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit. SDI uses the term "drug occurrences" to refer to the number of times a product has been reported on a patient information form during an office-based patient visit for that period. It is important to note that a "drug occurrence" does not necessarily result in a prescription being generated. A “drug occurrence” can result from a prescription written, a sample given, a recommendation for OTC products, recommendation with sample, a product dispensed or administered in the office, a hospital order, a nursing home order or a combination of these.

Unique patient counts may not be added across time periods due to the possibility of double counting those patients who are receiving treatment over multiple periods in the study. Furthermore, patient age subtotals may not sum exactly due to patients aging during the study period (“the cohort effect”), and may be counted more than once in the individual age categories. For this reason, summing across time periods or patient age bands is not advisable and will result in overestimates of patient counts.

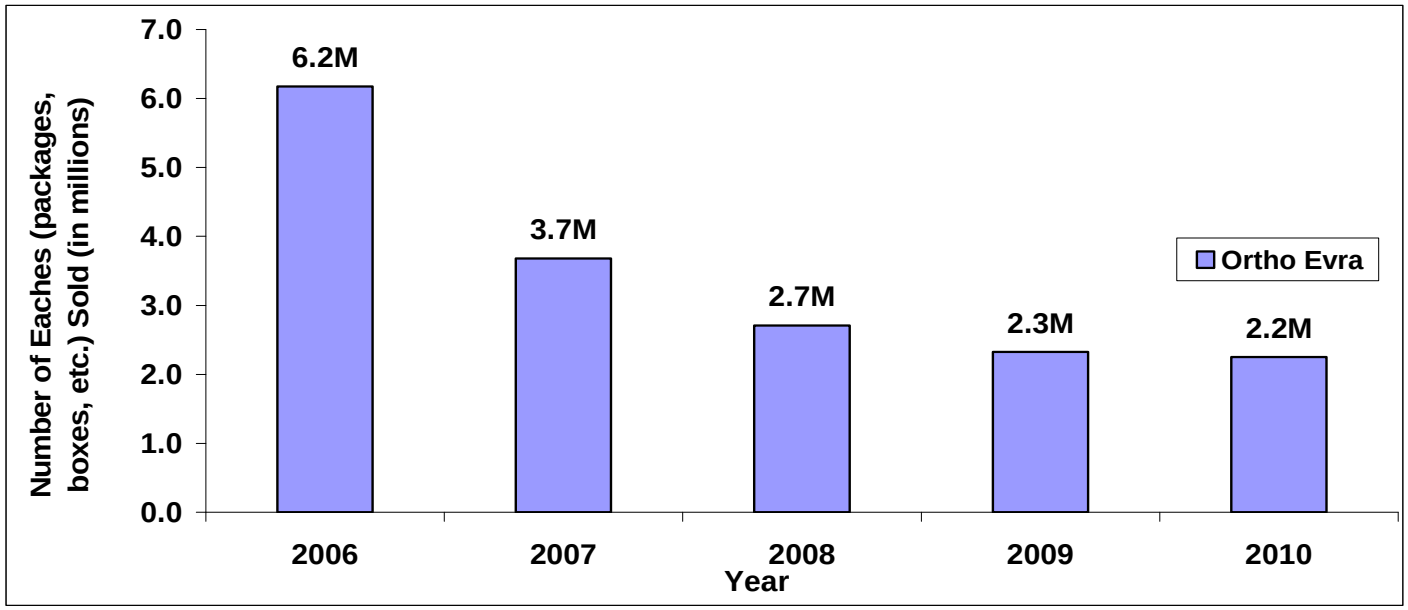
5 CONCLUSIONS

Findings for this analysis show that Ortho Evra® accounted for approximately 2% of the CHC market (1.3 million prescriptions) in year 2010. For the study combined hormonal contraceptive products (CHCs), Ortho Evra® (NGNM) and norgestimate (NGM), women aged 0-25 years accounted for a larger proportion of the prescription share followed by women aged 26-34 years and women aged 35 years or older. For Ortho Evra users, there appeared to be a slightly higher proportion of patients with higher BMIs (>25) than among users of other products but only in the younger (0-25yrs) and older (35+years) age groups. However, the BMI was unknown in a large proportion of drug occurrences, so these findings should be viewed with caution. For Ortho Evra®, lower proportions of patients had one or more diagnoses for Acne (ICD-9 706.1), Hirsutism (ICD-9 704.1), and/or Premenstrual Tension or PMDD (ICD-9 625.4), than any other CHC users across all age groups.

6 APPENDIX 1: FIGURES AND TABLES

Figure 1:

Number of eaches (packages, boxes, etc.) sold of Ortho Evra® from manufacturers to various retail and non-retail channels of distribution, years 2006-2010



IMS Health, IMS National Sales Perspectives™. Year 2010. Data extracted October 2011.
File: NSPC 2011-1044 Ortho Evra sales by channel Y2010 10-23-11.xls

Table 1. Projected number of dispensed prescriptions for the Contraceptive Market by Uniform System of Classification (USC) Code in U.S. outpatient retail pharmacies, Y2002-2010

	2002		2003		2004		2005		2006		2007		2008		2009		2010	
	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Grand Total	**92,794,053**	***100.0%***	**96,500,832**	***100.0%***	**98,513,746**	***100.0%***	**97,547,374**	***100.0%***	**87,342,536**	***100.0%***	**87,189,932**	***100.0%***	**89,088,773**	***100.0%***	**86,808,961**	***100.0%***	**83,699,311**	***100.0%***
33230 ESTROGEN-PROGEST.CMB,ORAL	**88,309,272**	***95.2%***	**83,880,397**	***86.9%***	**83,238,457**	***84.5%***	**81,966,281**	***84.0%***	**75,628,399**	***86.6%***	**76,705,704**	***88.0%***	**79,226,665**	***88.9%***	**77,346,691**	***89.1%***	**74,335,607**	***88.8%***
33390 CONTRACEPTIVES, OTHERS	**1,586,013**	***1.7%***	**9,492,589**	***9.8%***	**11,792,317**	***12.0%***	**11,973,278**	***12.3%***	**8,287,607**	***9.5%***	**7,306,862**	***8.4%***	**6,626,920**	***7.4%***	**6,203,319**	***7.1%***	**6,069,124**	***7.3%***
33210 W/O ESTROGENS, ORAL	2,768,491	*3.0%*	3,014,181	*3.1%*	3,381,447	*3.4%*	3,520,793	*3.6%*	3,354,818	*3.8%*	3,119,047	*3.6%*	3,189,055	*3.6%*	3,209,612	*3.7%*	3,263,123	*3.9%*
33330 DIAPHRAGMS & KITS	99,073	*0.1%*	80,749	*0.1%*	74,148	*0.1%*	62,571	*0.1%*	51,570	*0.1%*	43,005	*0.0%*	32,349	*0.0%*	38,067	*0.0%*	28,610	*0.0%*
33310 FOAMS	24,567	*0.0%*	26,710	*0.0%*	22,108	*0.0%*	18,580	*0.0%*	16,190	*0.0%*	10,853	*0.0%*	9,193	*0.0%*	6,545	*0.0%*	1,142	*0.0%*
33110 INTRA-UTERINE DEVICES	459	*0.0%*	634	*0.0%*	727	*0.0%*	1,787	*0.0%*	585	*0.0%*	1,348	*0.0%*	2,149	*0.0%*	2,499	*0.0%*	776	*0.0%*
33320 CREAMS & JELLIES	6,045	*0.0%*	5,336	*0.0%*	4,507	*0.0%*	4,051	*0.0%*	3,336	*0.0%*	2,995	*0.0%*	2,360	*0.0%*	1,959	*0.0%*	654	*0.0%*
33120 SUBDERMAL IMPLANTS	60	*0.0%*	21	0.0%	0	*0.0%*	0	*0.0%*	4	*0.0%*	95	*0.0%*	80	*0.0%*	267	*0.0%*	275	*0.0%*
33350 SUPPOSITORIES	73	*0.0%*	215	*0.0%*	35	*0.0%*	33	*0.0%*	28	*0.0%*	22	*0.0%*	2	*0.0%*	2	*0.0%*	1	*0.0%*

Source: SDI Vector One®: National, Years 2002-2010 Data Extracted September 2011. File: VONA_2011-1044_OC_Market_by_Class__09-27-11(1).xls

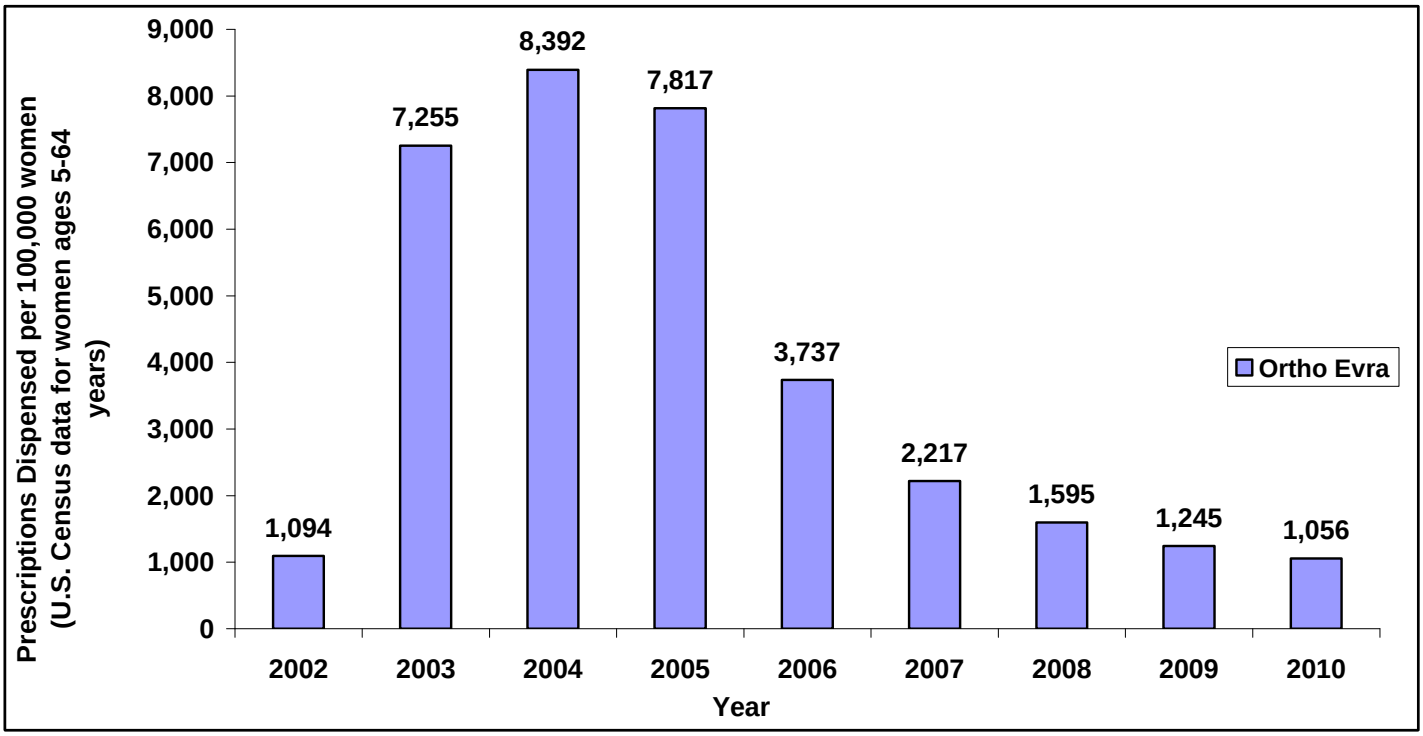
Table 2. Projected number of dispensed prescriptions for Ortho Evra® by Age (0-25, 26-34, 35+) in Combined Hormonal Contraceptive (CHC) Market (USC 33230, 33390)†, Y2002-2010

	2002		2003		2004		2005		2006		2007		2008		2009		2010	
	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
CHC Market (USC 33230, 33390)	**89,895,285**	***100.0%***	**93,372,986**	***100.0%***	**95,030,774**	***100.0%***	**93,939,559**	***100.0%***	**83,916,005**	***100.0%***	**84,012,566**	***100.0%***	**85,853,585**	***100.0%***	**83,550,009**	***100.0%***	**80,404,731**	***100.0%***
All Other CHC	**88,622,275**	***98.6%***	**84,866,050**	***90.9%***	**85,074,817**	***89.5%***	**84,584,950**	***90.0%***	**79,434,814**	***94.7%***	**81,332,772**	***96.8%***	**83,913,677**	***97.7%***	**82,025,720**	***98.2%***	**79,092,097**	***98.4%***
0-25 years	28,685,093	*32.4%*	27,944,979	*32.9%*	28,713,363	*33.8%*	29,296,439	*34.6%*	30,414,243	*38.3%*	32,034,819	*39.4%*	34,166,007	*40.7%*	34,354,101	*41.9%*	33,606,926	*42.5%*
26-34 years	29,983,871	*33.8%*	27,864,041	*32.8%*	27,265,541	*32.0%*	26,379,649	*31.2%*	23,680,833	*29.8%*	24,053,390	*29.6%*	24,629,813	*29.4%*	23,789,374	*29.0%*	23,190,649	*29.3%*
35+ years	29,824,722	*33.7%*	28,926,049	*34.1%*	28,869,786	*33.9%*	28,671,223	*33.9%*	25,338,346	*31.9%*	25,243,975	*31.0%*	25,117,665	*29.9%*	23,882,018	*29.1%*	22,294,319	*28.2%*
Unknown Age	128,589	*0.1%*	130,981	*0.2%*	226,127	*0.3%*	237,639	*0.3%*	1,393	*0.0%*	587	*0.0%*	192	*0.0%*	227	*0.0%*	203	*0.0%*
Ortho Evra	**1,273,010**	***1.4%***	**8,506,936**	***9.1%***	**9,955,957**	***10.5%***	**9,354,609**	***10.0%***	**4,481,192**	***5.3%***	**2,679,795**	***3.2%***	**1,939,908**	***2.3%***	**1,524,289**	***1.8%***	**1,312,634**	***1.6%***
0-25 years	638,294	*50.1%*	4,137,175	*48.6%*	4,684,190	*47.0%*	4,360,220	*46.6%*	2,202,276	*49.1%*	1,235,504	*46.1%*	867,653	*44.7%*	687,447	*45.1%*	603,240	*46.0%*
26-34 years	448,285	*35.2%*	3,026,884	*35.6%*	3,488,083	*35.0%*	3,189,801	*34.1%*	1,446,748	*32.3%*	893,421	*33.3%*	655,361	*33.8%*	507,097	*33.3%*	430,525	*32.8%*
35+ years	182,993	*14.4%*	1,323,648	*15.6%*	1,726,721	*17.3%*	1,744,179	*18.6%*	832,104	*18.6%*	550,835	*20.6%*	416,873	*21.5%*	329,741	*21.6%*	278,867	*21.2%*
Unknown Age	3,438	*0.3%*	19,229	*0.2%*	56,963	*0.6%*	60,409	*0.6%*	63	*0.0%*	35	*0.0%*	21	*0.0%*	5	*0.0%*	2	*0.0%*

Source: SDI Vector One®: National, Years 2002-2010 Data Extracted October 2011. File: VONA_2011-1044_Ortho_Evra_TRx_by_Age_10-16-11(1).xls

†USC 33230 Oral CHCs; USC 33390 Non-oral CHCs (e.g. patch (Ortho Evra®) or vaginal ring (Nuvaring®)

Figure 2: Projected number of Ortho Evra® dispensed prescriptions per 100,000 women in U.S. outpatient retail pharmacies, Y2002-2010



*Annual Estimates of the Resident Population by Sex and Selected Age Groups for the United States: April 1, 2002 to July 1, 2009. U.S. Census Bureau, Population Division, U.S. Dept of Commerce. September 2011.

*Projections of the Population by Selected Age Groups and Sex for the United States: 2010 to 2050 U.S. Census Bureau, Population Division, U.S. Dept of Commerce. September 2011

Table 3. Projected number of patients for Ortho Evra® by Age (0-25, 26-34, 35+) in Combined Hormonal Contraceptive (CHC) Market (USC 33230, 33390), Y2002-2010

	2002		2003		2004		2005		2006		2007		2008		2009		2010	
	Patient Count	*Share*	Patient Count	*Share*	Patient Count	*Share*	Patient Count	*Share*	Patient Count	*Share*	Patient Count	*Share*	Patient Count	*Share*	Patient Count	*Share*	Patient Count	*Share*
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
CHC Market (USC 33230, 33390)	**17,401,974**	***100.0%***	**16,682,308**	***100.0%***	**17,104,745**	***100.0%***	**16,424,936**	***100.0%***	**14,919,816**	***100.0%***	**15,330,180**	***100.0%***	**15,222,087**	***100.0%***	**15,084,305**	***100.0%***	**15,349,371**	***100.0%***
ALL OTHER CHC	**16,989,803**	***97.6%***	**15,006,020**	***90.0%***	**15,157,476**	***88.6%***	**14,690,493**	***89.4%***	**14,106,629**	***94.5%***	**14,830,399**	***96.7%***	**14,858,965**	***97.6%***	**14,781,564**	***98.0%***	**15,065,395**	***98.1%***
0-25 years	6,440,118	*37.9%*	5,822,599	*38.8%*	6,111,862	*40.3%*	6,078,076	*41.4%*	6,046,531	*42.9%*	6,472,434	*43.6%*	6,637,996	*44.7%*	6,710,645	*45.4%*	6,931,817	*46.0%*
26-34 years	5,852,178	*34.4%*	5,052,546	*33.7%*	5,033,605	*33.2%*	4,763,641	*32.4%*	4,483,307	*31.8%*	4,635,020	*31.3%*	4,630,468	*31.2%*	4,566,147	*30.9%*	4,669,806	*31.0%*
35+ years	5,170,656	*30.4%*	4,580,233	*30.5%*	4,491,534	*29.6%*	4,330,817	*29.5%*	4,019,064	*28.5%*	4,142,065	*27.9%*	4,008,994	*27.0%*	3,897,531	*26.4%*	3,842,438	*25.5%*
Unknown Age	6,839	*0.0%*	6,347	*0.0%*	917	*0.0%*	507	*0.0%*	341	*0.0%*	273	*0.0%*	133	*0.0%*	188	*0.0%*	153	*0.0%*
ORTHO EVRA	**594,179**	***3.4%***	**2,242,680**	***13.4%***	**2,421,525**	***14.2%***	**2,174,733**	***13.2%***	**1,047,149**	***7.0%***	**617,560**	***4.0%***	**449,777**	***3.0%***	**370,377**	***2.5%***	**345,018**	***2.2%***
0-25 years	320,563	*54.0%*	1,228,919	*54.8%*	1,327,308	*54.8%*	1,190,192	*54.7%*	565,058	*54.0%*	321,809	*52.1%*	231,580	*51.5%*	191,343	*51.7%*	179,780	*52.1%*
26-34 years	198,725	*33.5%*	751,167	*33.5%*	807,387	*33.3%*	713,033	*32.8%*	338,834	*32.4%*	203,474	*33.0%*	150,103	*33.4%*	121,716	*32.9%*	112,098	*32.5%*
35+ years	78,312	*13.2%*	302,681	*13.5%*	344,570	*14.2%*	326,856	*15.0%*	169,363	*16.2%*	107,040	*17.3%*	79,026	*17.6%*	64,848	*17.5%*	59,156	*17.2%*
Unknown Age	416	*0.1%*	1,392	*0.1%*	140	*0.0%*	57	*0.0%*	19	*0.0%*	15	*0.0%*	13	*0.0%*	5	*0.0%*	2	*0.0%*

*Subtotals may not sum exactly, due to rounding. Due to aging of patients during the study period ("the cohort effect"), patients may be counted more than once in the individual age categories. For this reason, summing across age bands is not advisable and will result in overestimates of patient counts. Source: SDI Total Patient Tracker. Years 2002-2010 Data Extracted October 2011 File: TPT 2011-1044 CHC Class by year 2002-2010 10-12-11.xls; TPT 2011-1044 Ortho Evra Yaz Yasmin by year 2002-2010 10-12-11.xls; TPT 2011-1044 Ortho Evra Yaz Yasmin total 10-12-11.xls, TPT 2011-1044 All CHC, no orthoevra display, oct2011.xls

Table 4. Projected number of dispensed prescriptions for Study CHCs and Comparator Groups by Age, years 2002-2007

	2002		2003		2004		2005		2006		2007	
	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*
	N	%	N	%	N	%	N	%	N	%	N	%
Grand Total	40,237,210	*100.0%*	47,121,338	*100.0%*	49,011,177	*100.0%*	49,191,419	*100.0%*	43,574,466	*100.0%*	42,788,698	*100.0%*
Study CHCs	4,723,969	*11.7%*	15,513,721	*32.9%*	20,200,316	*41.2%*	22,125,482	*45.0%*	18,676,490	*42.9%*	16,915,486	*39.5%*
Ortho Evra	1,273,010	*26.9%*	8,506,936	*54.8%*	9,955,957	*49.3%*	9,354,609	*42.3%*	4,481,192	*24.0%*	2,679,795	*15.8%*
0-25 years	638,294	*50.1%*	4,137,175	*48.6%*	4,684,190	*47.0%*	4,360,220	*46.6%*	2,202,276	*49.1%*	1,235,504	*46.1%*
26-34 years	448,285	*35.2%*	3,026,884	*35.6%*	3,488,083	*35.0%*	3,189,801	*34.1%*	1,446,748	*32.3%*	893,421	*33.3%*
35+ years	182,993	*14.4%*	1,323,648	*15.6%*	1,726,721	*17.3%*	1,744,179	*18.6%*	832,104	*18.6%*	550,835	*20.6%*
Unknown Age	3,438	*0.3%*	19,229	*0.2%*	56,963	*0.6%*	60,409	*0.6%*	63	*0.0%*	35	*0.0%*
Drospirenone (DRSP)	3,310,573	*70.1%*	6,021,892	*38.8%*	8,408,052	*41.6%*	10,152,236	*45.9%*	10,388,909	*55.6%*	9,608,647	*56.8%*
0-25 years	1,201,614	*36.3%*	2,392,633	*39.7%*	3,578,514	*42.6%*	4,495,409	*44.3%*	4,991,054	*48.0%*	4,576,617	*47.6%*
26-34 years	1,144,026	*34.6%*	2,011,012	*33.4%*	2,690,542	*32.0%*	3,135,612	*30.9%*	3,029,583	*29.2%*	2,829,538	*29.4%*
35+ years	960,355	*29.0%*	1,609,441	*26.7%*	2,118,985	*25.2%*	2,496,962	*24.6%*	2,368,127	*22.8%*	2,202,423	*22.9%*
Unknown Age	4,578	*0.1%*	8,806	*0.1%*	20,011	*0.2%*	24,253	*0.2%*	145	*0.0%*	70	*0.0%*
Etonogestrel (ETON)	140,386	*3.0%*	984,893	*6.3%*	1,836,307	*9.1%*	2,618,637	*11.8%*	3,806,389	*20.4%*	4,627,044	*27.4%*
0-25 years	51,594	*36.8%*	361,827	*36.7%*	668,149	*36.4%*	962,811	*36.8%*	1,627,623	*42.8%*	2,019,168	*43.6%*
26-34 years	56,208	*40.0%*	390,704	*39.7%*	714,925	*38.9%*	1,002,465	*38.3%*	1,387,804	*36.5%*	1,686,540	*36.4%*
35+ years	32,317	*23.0%*	230,788	*23.4%*	446,020	*24.3%*	641,269	*24.5%*	790,913	*20.8%*	921,298	*19.9%*
Unknown Age	267	*0.2%*	1,574	*0.2%*	7,213	*0.4%*	12,092	*0.5%*	49	*0.0%*	38	*0.0%*
Comparator CHCs	35,513,241	*88.3%*	31,607,617	*67.1%*	28,810,861	*58.8%*	27,065,937	*55.0%*	24,897,977	*57.1%*	25,873,212	*60.5%*
Norgestimate (NGM)	21,330,636	*60.1%*	18,707,260	*59.2%*	15,551,890	*54.0%*	14,011,538	*51.8%*	12,255,994	*49.2%*	11,520,980	*44.5%*
0-25 years	10,662,661	*50.0%*	9,271,377	*49.6%*	7,468,076	*48.0%*	6,439,629	*46.0%*	5,872,727	*47.9%*	5,368,966	*46.6%*
26-34 years	7,179,409	*33.7%*	6,281,596	*33.6%*	5,334,733	*34.3%*	4,927,957	*35.2%*	4,154,770	*33.9%*	3,963,849	*34.4%*
35+ years	3,453,252	*16.2%*	3,124,903	*16.7%*	2,702,269	*17.4%*	2,600,654	*18.6%*	2,228,223	*18.2%*	2,188,014	*19.0%*
Unknown Age	35,314	*0.2%*	29,384	*0.2%*	46,812	*0.3%*	43,298	*0.3%*	273	*0.0%*	151	*0.0%*
Norethindrone (NETA)	4,028,417	*11.3%*	3,521,175	*11.1%*	3,551,615	*12.3%*	3,701,560	*13.7%*	4,101,372	*16.5%*	6,242,520	*24.1%*
0-25 years	607,883	*15.1%*	540,496	*15.3%*	584,274	*16.5%*	637,618	*17.2%*	995,901	*24.3%*	2,084,504	*33.4%*
26-34 years	821,887	*20.4%*	720,810	*20.5%*	792,766	*22.3%*	854,491	*23.1%*	976,586	*23.8%*	1,541,226	*24.7%*
35+ years	2,596,266	*64.4%*	2,256,623	*64.1%*	2,169,160	*61.1%*	2,203,853	*59.5%*	2,128,818	*51.9%*	2,616,741	*41.9%*
Unknown Age	2,381	*0.1%*	3,246	*0.1%*	5,415	*0.2%*	5,598	*0.2%*	67	*0.0%*	49	*0.0%*
Levonorgestrel (LNG 1)	7,159,073	*20.2%*	6,707,423	*21.2%*	6,456,520	*22.4%*	5,954,249	*22.0%*	5,326,680	*21.4%*	4,983,652	*19.3%*
0-25 years	2,434,577	*34.0%*	2,284,265	*34.1%*	2,203,865	*34.1%*	2,032,186	*34.1%*	2,030,429	*38.1%*	1,964,105	*39.4%*
26-34 years	2,015,063	*28.1%*	1,845,169	*27.5%*	1,764,984	*27.3%*	1,630,665	*27.4%*	1,402,958	*26.3%*	1,336,061	*26.8%*
35+ years	2,698,320	*37.7%*	2,566,972	*38.3%*	2,471,015	*38.3%*	2,273,588	*38.2%*	1,893,179	*35.5%*	1,683,451	*33.8%*
Unknown Age	11,113	*0.2%*	11,017	*0.2%*	16,656	*0.3%*	17,810	*0.3%*	114	*0.0%*	36	*0.0%*
Levonorgestrel (LNG 2)	2,995,115	*8.4%*	2,671,759	*8.5%*	3,250,836	*11.3%*	3,398,590	*12.6%*	3,213,931	*12.9%*	3,126,060	*12.1%*
0-25 years	747,112	*24.9%*	668,837	*25.0%*	897,804	*27.6%*	1,002,266	*29.5%*	1,050,324	*32.7%*	1,013,960	*32.4%*
26-34 years	1,036,442	*34.6%*	885,304	*33.1%*	1,037,496	*31.9%*	1,045,382	*30.8%*	952,444	*29.6%*	935,484	*29.9%*
35+ years	1,207,155	*40.3%*	1,113,947	*41.7%*	1,306,126	*40.2%*	1,339,522	*39.4%*	1,211,143	*37.7%*	1,176,584	*37.6%*
Unknown Age	4,406	*0.1%*	3,671	*0.1%*	9,410	*0.3%*	11,420	*0.3%*	20	*0.0%*	31	*0.0%*

Source: SDI Vector One®: National, Years 2002-2007 Data Extracted October 2011. File: VONA_2011-1044_CHC_study_products_by_Age_10-27-11.xls

Table 5. Selected Diagnoses associated with the use* of Ortho Evra® and Study CHC Products† by patient age (0-25, 26-34, 35+) as reported by office-based physician practices, Y2001-2007

	1/2001-12/2007				
	Uses (000)	Share%		Uses (000)	Share%
Grand Total	**60,901**	***100.0%***		**60,901**	***100.0%***
Ortho Evra	**7,520**	***12.4%***	**Norgestimate (NGM)**	**17,451**	***28.7%***
0-25 years	3,918	*52.1%*	**0-25 years**	9,390	*53.8%*
V250 CONTRACEP MGMT-COUNSEL	2,742	*70.0%*	**V254 CONTRACEPT SURVEILLANCE**	4,961	*52.8%*
V254 CONTRACEPT SURVEILLANCE	1,023	*26.1%*	**V250 CONTRACEP MGMT-COUNSEL**	3,393	*36.1%*
6253 DYSMENORRHEA	142	*3.6%*	**6253 DYSMENORRHEA**	498	*5.3%*
All Others	11	*0.3%*	**7061 ACNE NEC**	448	*4.8%*
26-34 years	2,656	*35.3%*	**All Others**	90	*1.0%*
V250 CONTRACEP MGMT-COUNSEL	1,768	*66.6%*	**26-34 years**	5,954	*34.1%*
V254 CONTRACEPT SURVEILLANCE	816	*30.7%*	**V254 CONTRACEPT SURVEILLANCE**	3,797	*63.8%*
6253 DYSMENORRHEA	68	*2.5%*	**V250 CONTRACEP MGMT-COUNSEL**	1,888	*31.7%*
All Others	4	*0.2%*	**7061 ACNE NEC**	141	*2.4%*
35+ years	874	*11.6%*	**6253 DYSMENORRHEA**	92	*1.6%*
V250 CONTRACEP MGMT-COUNSEL	535	*61.1%*	**All Others**	36	*0.6%*
V254 CONTRACEPT SURVEILLANCE	284	*32.5%*	**35+ years**	1,876	*10.8%*
6270 PREMENOPAUSE MENORRHAGIA	35	*4.0%*	**V254 CONTRACEPT SURVEILLANCE**	1,329	*70.9%*
6253 DYSMENORRHEA	17	*2.0%*	**V250 CONTRACEP MGMT-COUNSEL**	413	*22.0%*
All Others	4	*0.5%*	**6253 DYSMENORRHEA**	83	*4.4%*
UNSPEC	72	*1.0%*	**All Others**	51	*2.7%*
Yasmin 28	**13,448**	***22.1%***	**UNSPEC**	232	*1.3%*
0-25 years	6,269	*46.6%*	**Levonorgestrel (LNG 1)**	**6,303**	***10.4%***
V250 CONTRACEP MGMT-COUNSEL	3,253	*51.9%*	**0-25 years**	2,753	*43.7%*
V254 CONTRACEPT SURVEILLANCE	2,390	*38.1%*	**V254 CONTRACEPT SURVEILLANCE**	1,389	*50.5%*
6253 DYSMENORRHEA	341	*5.4%*	**V250 CONTRACEP MGMT-COUNSEL**	1,197	*43.5%*
2564 POLYCYSTIC OVARIES	114	*1.8%*	**6253 DYSMENORRHEA**	138	*5.0%*
7061 ACNE NEC	100	*1.6%*	**All Others**	29	*1.1%*
All Others	70	*1.1%*	**26-34 years**	2,077	*33.0%*
26-34 years	5,056	*37.6%*	**V254 CONTRACEPT SURVEILLANCE**	1,395	*67.2%*
V254 CONTRACEPT SURVEILLANCE	2,434	*48.1%*	**V250 CONTRACEP MGMT-COUNSEL**	626	*30.2%*
V250 CONTRACEP MGMT-COUNSEL	2,205	*43.6%*	**6253 DYSMENORRHEA**	28	*1.3%*
6253 DYSMENORRHEA	135	*2.7%*	**All Others**	28	*1.3%*
6254 PREMENSTRUAL TENSION	99	*2.0%*	**35+ years**	1,419	*22.5%*
2564 POLYCYSTIC OVARIES	90	*1.8%*	**V254 CONTRACEPT SURVEILLANCE**	949	*66.9%*
7061 ACNE NEC	61	*1.2%*	**V250 CONTRACEP MGMT-COUNSEL**	339	*23.9%*
All Others	32	*0.6%*	**6253 DYSMENORRHEA**	78	*5.5%*
35+ years	1,871	*13.9%*	**6254 PREMENSTRUAL TENSION**	29	*2.0%*
V254 CONTRACEPT SURVEILLANCE	1,017	*54.4%*	**All Others**	24	*1.7%*
V250 CONTRACEP MGMT-COUNSEL	634	*33.9%*	**UNSPEC**	54	*0.9%*
6253 DYSMENORRHEA	124	*6.6%*	**Norethindrone (NETA)**	**4,864**	***8.0%***
6254 PREMENSTRUAL TENSION	31	*1.7%*	**0-25 years**	1,665	*34.2%*
2564 POLYCYSTIC OVARIES	25	*1.4%*	**V250 CONTRACEP MGMT-COUNSEL**	897	*53.9%*
3464 MENSTRUAL MIGRAINE	20	*1.1%*	**V254 CONTRACEPT SURVEILLANCE**	693	*41.6%*
All Others	18	*1.0%*	**6253 DYSMENORRHEA**	58	*3.5%*
UNSPEC	253	*1.9%*	**All Others**	18	*1.1%*
Yaz	**3,443**	***5.7%***	**26-34 years**	1,472	*30.3%*
0-25 years	1,797	*52.2%*	**V254 CONTRACEPT SURVEILLANCE**	741	*50.3%*
V250 CONTRACEP MGMT-COUNSEL	1,044	*58.1%*	**V250 CONTRACEP MGMT-COUNSEL**	648	*44.0%*
V254 CONTRACEPT SURVEILLANCE	542	*30.2%*	**6253 DYSMENORRHEA**	66	*4.5%*
6253 DYSMENORRHEA	125	*6.9%*	**All Others**	17	*1.2%*
7061 ACNE NEC	36	*2.0%*	**35+ years**	1,630	*33.5%*
6254 PREMENSTRUAL TENSION	35	*1.9%*	**V254 CONTRACEPT SURVEILLANCE**	1,050	*64.4%*
All Others	16	*0.9%*	**V250 CONTRACEP MGMT-COUNSEL**	492	*30.2%*
26-34 years	1,073	*31.2%*	**6253 DYSMENORRHEA**	43	*2.6%*
V250 CONTRACEP MGMT-COUNSEL	608	*56.6%*	**All Others**	45	*2.7%*
V254 CONTRACEPT SURVEILLANCE	415	*38.7%*	**UNSPEC**	97	*2.0%*
6253 DYSMENORRHEA	35	*3.3%*	**Levonorgestrel (LNG 2)**	**4,429**	***7.3%***
All Others	15	*1.4%*	**0-25 years**	1,389	*31.4%*
35+ years	547	*15.9%*	**V250 CONTRACEP MGMT-COUNSEL**	696	*50.1%*
V250 CONTRACEP MGMT-COUNSEL	267	*48.8%*	**V254 CONTRACEPT SURVEILLANCE**	562	*40.5%*
V254 CONTRACEPT SURVEILLANCE	195	*35.6%*	**6253 DYSMENORRHEA**	110	*8.0%*
6253 DYSMENORRHEA	30	*5.5%*	**All Others**	20	*1.5%*
6254 PREMENSTRUAL TENSION	24	*4.4%*	**26-34 years**	1,695	*38.3%*
2564 POLYCYSTIC OVARIES	11	*1.9%*	**V250 CONTRACEP MGMT-COUNSEL**	821	*48.4%*
7061 ACNE NEC	10	*1.8%*	**V254 CONTRACEPT SURVEILLANCE**	797	*47.0%*
V252 STERILIZATION	6	*1.0%*	**6253 DYSMENORRHEA**	54	*3.2%*
All Others	5	*0.9%*	**All Others**	23	*1.4%*
UNSPEC	26	*0.7%*	**35+ years**	1,264	*28.5%*
Etonogestrel (ETON)	**3,444**	***5.7%***	**V254 CONTRACEPT SURVEILLANCE**	738	*58.4%*
0-25 years	1,288	*37.4%*	**V250 CONTRACEP MGMT-COUNSEL**	395	*31.3%*
V250 CONTRACEP MGMT-COUNSEL	942	*73.1%*	**6253 DYSMENORRHEA**	95	*7.6%*
V254 CONTRACEPT SURVEILLANCE	301	*23.4%*	**3464 MENSTRUAL MIGRAINE**	22	*1.7%*
6253 DYSMENORRHEA	35	*2.7%*	**6254 PREMENSTRUAL TENSION**	14	*1.1%*
All Others	11	*0.8%*	**UNSPEC**	81	*1.8%*
26-34 years	1,572	*45.7%*			
V250 CONTRACEP MGMT-COUNSEL	1,060	*67.4%*			
V254 CONTRACEPT SURVEILLANCE	406	*25.8%*			
6253 DYSMENORRHEA	64	*4.1%*			
6254 PREMENSTRUAL TENSION	24	*1.6%*			
All Others	19	*1.2%*			
35+ years	535	*15.5%*			
V250 CONTRACEP MGMT-COUNSEL	364	*68.1%*			
V254 CONTRACEPT SURVEILLANCE	162	*30.3%*			
6253 DYSMENORRHEA	9	*1.6%*			
UNSPEC	49	*1.4%*			

Source: SDI Physician Drug and Diagnosis Audit, Years 2001-2007 Extracted October 2011. File: PDDA_2011-1044 _ CHC_ Study_ Products _by_AgeDx4_10-27-11.xls *Use - Projected uses for a product linked to a diagnosis. The projected number of times a product has been reported for treatment of a particular disease. See Appendix 4 for full list of ICD-9 Diagnosis Groups.

†Only study products with data available in PDDA were included

Table 6. Percentage of drug occurrences* for Ortho Evra and Study CHC Products by BMI and patient age (0-25, 26-34, 35+) as reported by office-based physician practices, Y2001-2007

	01/2001-12/2007							
	Yasmin 28	Yaz	Levonorgestrel (LNG 1)	Levonorgestrel (LNG 2)	Norethindrone (NETA)	Norgestimate (NGM)	Ortho Evra	Etonogestrel (ETON)
	Vertical Share%							
0-25 years	**45.3%**	**49.6%**	**40.4%**	**31.3%**	**29.1%**	**53.1%**	**50.9%**	**36.8%**
BMI 0-18	3.7%	2.0%	4.5%	2.2%	2.2%	4.1%	3.2%	4.5%
BMI 19-24	54.3%	57.3%	58.1%	41.5%	57.9%	51.4%	52.3%	45.5%
BMI 25-29	13.8%	13.2%	16.7%	12.6%	15.4%	18.4%	21.9%	17.5%
BMI 30-39	6.4%	6.9%	4.4%	8.2%	8.1%	7.7%	7.6%	9.6%
BMI 40+	1.8%	2.8%	1.9%	0.8%	1.0%	0.9%	0.1%	2.5%
Unknown BMI	19.9%	17.9%	14.4%	34.7%	15.4%	17.5%	14.9%	20.5%
26-34 years	**36.5%**	**32.5%**	**30.9%**	**36.2%**	**25.4%**	**34.1%**	**35.1%**	**43.8%**
BMI 0-18	1.1%	1.9%	2.3%	0.8%	0.9%	2.1%	2.3%	1.6%
BMI 19-24	44.5%	44.8%	44.7%	32.6%	43.3%	48.8%	47.0%	54.6%
BMI 25-29	22.1%	21.2%	22.6%	20.3%	22.7%	20.9%	23.1%	22.5%
BMI 30-39	10.1%	12.1%	11.5%	10.2%	11.9%	10.7%	10.3%	9.3%
BMI 40+	2.6%	2.7%	2.0%	3.2%	1.8%	1.3%	1.3%	1.3%
Unknown BMI	19.6%	17.3%	16.9%	32.9%	19.5%	16.3%	16.0%	10.6%
35+ years	**16.3%**	**17.3%**	**27.8%**	**30.9%**	**43.6%**	**11.5%**	**13.1%**	**17.9%**
BMI 0-18	2.2%	0.0%	0.7%	0.5%	0.7%	3.5%	2.2%	1.2%
BMI 19-24	37.5%	39.5%	39.8%	36.0%	42.4%	45.2%	30.8%	42.3%
BMI 25-29	25.1%	31.8%	27.5%	21.6%	25.5%	17.3%	30.2%	25.7%
BMI 30-39	11.8%	5.9%	16.9%	10.2%	11.1%	11.4%	18.2%	11.5%
BMI 40+	2.0%	4.2%	2.0%	2.2%	2.8%	2.5%	1.7%	2.1%
Unknown BMI	21.4%	18.7%	13.1%	29.5%	17.5%	20.1%	17.0%	17.2%

Source: SDI Physician Drug and Diagnosis Audit, Years 2001-2007 Extracted October 2011. File: PDDA_2011-1044_CHC_Study_Products_by_BMI_10-27-11(1).xls A *Drug occurrence can result from a prescription written, a sample given, a recommendation for OTC products, recommendation with sample, a product dispensed or administered in the office, a hospital order, a nursing home order or a combination of these.

†**Only study products with data available in PDDA were included**

Figure 3: Ortho Evra® and Study CHC Products by BMI Age 0-25 years, Y2001-2007

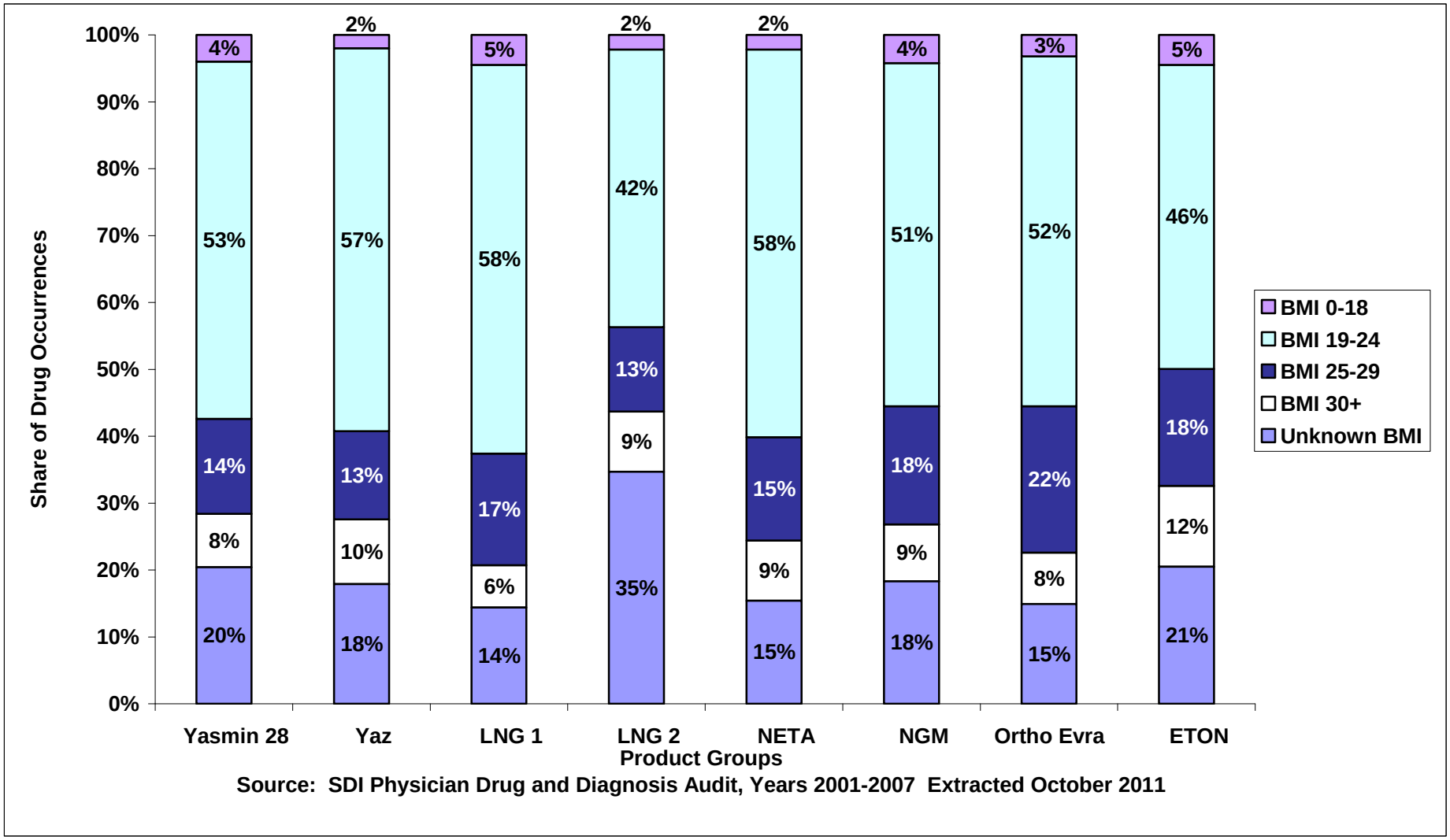


Figure 4: Ortho Evra® and Study CHC Products by BMI Age 26-34 years, Y2001-2007

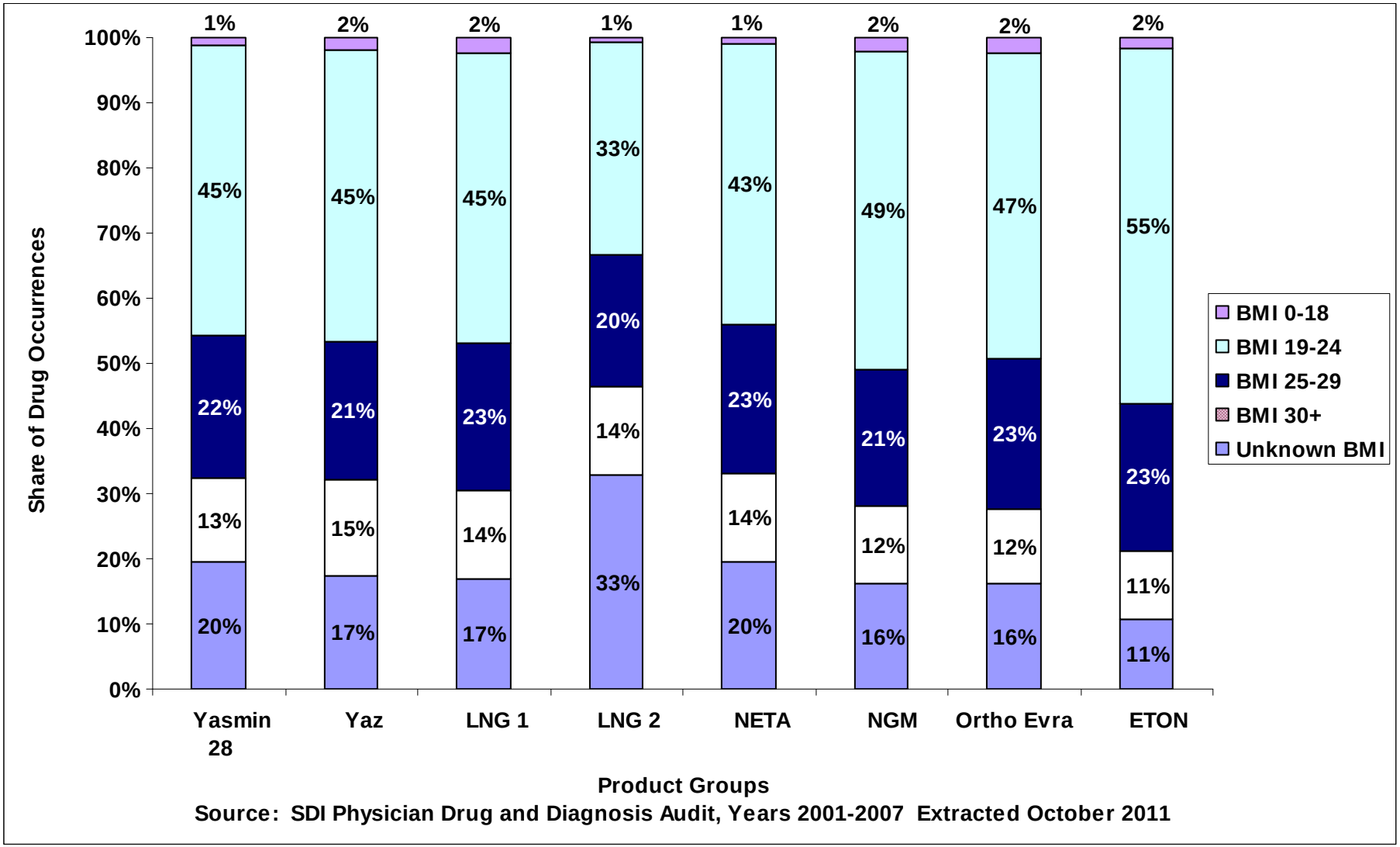


Figure 5: Ortho Evra® and Study CHC Products by BMI Age 35+ years, Y2001-2007

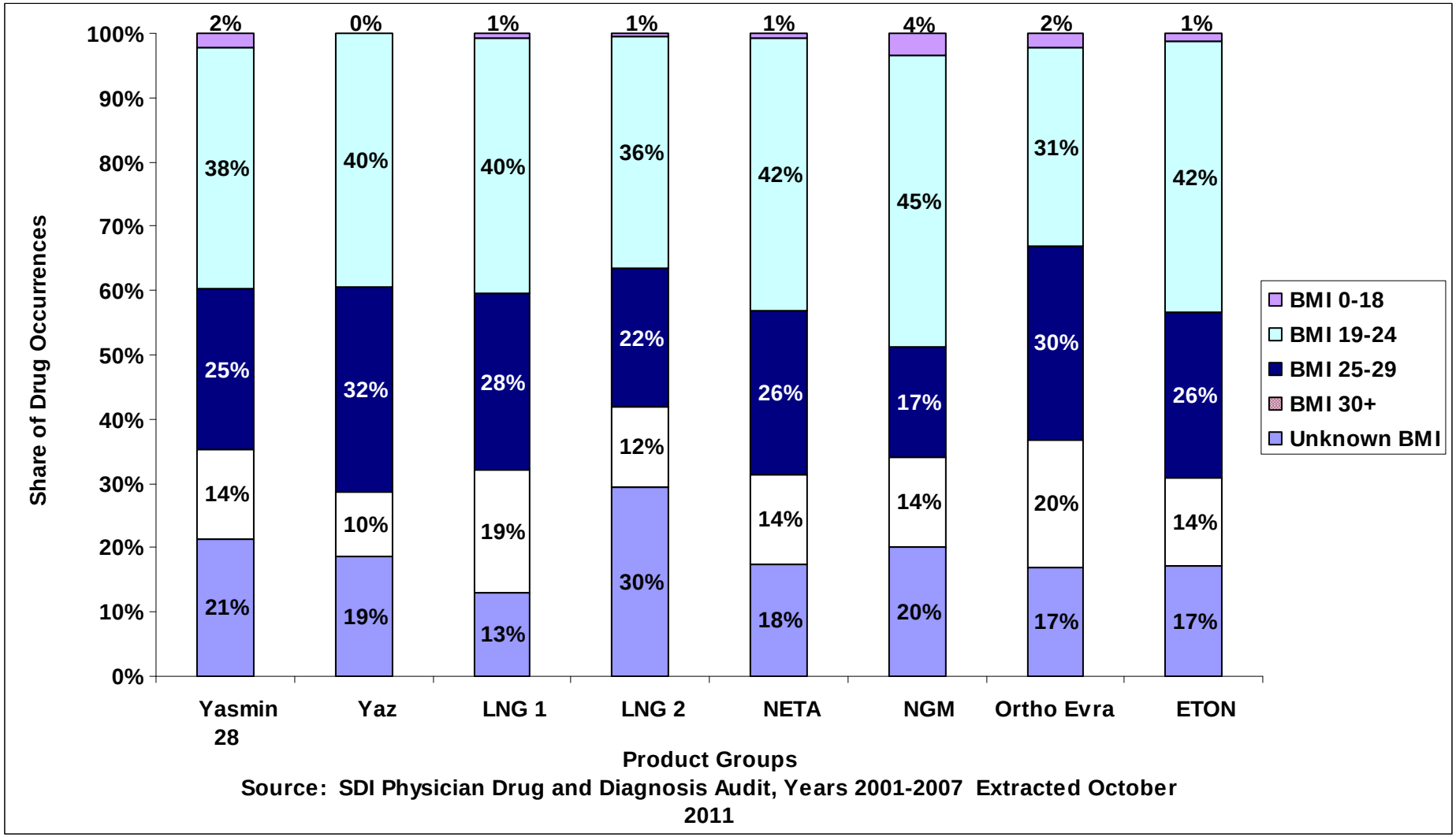


Figure 6: Ortho Evra® and Study CHC Products for One or More Selected Diagnoses (Age 0-25 years), Y2007-2010

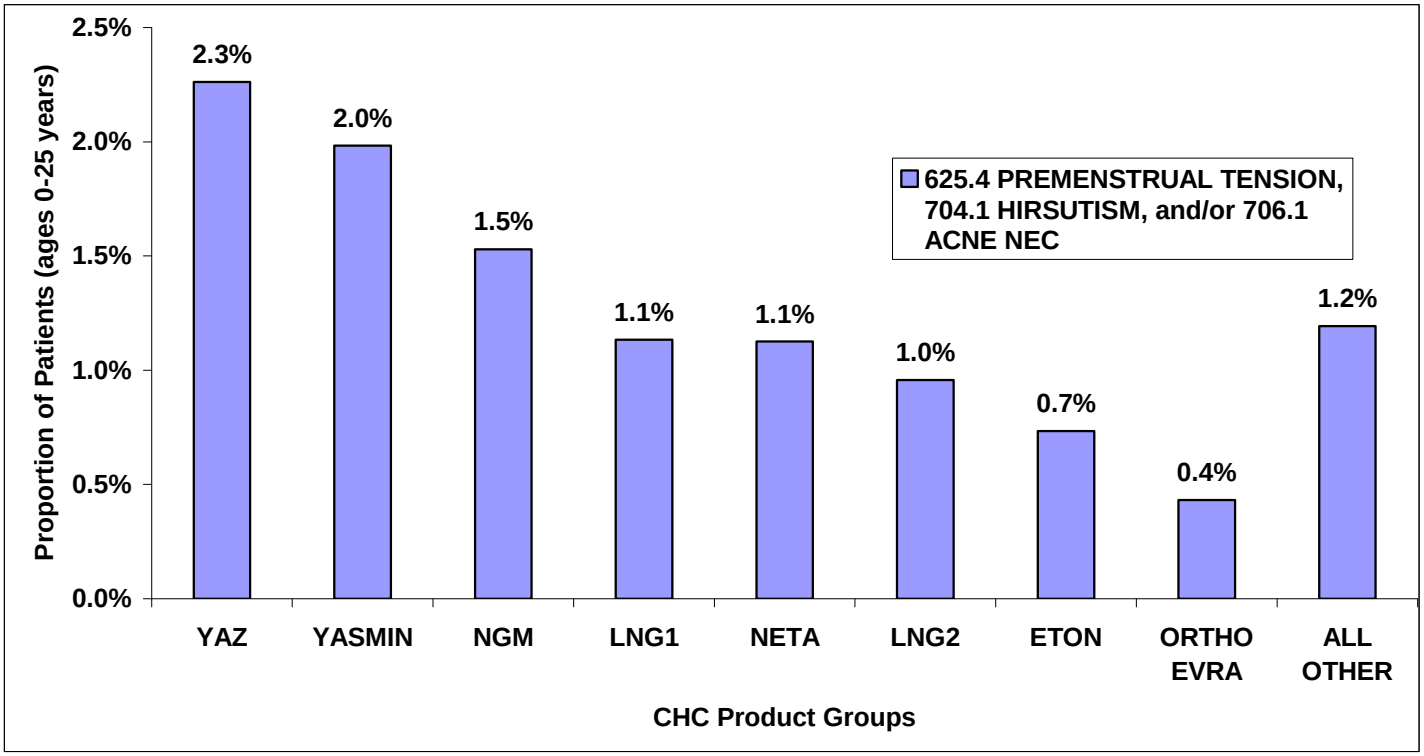


Figure 7: Ortho Evra® and Study CHC Products for One or More Selected Diagnoses (Age 26-34 years), Y2007-2010

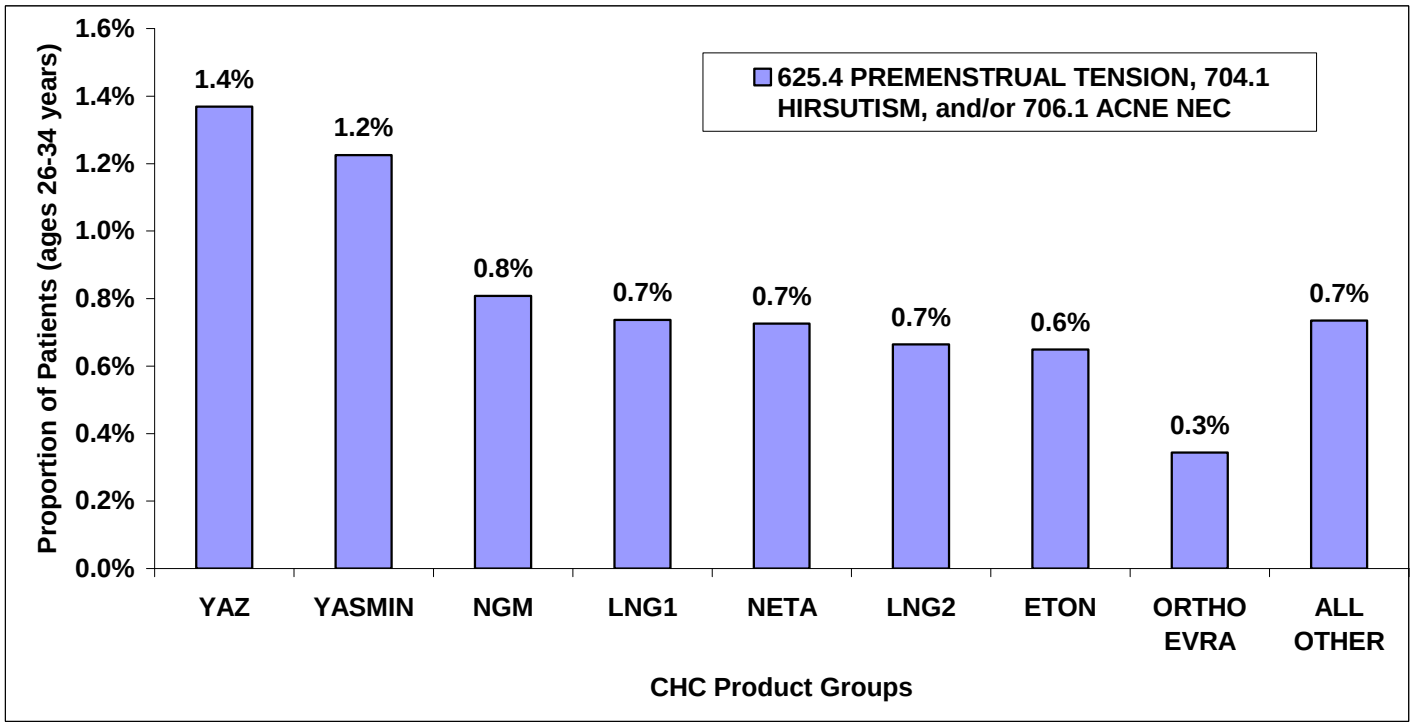
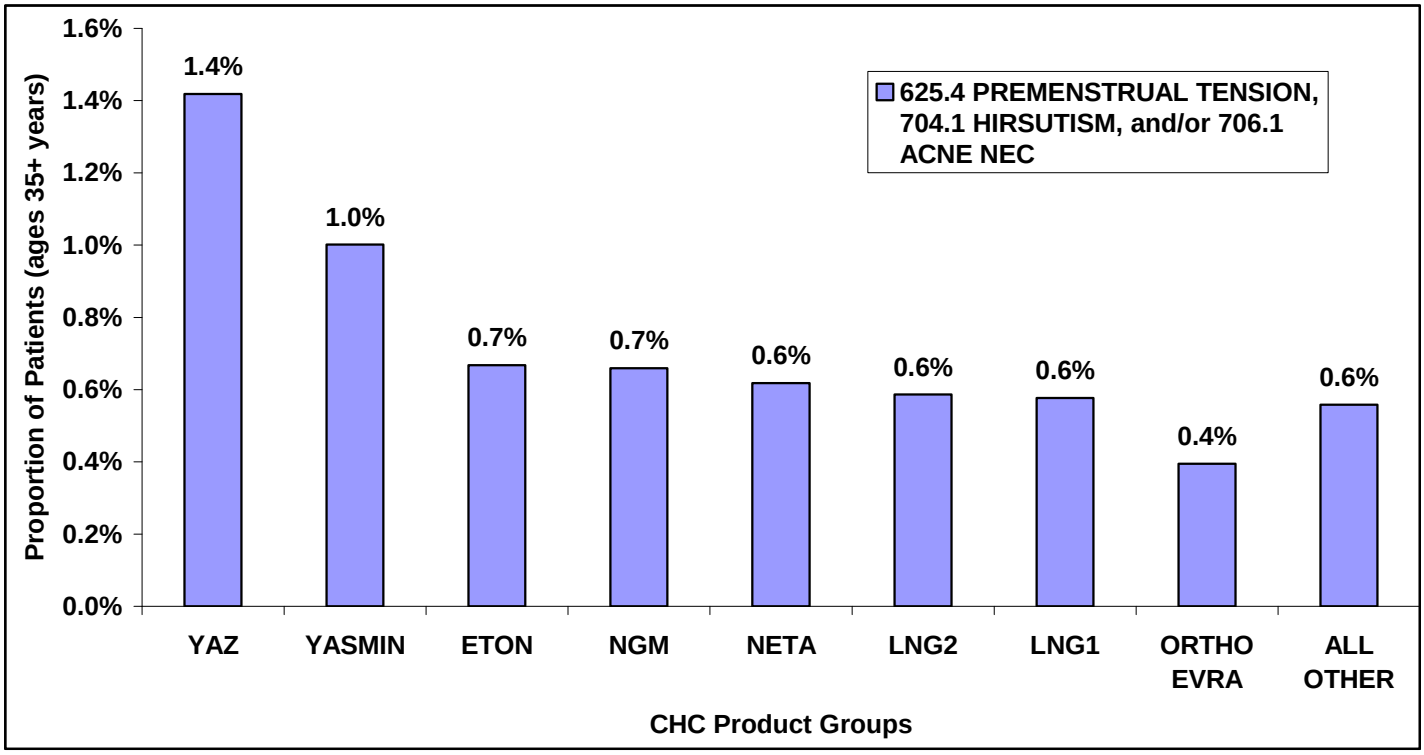


Figure 8: Ortho Evra® and Study CHC Products for One or More Selected Diagnoses (Age 35+ years), Y2007-2010



7 APPENDIX 2: DATABASE DESCRIPTIONS

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

SDI, Vector One®: National (VONA)

The SDI, Vector One®: National (VONA) database measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 1.4 billion prescription claims per year, representing over 120 million unique patients. Since 2002 Vector One® has captured information on over 8 billion prescriptions representing over 200 million unique patients.

Prescriptions are captured from a sample from the universe of approximately 59,000 pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. SDI receives all prescriptions from approximately one-third of stores and a significant sample of prescriptions from many of the remaining stores.

SDI, Vector One®: Total Patient Tracker (TPT)

The SDI, Vector One®: Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time.

TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 1.4 billion prescription claims per year, representing over 120 million unique patients. Since 2002 Vector One® has captured information on over 8 billion prescriptions representing over 200 million unique patients.

SDI, Physician Drug & Diagnosis Audit (PDDA) with Pain Panel

The SDI, Physician Drug & Diagnosis Audit (PDDA) with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

Wolters Kluwer SOURCE Lx®

The Wolters Kluwer Pharma Solutions Source® Lx database is a longitudinal patient data source which captures adjudicated claims across the United States from a mix of prescription claims from commercial plans, Medicare Part D plans, Cash and Medicaid claims. The database contains approximately 4.8 billion paid, non-reversed prescriptions claims linked to over 172 million unique prescription patients of which approximately 70 million patients have 2 or more years of prescription drug history. Claims from hospital and physician practices include over 190 million patients with CPT/HCPCS medical procedure history as well as ICD-9 diagnosis history of which nearly 91 million prescription drug patients are linked to a diagnosis. The overall sample represents 27,000 pharmacies, 1,000 hospitals, 800 clinics/outpatient facilities, and 80,000 physician practices.

8 APPENDIX 3: STUDY CHCS PRODUCT GROUP

PRODUCT NAME	NDC	STUDY CHC GROUP
0.10 mg of Levonorgesetrel and 20 µg Ethinyl Estradiol		
ALESSE-21	00008091202	LNG 1
ALESSE-28	00008257601	LNG 1
ALESSE-28	00008257602	LNG 1
ALESSE-28	54868395100	LNG 1
LESSINA-28	00555901458	LNG 1
LESSINA-28	00555901467	LNG 1
AVIANE	00555904558	LNG 1
AVIANE	51285001728	LNG 1
AVIANE	54868535600	LNG 1
LEVLITE-28	50419040803	LNG 1
LEVLITE-28	50419040872	LNG 1
LEVLITE-28	54569471000	LNG 1
LEVLITE-28	54868436800	LNG 1
LEVLITE-28	50419040603	LNG 1
LUTERA	52544094928	LNG 1
LUTERA	54569579800	LNG 1
LUTERA	54868621000	LNG 1
ORSYTHIA	00603763417	LNG 1
ORSYTHIA	00603763449	LNG 1
SRONYX	52544096728	LNG 1
0.15 mg of Levonorgesetrel and 30 µg Ethinyl Estradiol		
ALTAVERA	00781558307	LNG 2
ALTAVERA	00781558336	LNG 2
INTROVALE	00781558436	LNG 2
INTROVALE	00781558491	LNG 2
LEVLEN-21	50419041021	LNG 2
LEVLEN-28	50419041112	LNG 2
LEVLEN-28	50419041128	LNG 2
LEVLEN-28	54569384400	LNG 2
LEVLEN-28	54868156400	LNG 2
NORDETTE-21	00008007501	LNG 2
NORDETTE-28	00008007502	LNG 2
NORDETTE-28	00008253301	LNG 2
NORDETTE-28	00008253302	LNG 2
NORDETTE-28	00008253303	LNG 2
NORDETTE-28	51285009158	LNG 2
NORDETTE-28	54569068200	LNG 2
NORDETTE-28	54569068201	LNG 2

NORDETTE-28	54868050700	LNG 2
PORTIA-28	00555902058	LNG 2
JOLESSA	00555912366	LNG 2
LEVORA	00905027721	LNG 2
LEVORA	00905027928	LNG 2
LEVORA	52544027928	LNG 2
LEVORA	54569499700	LNG 2
LEVORA	54868460700	LNG 2
LEVORA	60322014521	LNG 2
LEVORA	60322014728	LNG 2
LEVORA	52544027721	LNG 2
SEASONALE	51285005866	LNG 2
SEASONALE	54868231600	LNG 2
QUASENSE	52544096691	LNG 2
1 mg Norethindrone Acetate and 20 µg Ethinyl Estradiol		
LOESTRIN 1/20	00071091511	NETA
LOESTRIN 1/20	00071091546	NETA
LOESTRIN 1/20	00071091547	NETA
LOESTRIN 1/20	00071091548	NETA
LOESTRIN 1/20	00710091511	NETA
LOESTRIN 1/20	00710091545	NETA
LOESTRIN 1/20	00710091546	NETA
LOESTRIN 1/20	00710091547	NETA
LOESTRIN 1/20	51285007997	NETA
LOESTRIN 24 FE	00430053014	NETA
LOESTRIN 24 FE	35356047605	NETA
LOESTRIN 24 FE	35356047628	NETA
LOESTRIN 24 FE	54868610000	NETA
LOESTRIN FE 1/20	00710091346	NETA
LOESTRIN FE 1/20	00710091347	NETA
LOESTRIN FE 1/20	00071091315	NETA
LOESTRIN FE 1/20	00071091335	NETA
LOESTRIN FE 1/20	00071091336	NETA
LOESTRIN FE 1/20	00071091338	NETA
LOESTRIN FE 1/20	00071091345	NETA
LOESTRIN FE 1/20	00071091347	NETA
LOESTRIN FE 1/20	00071091348	NETA
LOESTRIN FE 1/20	00710091335	NETA
LOESTRIN FE 1/20	00710091336	NETA
LOESTRIN FE 1/20	00710091337	NETA
LOESTRIN FE 1/20	35356036328	NETA
LOESTRIN FE 1/20	51285008070	NETA
LOESTRIN FE 1/20	51285008198	NETA
LOESTRIN FE 1/20	54569325400	NETA

LOESTRIN FE 1/20	54569325401	NETA
LOESTRIN FE 1/20	54868151200	NETA
MICROGESTIN 1/20	52544095021	NETA
MICROGESTIN 1/20	54868621300	NETA
MICROGESTIN FE 1MG-20MCG	52544063028	NETA
MICROGESTIN FE 1MG-20MCG	54868474400	NETA
JUNEL 1/20	00555902542	NETA
JUNEL 1/20	00555902557	NETA
JUNEL 1/20	58016474701	NETA
JUNEL FE 1/20	00555902858	NETA
JUNEL FE 1/20	00555902658	NETA
JUNEL FE 1/20	54868532600	NETA
11.7 mg Etonogestrel and 2700 µg Ethinyl Estradiol		
NUVARING	00052027301	ETON
NUVARING	00052027303	ETON
NUVARING	35356041003	ETON
NUVARING	54868483200	ETON
NUVARING	54868483201	ETON
6.0 mg Norelgestromin and 750 µg Ethinyl Estradiol		
ORTHO EVRA	00062192001	NGNM
ORTHO EVRA	00062192015	NGNM
ORTHO EVRA	50458019201	NGNM
ORTHO EVRA	50458019215	NGNM
ORTHO EVRA	54569541300	NGNM
ORTHO EVRA	54868467000	NGNM
0.18-0.25 mg Norgestimate and 35 µg Ethinyl Estradiol		
ORTHO TRI-CYCLEN	00062190215	NGM
ORTHO TRI-CYCLEN	54868409300	NGM
ORTHO TRI-CYCLEN	00062190315	NGM
ORTHO TRI-CYCLEN	00062191015	NGM
ORTHO TRI-CYCLEN	35356002168	NGM
ORTHO TRI-CYCLEN	50458019115	NGM
ORTHO TRI-CYCLEN	54569426900	NGM
TRI-PREVIFEM	00093531528	NGM
TRI-PREVIFEM	00093531581	NGM
TRI-PREVIFEM	00603766317	NGM
TRI-PREVIFEM	00603766517	NGM
TRI-PREVIFEM	35356001568	NGM
TRI-SPRINTEC	54569555100	NGM
TRI-SPRINTEC	00555901858	NGM
TRI-SPRINTEC	21695077001	NGM
TRI-SPRINTEC	21695077028	NGM

TRI-SPRINTEC	54868502800	NGM
TRI-SPRINTEC	55045378106	NGM
TRINESSA	35356036828	NGM
TRINESSA	52544024828	NGM
TRINESSA	52544093528	NGM
TRINESSA	54569579600	NGM
TRINESSA	54868582600	NGM
3.0 mg Drospirenone and 30 ug Ethinyl Estradiol		
YASMIN 28	50419040203	DRSP
YASMIN 28	54569534900	DRSP
YASMIN 28	54868459000	DRSP
OCELLA	00555913167	DRSP
SYEDA	007815658	DRSP
SAFYRAL	504190407	DRSP
ZARAH	525440981	DRSP
3.0 mg Drospirenone and 20 ug Ethinyl Estradiol		
YAZ	35356025528	DRSP
YAZ	50419040503	DRSP
YAZ	54868582800	DRSP
BEYAZ	504190407	DRSP
GIANVI	000935423	DRSP
LORYNA	007815656	DRSP

9 APPENDIX 4: ICD-9 DIAGNOSIS CODES

Diagnosis Group Name	*Code*
706.1 ACNE NEC	**706.1**
704.1 HIRSUTISM	**704.1**
256.4 POLYCYSTIC OVARIES	**256.4**
625.4 PREMENSTRUAL TENSION	**625.4**
625.3 DYSMENORRHEA	**625.3**
627.0 PREMENOPAUSE MENORRHAGIA	**627.0**
346.4 MENSTRUAL MIGRAINE	**346.42** **346.43** **346.41** **346.40**
V25.0 CONTRACEPTIVE COUNSELING	**V25.0**
V25.01 PRESCRIP-ORAL CONTRACEPTION COUNSELING	**V25.01**
V25.02 INITIATE CONTRACEPTION NEC	**V25.02**
V25.03 CONTRACEPTION MGMT-EMERGENCY	**V25.03**
V25.04 COUNSEL NATURAL FAMILY PLANNING	**V25.04**
V25.09 CONTRACEPTIVE MGMT NEC	**V25.09**
V25.4 CONTRACEPTIVE SURVELLIANCE	**V25.4** **V25.40** **V25.41** **V25.42** **V25.43** **V25.49**
V25.1 INSERTION OF IUD	**V25.1** **V25.11** **V25.12** **V25.13**
V25.2 STERILIZATION	**V25.2**
V25.3 MENSTUAL EXTRACTION	**V25.3**
V25.5 INSERTION OF IMPLANTABLE SUBDERM CONTRACEP	**V25.5**
V25.8 CONTRACEPTIVE MGMT NEC	**V25.8**
V25.9 CONTRACEPTIVE MGMT NOS	**V25.9**

Appendix D

US Approved Labeling for Ortho Evra (norelgestromin/ethinyl estradiol transdermal system)

ORTHO EVRA®
(norelgestromin / ethinyl estradiol
TRANSDERMAL SYSTEM)

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.)*

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

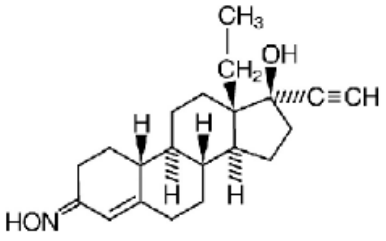
DESCRIPTION

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 [Css]) 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).

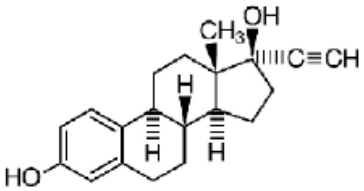
ORTHO EVRA® is a thin, matrix-type transdermal contraceptive patch consisting of three layers. The backing layer is composed of a beige flexible film consisting of a low-density pigmented polyethylene outer layer and a polyester inner layer. It provides structural support and protects the middle adhesive 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 $AUC_{0\text{-}168}$ for NGMN and EE following a single buttock application of ORTHO EVRA® are summarized in Table 1.

In multiple dose studies, $AUC_{0\text{-}168}$ 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)
	$AUC_{0\text{-}168}$ (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)
	$AUC_{0\text{-}168}$ (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)

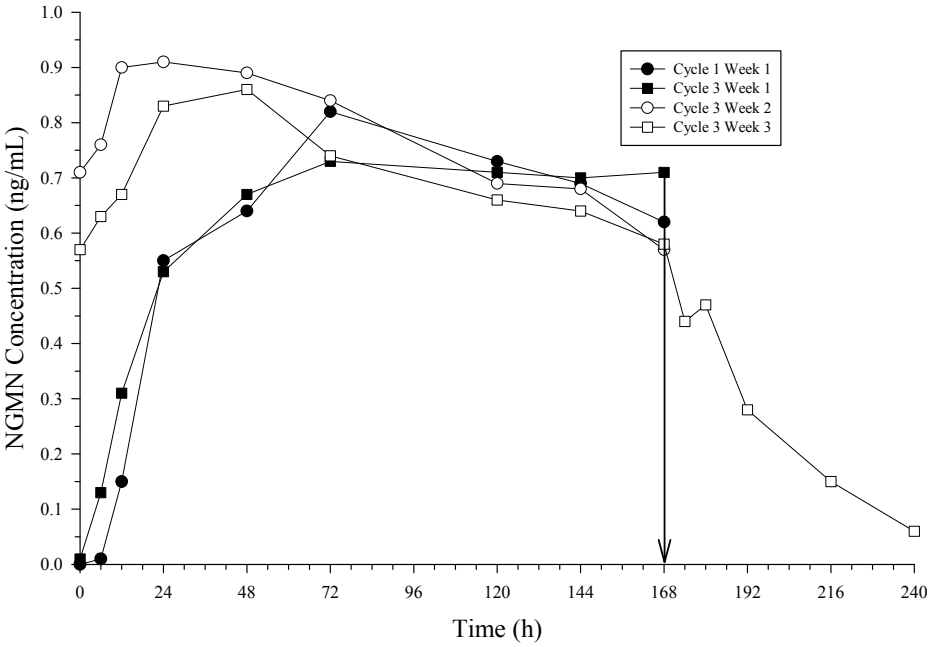
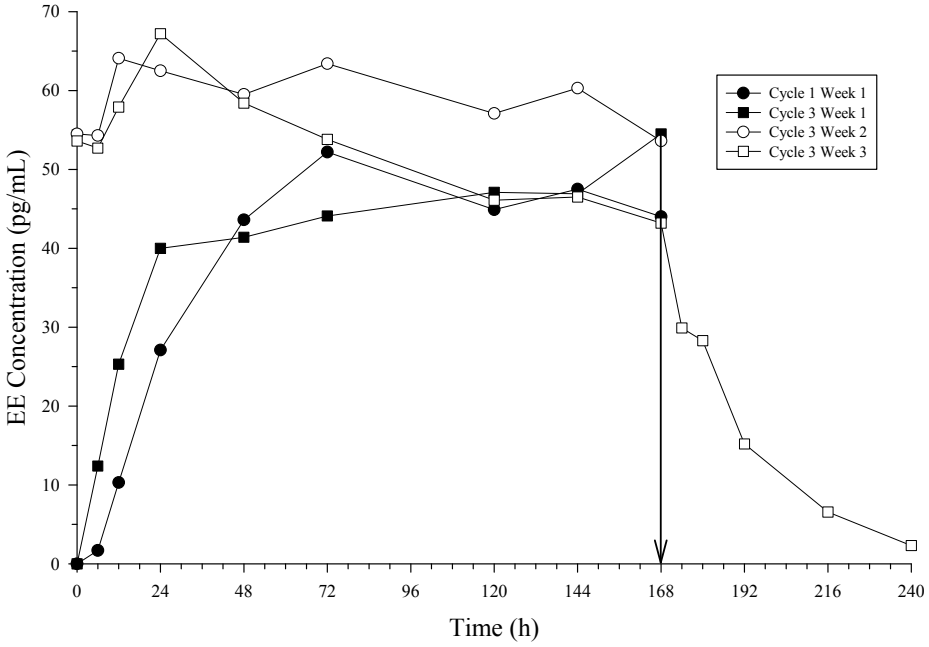


Figure 2: Mean Serum EE Concentrations (pg/mL) in Healthy Female Volunteers Following Application of ORTHO EVRA® on the Buttock for Three Consecutive Cycles (Vertical arrow indicates time of patch removal.)



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]

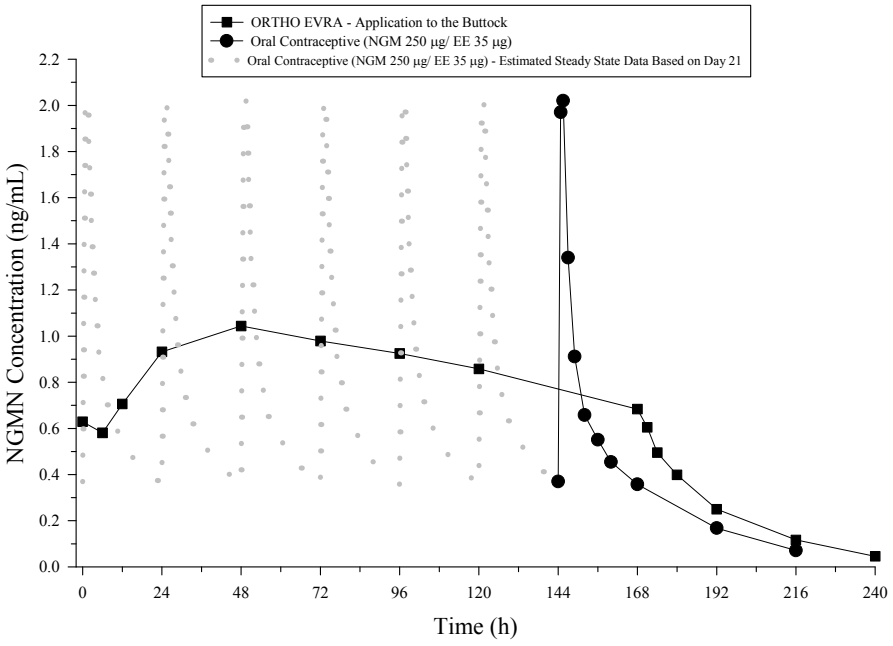


Figure 4: Mean Serum Concentration-Time Profiles of EE Following Once-Daily Administration of an Oral Contraceptive for 2 Cycles or Application of ORTHO EVRA® for 2 Cycles to the Buttock in Healthy Female Volunteers. [Oral contraceptive: Cycle 2, Days 15-21, ORTHO EVRA®: Cycle 2, Week 3]

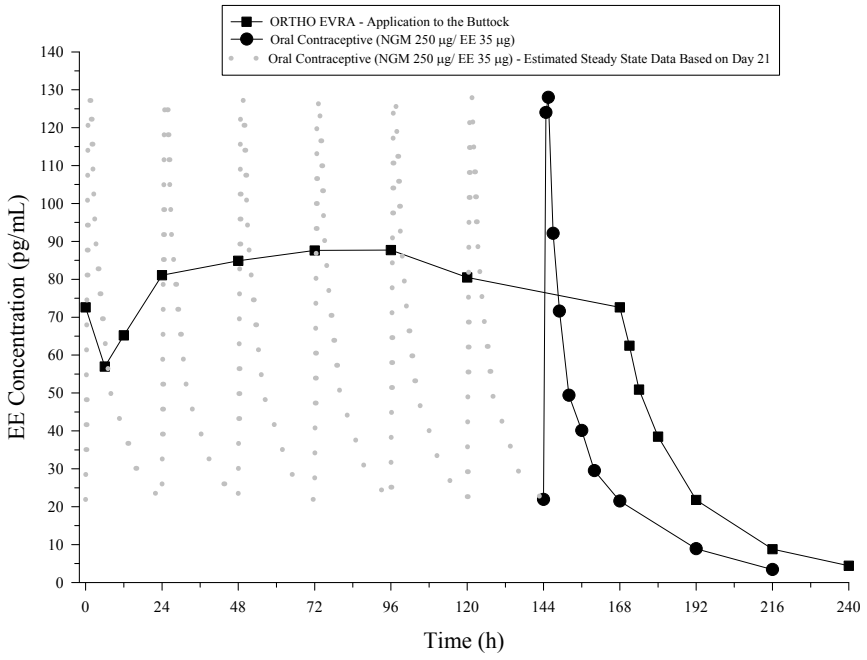


Table 2 provides the mean (%CV) for NGMN and EE pharmacokinetic (PK) parameters.

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 $\geq$ 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.

	% of Women Experiencing an Unintended Pregnancy within the First Year of Use		% of Women Continuing Use at One Year*
Method (1)	Typical Use† (2)	Perfect Use‡ (3)	(4)
Chance#	85	85	
Spermicidesᵖ	26	6	40
Periodic abstinence	25		63
Calendar		9	
Ovulation Method		3	
Sympto-Thermalᵝ		2	
Post-Ovulation		1	
Capà			
Parous Women	40	26	42
Nulliparous Women	20	9	56
Sponge			
Parous Women	40	20	42
Nulliparous Women	20	9	56
Diaphragmà	20	6	56
Withdrawal	19	4	
Condomè			
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.

Þ 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.

è 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[103]
- 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)[Þ]**
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
[Þ]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

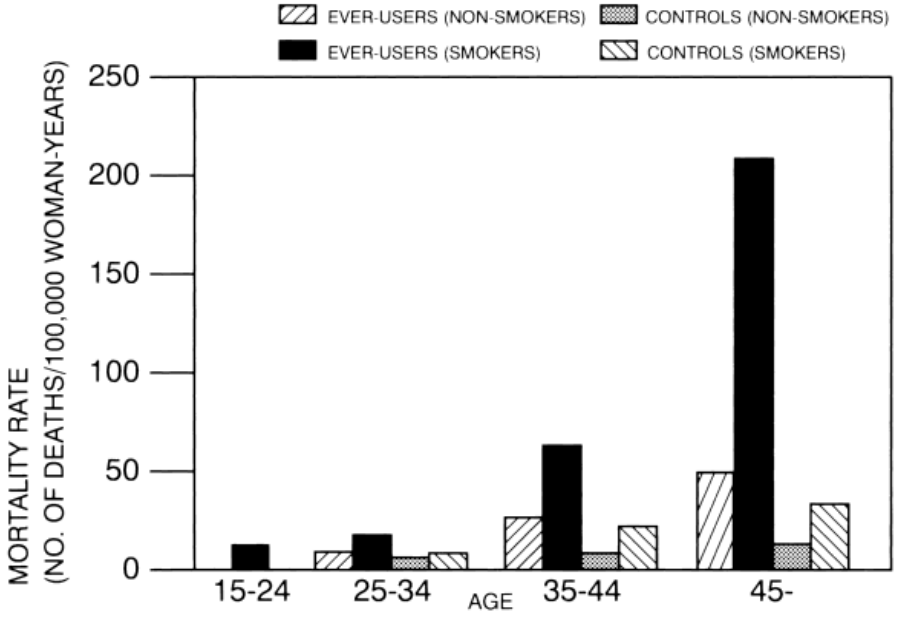
contraceptives should be discontinued at least four weeks prior to and for two weeks after elective surgery of a type associated with an increase in risk of thromboembolism and during and following prolonged immobilization. Since the immediate postpartum period is also associated with an increased risk 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 ($\geq$ 160 mm Hg systolic or $\geq$ 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

HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors: 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.

Antibiotics**:** 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

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

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

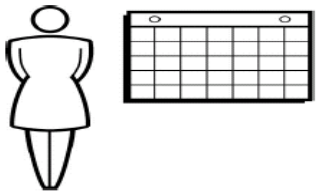
ORTHO EVRA® is a combination transdermal contraceptive that contains 6.00 mg norelgestromin (NGMN) and 0.75 mg ethinyl estradiol (EE). Systemic exposures (as measured by AUC and C_{ss}) of NGMN and EE during use of ORTHO EVRA® are higher and peak concentrations (C_{max}) are lower than those produced 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.



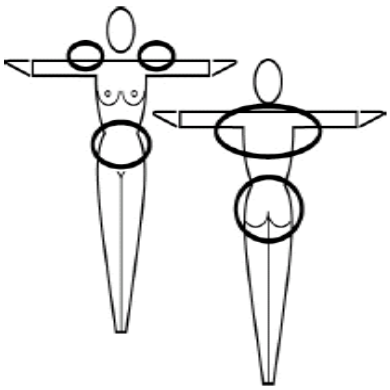
If the woman is starting ORTHO EVRA® for the **first time**, she should **wait until the day she begins her menstrual period.** Either a First Day start or Sunday start may be chosen (see below). The day she applies her first patch will be Day 1. Her "Patch Change Day" will be on this day every week.

- 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.

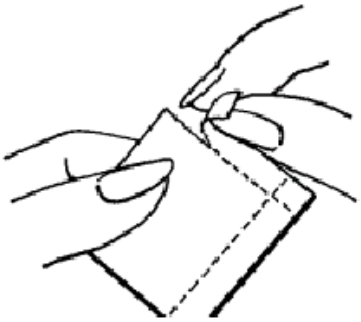
If the menstrual period begins on a Sunday, the first patch should be applied on that day, and no back-up contraception is needed.



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.

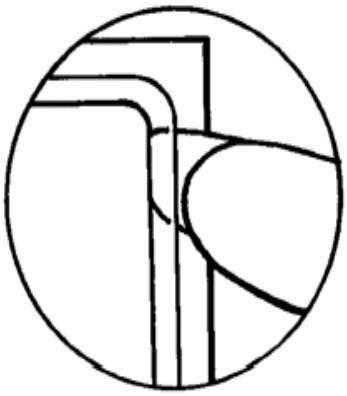
To prevent interference with the adhesive properties of ORTHO EVRA®, no make-up, creams, lotions, powders or other topical products should be applied to the skin area where the ORTHO EVRA® patch is or will be placed.

Application of the ORTHO EVRA® patch

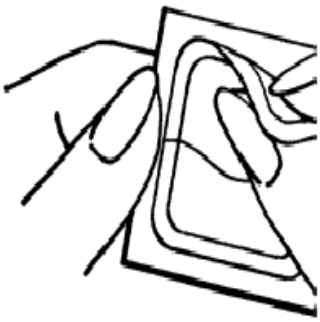


The foil pouch is opened by tearing it along the edge using the fingers.

The foil pouch should be peeled apart and opened flat.



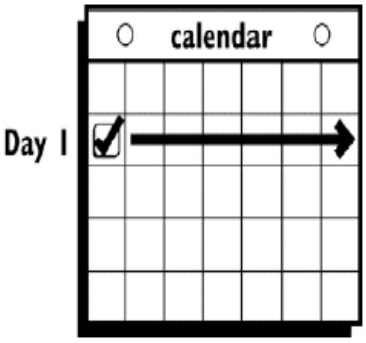
A corner of the patch is grasped firmly and it is gently removed from the foil pouch.



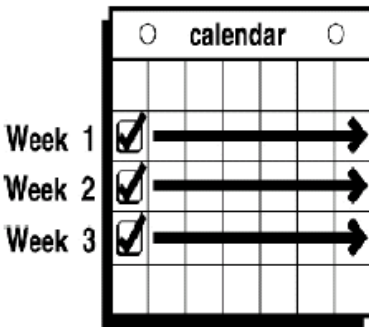
The woman should be instructed to use her fingernail to lift one corner of the patch and peel the patch **and** the plastic liner off the foil liner. **Sometimes patches can stick to the inside of the pouch – the woman should be careful not to accidentally remove the clear liner as she removes the patch.**

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

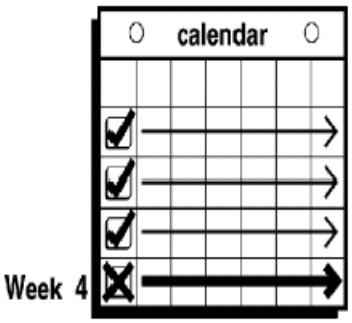
The sticky surface of the patch is applied to the skin and the other half of the liner is removed. The woman should press down firmly on the patch with the palm of her hand for 10 seconds, making sure that the edges stick well. She should check her patch every day to make sure it is sticking.



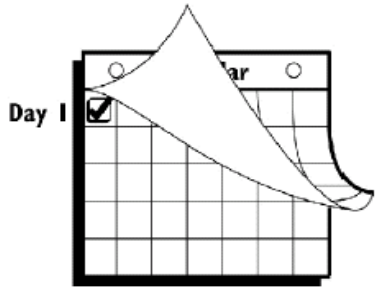
The patch is worn for seven days (one week). On the "Patch Change Day", Day 8, the used patch is removed and a new one is applied immediately. The used patch still contains some active hormones. Used patches should not be flushed down the toilet. For disposal directions, see HOW SUPPLIED: Special Precautions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

REFERENCES

1. 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.
2. Stadel BV. Oral contraceptives and cardiovascular disease. (Pt.1). N Engl J Med 1981; 305:612-618.
3. Stadel BV. Oral contraceptives and cardiovascular disease. (Pt.2). N Engl J Med 1981; 305:672-677.
4. Adam SA, Thorogood M. Oral contraception and myocardial infarction revisited: the effects of new preparations and prescribing patterns. Br J Obstet Gynaecol 1981; 88:838-845.
5. Mann J, Inman WH. Oral contraceptives and death from myocardial infarction. Br Med J 1975; 2(5965):245-248.
6. Mann J, Vessey MP, Thorogood M, Doll R. Myocardial infarction in young women with special reference to oral contraceptive practice. Br Med J 1975; 2(5956):241-245.
7. Royal College of General Practitioners' Oral Contraception Study: Further analyses of mortality in oral contraceptive users. Lancet 1981; 1:541-546.
8. Slone D, Shapiro S, Kaufman DW, Rosenberg L, Miettinen OS, Stolley PD. Risk of myocardial infarction in relation to current and discontinued use of oral contraceptives. N Engl J Med 1981:305:420-424.
9. Vessey MP. Female hormones and vascular disease-an epidemiological overview. Br J Fam Plann 1980; 6 (Supplement): 1-12.
10. Russell-Briefel RG, Ezzati TM, Fulwood R, Perlman JA, Murphy RS. Cardiovascular risk status and oral contraceptive use, United States, 1976-80. Prevent Med 1986; 15:352-362.

11. Goldbaum GM, Kendrick JS, Hogelin GC, Gentry EM. The relative impact of smoking and oral contraceptive use on women in the United States. JAMA 1987; 258:1339-1342.

12. Layde PM, Beral V. Further analyses of mortality in oral contraceptive users; Royal College of General Practitioners' Oral Contraception Study. (Table 5) Lancet 1981; 1:541-546.

13. Knopp RH. Arteriosclerosis risk: the roles of oral contraceptives and postmenopausal estrogens. J Reprod Med 1986; 31(9) (Supplement):913-921.

14. Krauss RM, Roy S, Mishell DR, Casagrande J, Pike MC. Effects of two low-dose oral contraceptives on serum lipids and lipoproteins: Differential changes in high-density lipoproteins subclasses. Am J Obstet 1983; 145:446-452.

15. Wahl P, Walden C, Knopp R, Hoover J, Wallace R, Heiss G, Rifkind B. Effect of estrogen/progestin potency on lipid/lipoprotein cholesterol. N Engl J Med 1983; 308:862-867.

16. Wynn V, Niththyananthan R. The effect of progestin in combined oral contraceptives on serum lipids with special reference to high density lipoproteins. Am J Obstet Gynecol 1982;142:766-771.

17. Wynn V, Godsland I. Effects of oral contraceptives on carbohydrate metabolism. J Reprod Med 1986;31(9)(Supplement):892-897.

18. LaRosa JC. Atherosclerotic risk factors in cardiovascular disease. J Reprod Med 1986;31(9)(Supplement):906-912.

19. Inman WH, Vessey MP. Investigation of death from pulmonary, coronary, and cerebral thrombosis and embolism in women of child-bearing age. Br Med J 1968;2(5599):193-199.

20. Maguire MG, Tonascia J, Sartwell PE, Stolley PD, Tockman MS. Increased risk of thrombosis due to oral contraceptives: a further report. Am J Epidemiol 1979;110(2):188-195.

21. Petitti DB, Wingerd J, Pellegrin F, Ramacharan S. Risk of vascular disease in women: smoking, oral contraceptives, noncontraceptive estrogens, and other factors. JAMA 1979;242:1150-1154.

22. Vessey MP, Doll R. Investigation of relation between use of oral contraceptives and thromboembolic disease. Br Med J 1968;2(5599):199-205.

23. Vessey MP, Doll R. Investigation of relation between use of oral contraceptives and thromboembolic disease. A further report. Br Med J 1969; 2(5658):651-657.

24. Porter JB, Hunter JR, Danielson DA, Jick H, Stergachis A. Oral contraceptives and non-fatal vascular disease-recent experience. Obstet Gynecol 1982;59(3):299-302.

25. Vessey M, Doll R, Peto R, Johnson B, Wiggins P. A long-term follow-up study of women using different methods of contraception: an interim report. J Biosocial Sci 1976;8:375-427.

26. Royal College of General Practitioners: Oral Contraceptives, venous thrombosis, and varicose veins. J Royal Coll Gen Pract 1978; 28:393-399.

27. Collaborative Group for the Study of Stroke in Young Women: Oral contraception and increased risk of cerebral ischemia or thrombosis. N Engl J Med 1973;288:871-878.

28. Petitti DB, Wingerd J. Use of oral contraceptives, cigarette smoking, and risk of subarachnoid hemorrhage. Lancet 1978;2:234-236.

29. Inman WH. Oral contraceptives and fatal subarachnoid hemorrhage. Br Med J 1979:2(6203):1468-1470.

30. Collaborative Group for the Study of Stroke in Young Women: Oral Contraceptives and stroke in young women: associated risk factors. JAMA 1975; 231:718-722.

31. Inman WH, Vessey MP, Westerholm B, Engelund A. Thromboembolic disease and the steroidal content of oral contraceptives. A report to the Committee on Safety of Drugs. Br Med J 1970;2:203-209.

32. Meade TW, Greenberg G, Thompson SG. Progestogens and cardiovascular reactions associated with oral contraceptives and a comparison of the safety of 50- and 35-mcg oestrogen preparations. Br Med J 1980;280(6224):1157-1161.

33. Kay CR. Progestogens and arterial disease-evidence from the Royal College of General Practitioners' Study. Am J Obstet Gynecol 1982;142:762-765.

34. Royal College of General Practitioners: Incidence of arterial disease among oral contraceptive users. J Royal Coll Gen Pract 1983;33:75-82.

35. Ory HW. Mortality associated with fertility and fertility control: 1983. Family Planning Perspectives 1983;15:50-56.

36. The Cancer and Steroid Hormone Study of the Centers for Disease Control and the National Institute of Child Health and Human Development: Oral contraceptive use and the risk of breast cancer. N Engl J Med 1986;315:405-411.

37. Pike MC, Henderson BE, Krailo MD, Duke A, Roy S. Breast cancer in young women and use of oral contraceptives: possible modifying effect of formulation and age at use. Lancet 1983;2:926-929.

38. Paul C, Skegg DG, Spears GFS, Kaldor JM. Oral contraceptives and breast cancer: A national study. Br Med J 1986; 293:723-725.

39. Miller DR, Rosenberg L, Kaufman DW, Schottenfeld D, Stolley PD, Shapiro S. Breast cancer risk in relation to early oral contraceptive use. Obstet Gynecol 1986;68:863-868.

40. Olson H, Olson KL, Moller TR, Ranstam J, Holm P. Oral contraceptive use and breast cancer in young women in Sweden (letter). Lancet 1985; 2:748-749.

41. McPherson K, Vessey M, Neil A, Doll R, Jones L, Roberts M. Early contraceptive use and breast cancer: Results of another case-control study. Br J Cancer 1987; 56:653-660.

42. Huggins GR, Zucker PF. Oral contraceptives and neoplasia; 1987 update. Fertil Steril 1987; 47:733-761.

43. McPherson K, Drife JO. The pill and breast cancer: why the uncertainty? Br Med J 1986; 293:709-710.

44. Shapiro S. Oral contraceptives-time to take stock. N Engl J Med 1987; 315:450-451.

45. Ory H, Naib Z, Conger SB, Hatcher RA, Tyler CW. Contraceptive choice and prevalence of cervical dysplasia and carcinoma in situ. Am J Obstet Gynecol 1976; 124:573-577.

46. Vessey MP, Lawless M, McPherson K, Yeates D. Neoplasia of the cervix uteri and contraception: a possible adverse effect of the pill. Lancet 1983; 2:930.

47. Brinton LA, Huggins GR, Lehman HF, Malli K, Savitz DA, Trapido E, Rosenthal J, Hoover R. Long term use of oral contraceptives and risk of invasive cervical cancer. Int J Cancer 1986; 38:339-344.

48. WHO Collaborative Study of Neoplasia and Steroid Contraceptives: Invasive cervical cancer and combined oral contraceptives. Br Med J 1985; 290:961-965.

49. Rooks JB, Ory HW, Ishak KG, Strauss LT, Greenspan JR, Hill AP, Tyler CW. Epidemiology of hepatocellular adenoma: the role of oral contraceptive use. JAMA 1979; 242:644-648.

50. Bein NN, Goldsmith HS. Recurrent massive hemorrhage from benign hepatic tumors secondary to oral contraceptives. Br J Surg 1977; 64:433-435.

51. Klatskin G. Hepatic tumors: possible relationship to use of oral contraceptives. Gastroenterology 1977; 73:386-394.

52. Henderson BE, Preston-Martin S, Edmondson HA, Peters RL, Pike MC. Hepatocellular carcinoma and oral contraceptives. Br J Cancer 1983;48:437-440.

53. Neuberger J, Forman D, Doll R, Williams R. Oral contraceptives and hepatocellular carcinoma. Br Med J 1986; 292:1355-1357.

54. Forman D, Vincent TJ, Doll R. Cancer of the liver and oral contraceptives. Br Med J 1986; 292:1357-1361.

55. Harlap S, Eldor J. Births following oral contraceptive failures. Obstet Gynecol 1980; 55:447-452.

56. Savolainen E, Saksela E, Saxen L. Teratogenic hazards of oral contraceptives analyzed in a national malformation register. Am J Obstet Gynecol 1981: 140:521-524.

57. Janerich DT, Piper JM, Glebatis DM. Oral contraceptives and birth defects. Am J Epidemiol 1980; 112:73-79.

58. Ferencz C, Matanoski GM, Wilson PD, Rubin JD, Neill CA, Gutberlet R. Maternal hormone therapy and congenital heart disease. Teratology 1980; 21:225-239.

59. Rothman KJ, Fyler DC, Goldblatt A, Kreidberg MB. Exogenous hormones and other drug exposures of children with congenital heart disease. Am J Epidemiol 1979; 109:433-439.

60. Boston Collaborative Drug Surveillance Program: Oral contraceptives and venous thromboembolic disease, surgically confirmed gallbladder disease, and breast tumors. Lancet 1973; 1:1399-1404.

61. Royal College of General Practitioners: Oral contraceptives and health. New York, Pittman 1974.

62. Layde PM, Vessey MP, Yeates D. Risk of gallbladder disease: a cohort study of young women attending family planning clinics. J Epidemiol Community Health 1982; 36:274-278.

63. Rome Group for Epidemiology and Prevention of Cholelithiasis (GREPCO): Prevalence of gallstone disease in an Italian adult female population. Am J Epidemiol 1984; 119:796-805.

64. Strom BL, Tamragouri RT, Morse ML, Lazar EL, West SL, Stolley PD, Jones JK. Oral contraceptives and other risk factors for gallbladder disease. Clin Pharmacol Ther 1986; 39:335-341.

65. Wynn V, Adams PW, Godsland IF, Melrose J, Niththyananthan R, Oakley NW, Seedj A. Comparison of effects of different combined oral contraceptive formulations on carbohydrate and lipid metabolism. Lancet 1979; 1:1045-1049.

66. Wynn V. Effect of progesterone and progestins on carbohydrate metabolism. In: Progesterone and Progestin. Bardin CW, Milgrom E, Mauvis-Jarvis P. eds. New York, Raven Press 1983; pp. 395-410.

67. Perlman JA, Roussell-Briefel RG, Ezzati TM, Lieberknecht G. Oral glucose tolerance and the potency of oral contraceptive progestogens. J Chronic Dis 1985;38:857-864.

68. Royal College of General Practitioners' Oral Contraception Study: Effect on hypertension and benign breast disease of progestogen component in combined oral contraceptives. Lancet 1977; 1:624.

69. Fisch IR, Frank J. Oral contraceptives and blood pressure. JAMA 1977; 237:2499-2503.

70. Laragh AJ. Oral contraceptive induced hypertension-nine years later. Am J Obstet Gynecol 1976; 126:141-147.

71. Ramcharan S, Peritz E, Pellegrin FA, Williams WT. Incidence of hypertension in the Walnut Creek Contraceptive Drug Study cohort: In: Pharmacology of steroid contraceptive drugs. Garattini S, Berendes HW. Eds. New York, Raven Press, 1977; pp. 277-288, (Monographs of the Mario Negri Institute for Pharmacological Research Milan.)

72. Stockley I. Interactions with oral contraceptives. J Pharm 1976;216:140-143.

73. The Cancer and Steroid Hormone Study of the Centers for Disease Control and the National Institute of Child Health and Human Development: Oral contraceptive use and the risk of ovarian cancer. JAMA 1983; 249:1596-1599.

74. The Cancer and Steroid Hormone Study of the Centers for Disease Control and the National Institute of Child Health and Human Development: Combination oral contraceptive use and the risk of endometrial cancer. JAMA 1987; 257:796-800.

75. Ory HW. Functional ovarian cysts and oral contraceptives: negative association confirmed surgically. JAMA 1974; 228:68-69.

76. Ory HW, Cole P, MacMahon B, Hoover R. Oral contraceptives and reduced risk of benign breast disease. N Engl J Med 1976; 294:419-422.

77. Ory HW. The noncontraceptive health benefits from oral contraceptive use. Fam Plann Perspect 1982; 14:182-184.

78. Ory HW, Forrest JD, Lincoln R. Making choices: Evaluating the health risks and benefits of birth control methods. New York, The Alan Guttmacher Institute, 1983; p.1.

79. Schlesselman J, Stadel BV, Murray P, Lai S. Breast cancer in relation to early use of oral contraceptives. JAMA 1988; 259:1828-1833.

80. Hennekens CH, Speizer FE, Lipnick RJ, Rosner B, Bain C, Belanger C, Stampfer MJ, Willett W, Peto R. A case-control study of oral contraceptive use and breast cancer. JNCI 1984; 72:39-42.

81. LaVecchia C, Decarli A, Fasoli M, Franceschi S, Gentile A, Negri E, Parazzini F, Tognoni G. Oral contraceptives and cancers of the breast and of the female genital tract. Interim results from a case-control study. Br J Cancer 1986; 54:311-317.

82. Meirik O, Lund E, Adami H, Bergstrom R, Christoffersen T, Bergsjo P. Oral contraceptive use and breast cancer in young women. A Joint National Case-control study in Sweden and Norway. Lancet 1986; 11:650-654.

83. Kay CR, Hannaford PC. Breast cancer and the pill-A further report from the Royal College of General Practitioners' oral contraception study. Br J Cancer 1988; 58:675-680.

84. Stadel BV, Lai S, Schlesselman JJ, Murray P. Oral contraceptives and premenopausal breast cancer in nulliparous women. Contraception 1988; 38:287-299.

85. Miller DR, Rosenberg L, Kaufman DW, Stolley P, Warshauer ME, Shapiro S. Breast cancer before age 45 and oral contraceptive use: New Findings. Am J Epidemiol 1989; 129:269-280.

86. The UK National Case-Control Study Group, Oral contraceptive use and breast cancer risk in young women. Lancet 1989; 1:973-982.

87. Schlesselman JJ. Cancer of the breast and reproductive tract in relation to use of oral contraceptives. Contraception 1989; 40:1-38.

88. Vessey MP, McPherson K, Villard-Mackintosh L, Yeates D. Oral contraceptives and breast cancer: latest findings in a large cohort study. Br J Cancer 1989; 59:613-617.

89. Jick SS, Walker AM, Stergachis A, Jick H. Oral contraceptives and breast cancer. Br J Cancer 1989; 59:618-621.

90. Anderson FD, Selectivity and minimal androgenicity of norgestimate in monophasic and triphasic oral contraceptives. Acta Obstet Gynecol Scand 1992; 156 (Supplement):15-21.

91. Chapdelaine A, Desmaris J-L, Derman RJ. Clinical evidence of minimal androgenic activity of norgestimate. Int J Fertil 1989; 34(51):347-352.

92. Phillips A, Demarest K, Hahn DW, Wong F, McGuire JL. Progestational and androgenic receptor binding affinities and in vivo activities of norgestimate and other progestins. Contraception 1989; 41(4):399-409.

93. Phillips A, Hahn DW, Klimek S, McGuire JL. A comparison of the potencies and activities of progestogens used in contraceptives. Contraception 1987; 36(2):181-192.

94. Janaud A, Rouffy J, Upmalis D, Dain M-P. A comparison study of lipid and androgen metabolism with triphasic oral contraceptive formulations containing norgestimate or levonorgestrel Acta Obstet Gynecol Scand 1992; 156 (Supplement):34-38.

95. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. Lancet 1996; 347:1713-1727.

96. Palmer JR, Rosenberg L, Kaufman DW, Warshauer ME, Stolley P, Shapiro S. Oral Contraceptive Use and Liver Cancer. Am J Epidemiol 1989;130:878-882.

97. Lewis M, Spitzer WO, Heinemann LAJ, MacRae KD, Bruppacher R, Thorogood M on behalf of Transnational Research Group on Oral Contraceptives and Health of Young Women. Third generation oral contraceptives and risk of myocardial infarction: an international case-control study. Br Med J, 1996;312:88-90.

98. Vessey MP, Smith MA, Yeates D. Return of fertility after discontinuation of oral contraceptives: influence of age and parity. Brit J Fam Plan; 1986; 11:120-124.

99. Back DJ, Orme M.L'E. Pharmacokinetic drug interactions with oral contraceptives. Clin Pharmacokinet 1990; 18:472-484.

100. Rosenfeld WE, Doose DR, Walker SA, Nayak RK. Effect of topiramate on the pharmacokinetics of an oral contraceptive containing norethindrone and ethinyl estradiol in patients with epilepsy. Epilepsia 1997 Mar;38(3):317-323.

101. Shenfield GM. Oral Contraceptives. Are drug interaction of clinical significance? Drug Saf 1993 Jul;9(1):21-37.

102. Ouellet D, Hsu A, Qian J, Locke CS, Eason CJ, Cavanaugh JH, Leonard JM, Granneman GR. Effect of ritonavir on the pharmacokinetics of ethinyl oestradiol in healthy female volunteers. Br J Clin Pharmacol 1998;46(2):111-116.

103. Improving access to quality care in family planning: Medical eligibility criteria for contraceptive use. Geneva, WHO, Family and Reproductive Health, 1996 (WHO/FRH/FPP/96.9).

104.Skolnick JL, Stoler BS, Katz DG, Anderson WH. Rifampicin, oral contraceptives and pregnancy. J Am Med Assoc 1976;236-1382.

105.Henney JE. Risk of drug interactions with St. John's Wort. JAMA 2000;283(13).

106.Lahteennmaki P et al, Coagulation factors in women using oral contraceptives or intrauterine devices immediately after abortion. American Journal of Obstetrics and Gynecology, (1981); 141: 175-179.

107.Cole JA, Norman H, Doherty M, Walker AM. Venous Thromboembolism, Myocardial Infarction, and Stroke Among Transdermal Contraceptive System Users. Obstetrics & Gynecology 2007; 109(2):339-346.

108.Jick SS, Kaye JA, Russmann S, Jick H. Risk of nonfatal venous thromboembolism in women using a contraceptive transdermal patch and oral contraceptives containing norgestimate and 35 mcg of ethinyl estradiol. Contraception 73 (2006): 223-228.

109.Jick S, Kaye JA, Jick H. Further results on the risk of nonfatal venous thromboembolism in users of the contraceptive transdermal patch compared to users of oral contraceptives containing norgestimate and 35 μg of EE. Contraception 2007;76:4-7.

110.Jick S, Hagberg K, Hernandez R, Kaye J. Postmarketing study of ORTHO EVRA® and levonorgestrel oral contraceptives containing hormonal contraceptives with 30 mcg of ethinyl estradiol in relation to nonfatal venous thromboembolism. Contraception 81 (2010):16-21.

111.Jick S, Hagberg K, Kaye J. ORTHO EVRA® and venous thromboembolism: an update. Letter to the Editor. Contraception 81 (2010):452-453.

112.Chobanian et al. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. Hypertension 2003;42;1206-1252.

113.Dore D, Norman H, Loughlin J, Seeger D. Extended case-control study results on thromboembolic outcomes among transdermal contraceptive users. Contraception 81 (2010):408-413.

114. Cole JA, Norman H, Doherty M, Walker AM. Venous thromboembolism, myocardial infarction, and stroke among transdermal contraceptive system users [published erratum appears in Obstet Gynecol 2008:111:1449].

115. Dore D, Norman H, Seeger, J. Eligibility criteria in venous thromboembolism, myocardial infarction, and stroke among transdermal contraceptive system users. Letter to the Editor. Obstetrics & Gynecology 2009; 114(1):175.

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

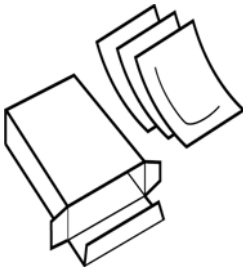
Blood levels of estrogen from this hormonal contraceptive may be increased if you take certain medicines or drink grapefruit juice. Also, your hormonal contraceptive may make some other medicines less effective. As with all prescription products, you should notify your healthcare professional of any 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.

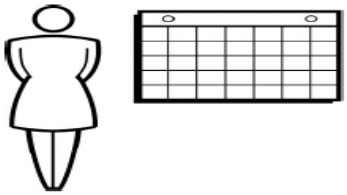
This method uses a 28 day (four week) cycle. You should apply a new patch each week for three weeks (21 total days). You should not apply a patch during the fourth week. Your menstrual period should start during this patch-free week.

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.*

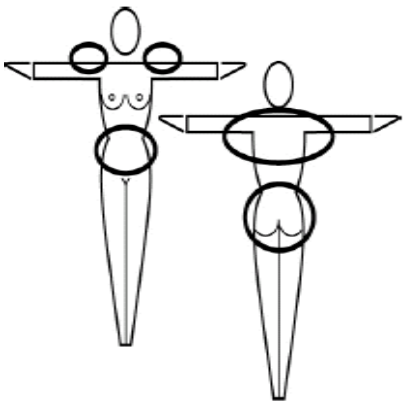
2

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

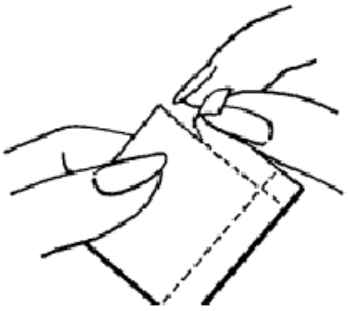
OR

- *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.*

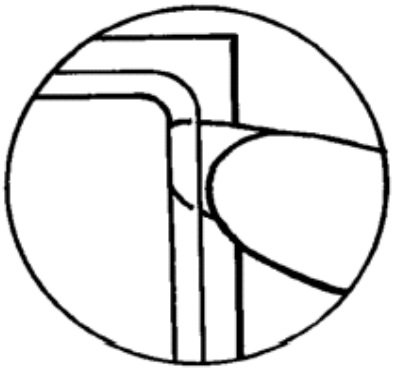


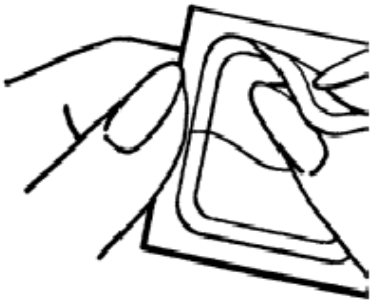
4

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.

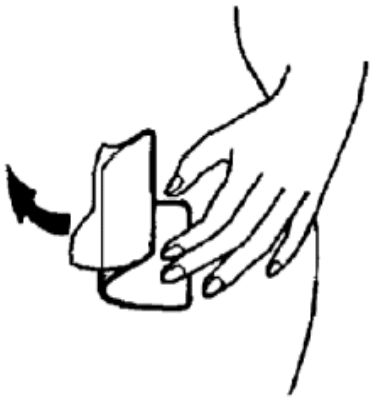




Sometimes patches can stick to the inside of the pouch – be careful not to accidentally remove the clear liner as you remove the patch.

6

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

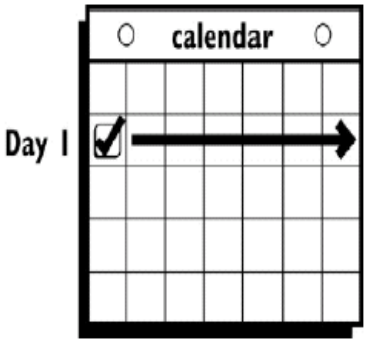


7

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

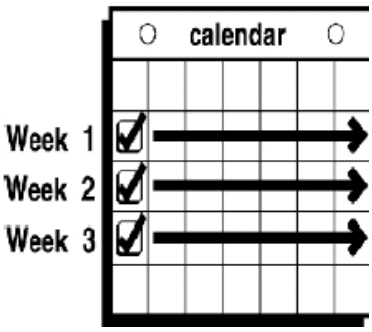
Press firmly on the patch with the palm of your hand for 10 seconds, making sure the edges stick well. Run your finger around the edge of the patch to make sure it is sticking properly.

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



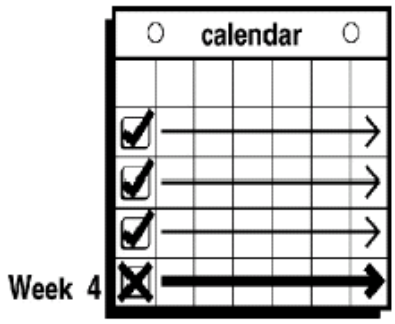
8

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.



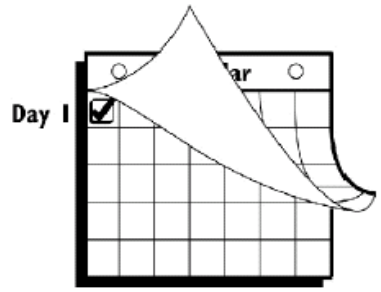
9

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.

(INSERT LOGO)

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

Mfd. by:
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Manati, Puerto Rico 00674

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Appendix E

List of Selected References for Epidemiologic Studies for Ortho Evra

1. Cole JA, Norman H, Doherty M, and Walker AM. 2007. Venous Thromboembolism, Myocardial Infarction, and Stroke among Transdermal Contraceptive System Users. Obstetrics & Gynecology; 109(2): 339-346. Erratum 2008: 111(6):1449.
2. Dore DD, Norman H, Loughlin J, Seeger JD. 2010. Extended case-control study results on thromboembolic outcomes among transdermal contraceptive users. Contraception; 81:408 413.
3. Jick SS, Kaye JA, Russmann S, and Jick H. 2006. Risk of nonfatal venous thromboembolism in women using a contraceptive transdermal patch and oral contraceptives containing norgestimate and 35 μg of ethinyl estradiol. Contraception; 73:223-228.
4. Jick S, Kaye JA, Li L and Jick H. 2007. Further results on the risk of nonfatal venous thromboembolism in users of the contraceptive transdermal patch compared to users of oral contraceptives containing norgestimate and 35 μg of ethinyl estradiol. Contraception; 76:4-7.
5. Jick S, Hagberg, K. 2010. ORTHO-EVRA and venous thromboembolism: an update. Letter to the Editor. Contraception; 81:452-453.
6. Jick SS and Jick H. 2007. The Contraceptive Patch in Relation to Ischemic Stroke and Acute Myocardial Infarction. Brief Reports. Pharmacotherapy; 27:218-220.
7. Jick SS, Hagberg KW, Hernandez R, and Kaye JA. 2010. Postmarketing study of Ortho Evra® and levonorgestrel oral contraceptives containing hormonal contraceptives with 30 mcg of ethinyl estradiol in relation to nonfatal venous thromboembolism. Contraception 81:16-21.