

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 several different oral contraceptives was assessed in five U.S. epidemiologic studies using electronic healthcare claims data. The relative risk estimates ranged from 1.2 to 2.2; one of the studies found a statistically significant increased relative 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.

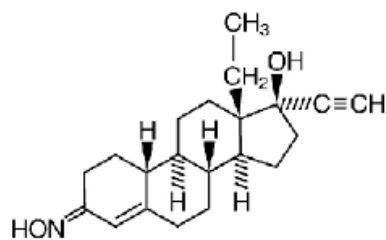
DESCRIPTION

ORTHO EVRA[®] is a combination transdermal contraceptive patch with a contact surface area of 20 cm². It contains 6.00 mg norelgestromin (NGMN) and 0.75 mg ethinyl estradiol (EE). Systemic exposures (as measured by area under the curve [AUC] and steady state concentration [C_{ss}]) of NGMN and EE during use of ORTHO EVRA[®] are higher and peak concentrations (C_{max}) are lower than those produced by an oral contraceptive containing norgestimate 250 mcg / EE 35 mcg. (See BOLDED WARNING; CLINICAL PHARMACOLOGY, Transdermal versus Oral Contraceptives).

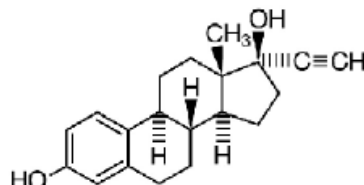
ORTHO EVRA[®] is a thin, matrix-type transdermal contraceptive patch consisting of three layers. The backing layer is composed of a beige flexible film consisting of a low-density pigmented polyethylene outer layer and a polyester inner layer. It provides structural support and protects the middle adhesive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

The outside of the backing layer is heat-stamped “ORTHO EVRA[®].”

The structural formulas of the components are:



norelgestromin



ethinyl estradiol

Molecular weight, norelgestromin: 327.47

Molecular weight, ethinyl estradiol: 296.41

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

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

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. In one of the clinical studies, steady state C_{ss} concentrations across all subjects ranged from 0.305 to 1.53 ng/mL for NGMN and from 23 to 137 pg/mL for EE.

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

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

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

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

Analyte	Parameter	Cycle 1 Week 1	Cycle 3 Week 1	Cycle 3 Week 2	Cycle 3 Week 3
NGMN	C_{ss} (ng/mL)	0.70 (39.4)	0.70 (41.8)	0.80 (28.7)	0.70 (45.3)
	AUC_{0-168}	107 (44.2)	105 (43.2)	132 (43.4)	120 (43.9)
	(ng-h/mL)				
	$t_{1/2}$ (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}	6796 (39.3)	7160 (40.4)	10054 (41.8)	8840 (58.6)
	(pg-h/mL)				
	$t_{1/2}$ (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)

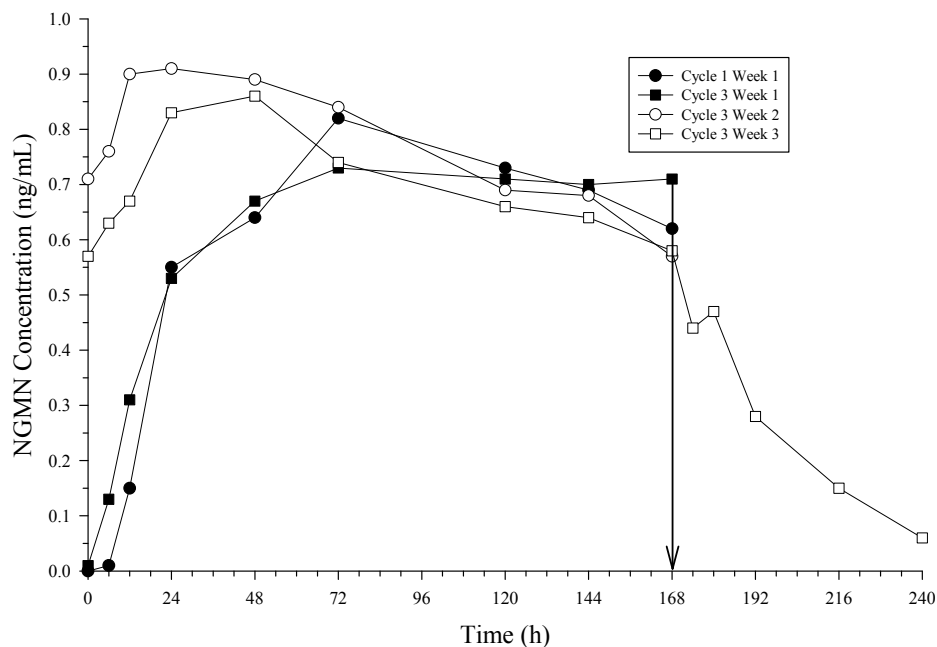
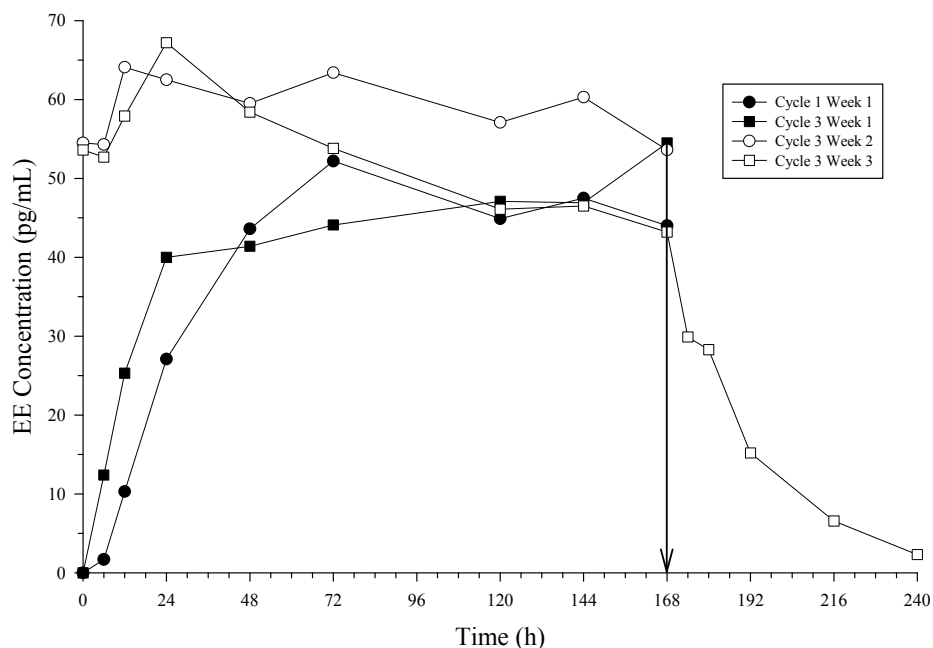


Figure 2: Mean Serum EE Concentrations (pg/mL) in Healthy Female Volunteers Following Application of ORTHO EVRA[®] on the Buttock for Three Consecutive Cycles (Vertical arrow indicates time of patch removal.)



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]

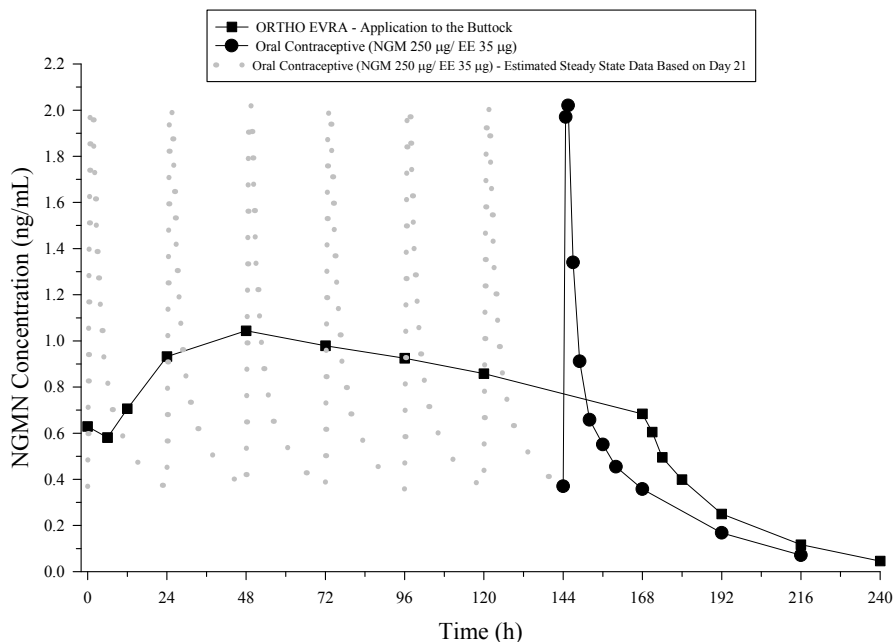


Figure 4: Mean Serum Concentration-Time Profiles of EE Following Once-Daily Administration of an Oral Contraceptive for 2 Cycles or Application of ORTHO EVRA[®] for 2 Cycles to the Buttock in Healthy Female Volunteers. [Oral contraceptive: Cycle 2, Days 15-21, ORTHO EVRA[®]: Cycle 2, Week 3]

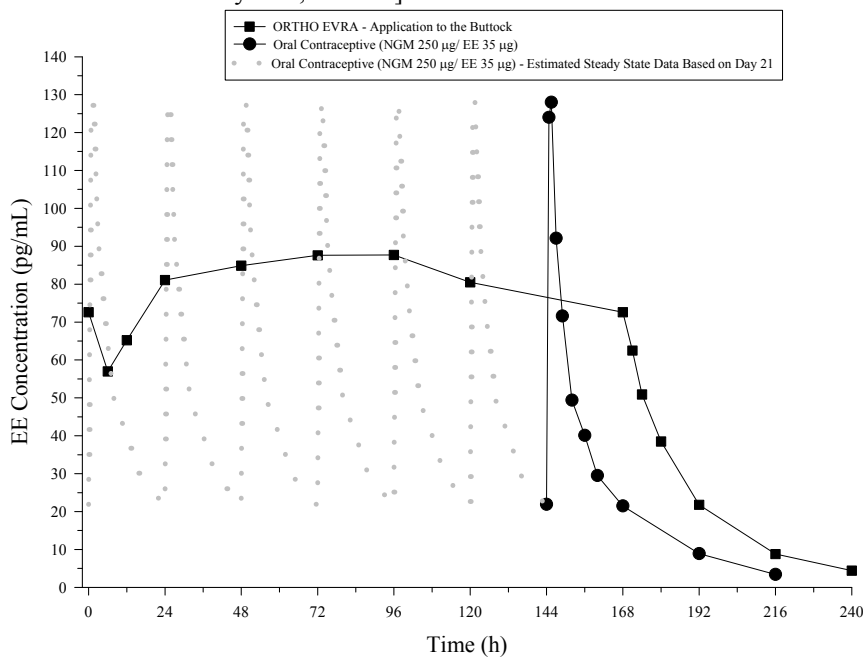


Table 2 provides the mean (%CV) for NGMN and EE pharmacokinetic (PK) parameters.

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 AUC₂₄ 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, AUC₀₋₁₆₈ 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 (VTE)

with ORTHO EVRA[®] compared to some oral contraceptives against the chance of pregnancy if the patient cannot reliably take a contraceptive pill on a daily basis. (See **BOLDED WARNING**; **WARNINGS**; and **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.

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

Hatcher et al, 1998, Ref. # 1.

Emergency Contraceptive Pills:

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

Lactational Amenorrhea Method:

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

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

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

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

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

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

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

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

^p Foams, creams, gels, vaginal suppositories, and vaginal film.

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

^à With spermicidal cream or jelly.

^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 complications¹⁰³
- Persistent blood pressure values of ≥ 160 mm Hg systolic or ≥ 100 mm Hg diastolic^{103, 112}
- Diabetes with vascular involvement¹⁰³
- 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 function¹⁰³
- 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).

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

Five epidemiologic studies^{107-111,113-115,116} are described below. These are 4 case control studies, that compared VTE rates among women using ORTHO EVRA[®] to rates among women using an OC comparator, and an FDA-funded cohort study that estimated and compared VTE rates among women using various hormonal contraceptives, including ORTHO EVRA[®]. All five studies were retrospective studies from U.S. electronic healthcare databases and included women aged 15-44 (10-55 in the FDA-funded study) who used ORTHO EVRA[®] or oral contraceptives containing 20-35 mcg of ethinyl estradiol (EE) and levonorgestrel (LNG), norethindrone, or norgestimate (NGM). NGM is the prodrug for norelgestromin, the progestin in ORTHO EVRA[®].

Some of the data from the epidemiologic studies suggest an increased risk of VTE with use of ORTHO EVRA[®] compared to use of some combined oral contraceptives (see Table 5). The studies used slightly different designs and reported relative risk estimates ranging from 1.2 to 2.2. None of the studies have adjusted for body mass index, smoking, and family history of VTE, which are potential confounders. The interpretations of these relative risk estimates 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 five 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; 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,

using only non-fatal idiopathic cases. VTE cases were not confirmed by chart review.

- BCDSF with LNG-containing oral contraceptives as the comparator, based on the Pharmetrics database, using only non-fatal idiopathic cases. VTE cases were not confirmed by chart review.
- BCDSF with LNG-containing oral contraceptives as the comparator, based on the Marketscan database, using only non-fatal idiopathic cases. VTE cases were not confirmed by chart review.
- FDA-funded study with two groups of comparators [1) LNG-containing oral contraceptives, and 2) oral contraceptives that contain LNG, norethindrone or norgestimate], based on Kaiser Permanente and Medicaid databases. This study used all cases of VTE (idiopathic and non-idiopathic) and included patient chart review to confirm the VTE occurrence.

The i3 Ingenix and BCDSF 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. Risk ratios from the original and various extensions of the i3 Ingenix and BCDSF NGM studies are provided in the footnotes to Table 5. The results of these studies are presented in Figure 5.

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

Epidemiologic Study^A	Comparator Product	Risk Ratios (95% CI)
i3 Ingenix NGM Study in Ingenix Research Datamart ^{107,113,114,115}	NGM/35 mcg EE ^B	2.2^C (1.2-4.0)^D
BCDSP ^E NGM Study in Pharmetrics database ^{108,109,111}	NGM/35 mcg EE	1.2 (0.9-1.8)^F
BCDSP ^E LNG Study in Pharmetrics database ¹¹⁰	LNG ^G /30 mcg EE	2.0 (0.9-4.1)^H
BCDSP ^E LNG Study in Marketscan database ¹¹⁰	LNG/30 mcg EE	1.3 (0.8-2.0)^I
FDA-funded Study in Kaiser Permanente and Medicaid databases ^{J, K, 116}	“All progestins ^L ”/20-35 mcg EE	1.4 (0.9-2.0)
	LNG/ 30 mcg EE	1.2 (0.8-1.9)

^A “New users” – i.e., women with no prior exposure to the drug studied during a pre-specified time period – are considered to be the most informative population to study in pharmacoepidemiologic safety studies. All estimates took account of new-user status. The method and time period used to identify “new users” varied from study to study.

^B NGM = norgestimate; EE = ethinyl estradiol

^C Increase in risk of VTE is statistically significant

^D Pooled risk ratio from references 107 and 113 covering the initial 33-month study plus 24-month extension. [Initial 33 months of data: Risk Ratio (95% CI) = 2.5^C (1.1-5.5); Separate estimate from the 24 months of data on new cases not included in the previous estimate: Risk Ratio (95% CI) = 1.4 (0.5-3.7)]. These risk ratios are based on idiopathic cases (those in women without other known risk factors for VTE). If all VTE cases are considered, the pooled risk ratio and 95% CI are 2.0 (1.2-3.3).

^E BCDSPP = Boston Collaborative Drug Surveillance Program; the risk ratios are based on idiopathic cases.

^F Pooled risk ratio from references 108, 109 and 111 covering the initial 36-month study, plus 17-month and 14-month extensions. [Initial 36 months of data: Risk 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: Risk 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: Risk Ratio (95% CI) = 2.4^C (1.2-5.0)]

^G LNG = levonorgestrel

^H 48 months of data.

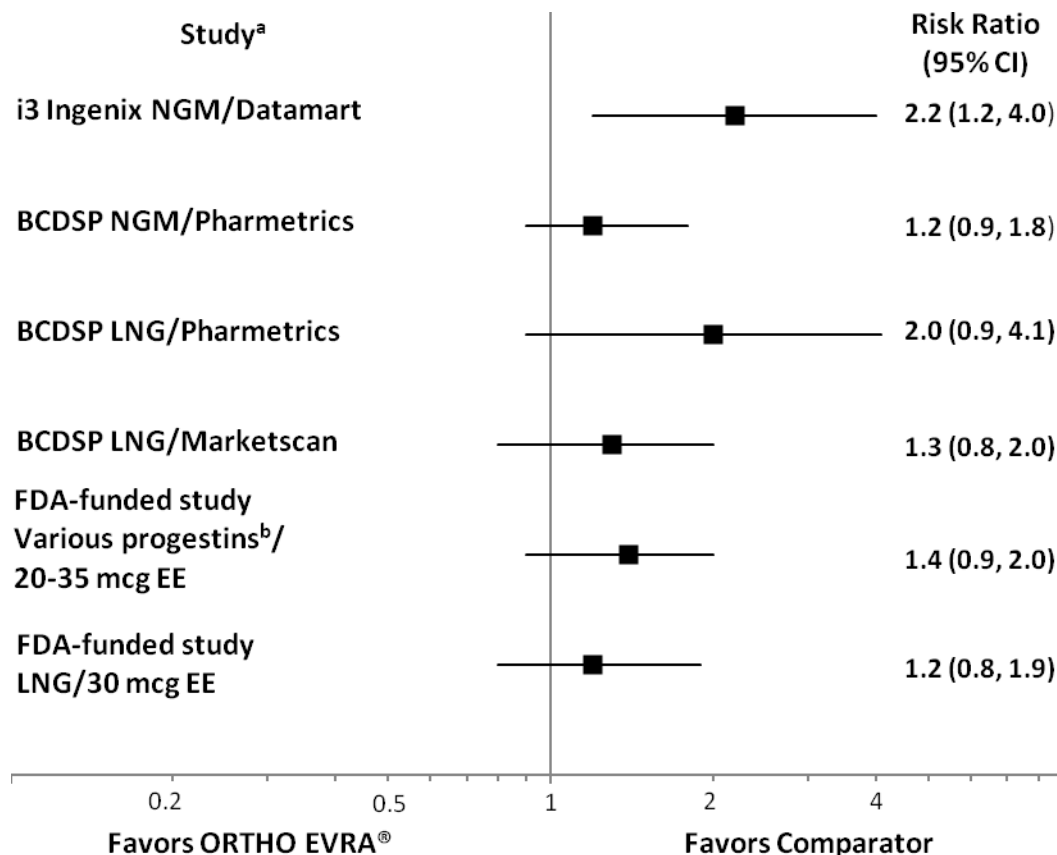
^I 69 months of data.

^J 84 months of data in FDA-funded study

^K Results for “All users,” i.e., initiation and continuing use of study combination hormonal contraception: “All progestins”/20-35 mcg EE, Risk Ratio (95% CI) = 1.6 (1.2-2.1) and LNG/30 mcg EE, Risk Ratio (95% CI) = 1.3 (1.0-1.8).

^L Includes the following progestins: LNG, norethindrone, norgestimate.

Figure 5: VTE Risk of ORTHO EVRA[®] Relative to Combined Oral Contraceptives



^a All estimates took account of new-user status. The method and time period used to identify “new users” varied from study to study.

^b Includes the following progestins: levonorgestrel (LNG), norethindrone, norgestimate (NGM).
BCDSP = Boston Collaborative Drug Surveillance Program
EE = ethinyl estradiol

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.

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 label, the retrospective epidemiologic studies reported are of two types: case control or 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. 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 non-users or users of comparator drug products. 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 combination hormonal contraceptives (CHCs) is well established. Although the absolute VTE rates are increased for users of CHCs compared to non-users, the rates associated with pregnancy are even greater, especially during the post-partum period (see Figure 6).

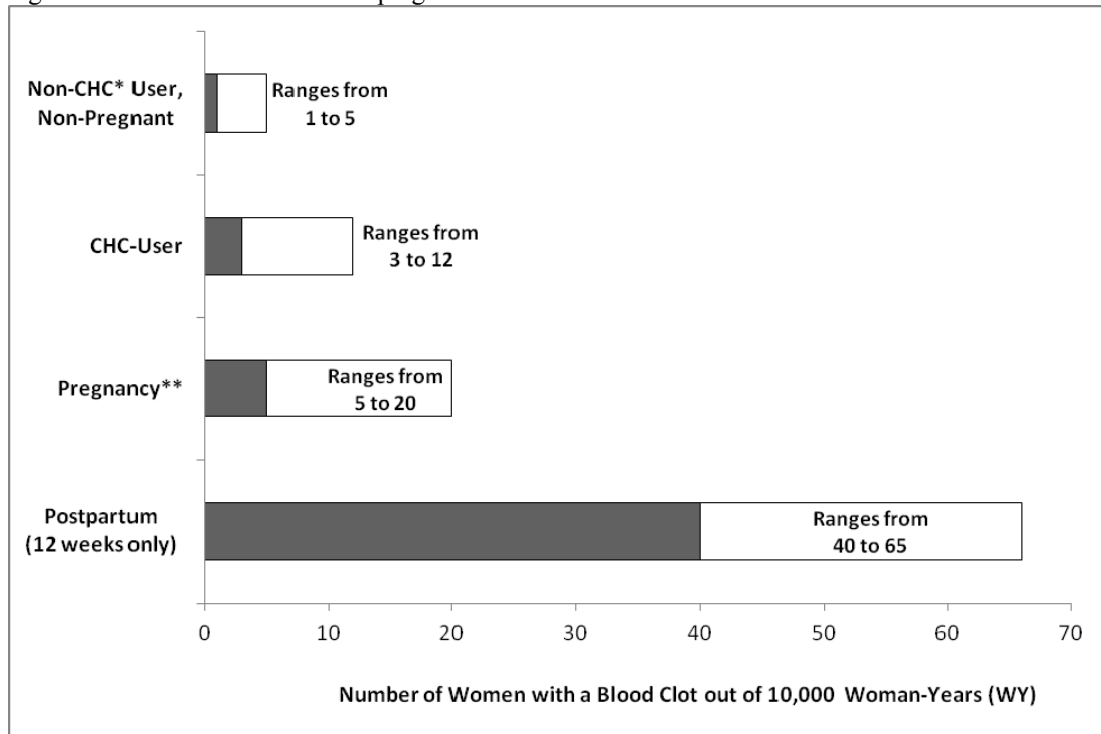
The frequency of VTE in women using CHCs has been estimated to be 3 to 12 cases per 10,000 woman-years.

The risk of VTE is highest during the first year of use of combination hormonal contraception. The risk of thromboembolic disease due to combination hormonal contraceptives gradually disappears after use is discontinued.

Figure 6 shows the risk of developing a VTE for women who are not pregnant and do not use CHCs, for women who use CHCs, for pregnant women, and for women in the post-partum period.

To put the risk of developing a VTE into perspective: If 10,000 women who are not pregnant and do not use CHCs are followed for one year, between 1 and 5 of these women will develop a VTE.

Figure 6: Likelihood of Developing a VTE



*CHC=combination hormonal contraception

**Pregnancy data based on actual duration of pregnancy in the reference studies. Based on a model assumption that pregnancy duration is nine months, the rate is 7 to 27 per 10,000 WY.

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 risk factors, such as smoking, obesity or family history of VTE, is twice that of women without such risk factors.^{9,26}

If feasible, discontinue hormonal contraceptives 1) at least four weeks prior to and for two weeks after major surgery or other surgeries known to have an elevated risk of thromboembolism and 2) during and following prolonged immobilization.

Because 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.

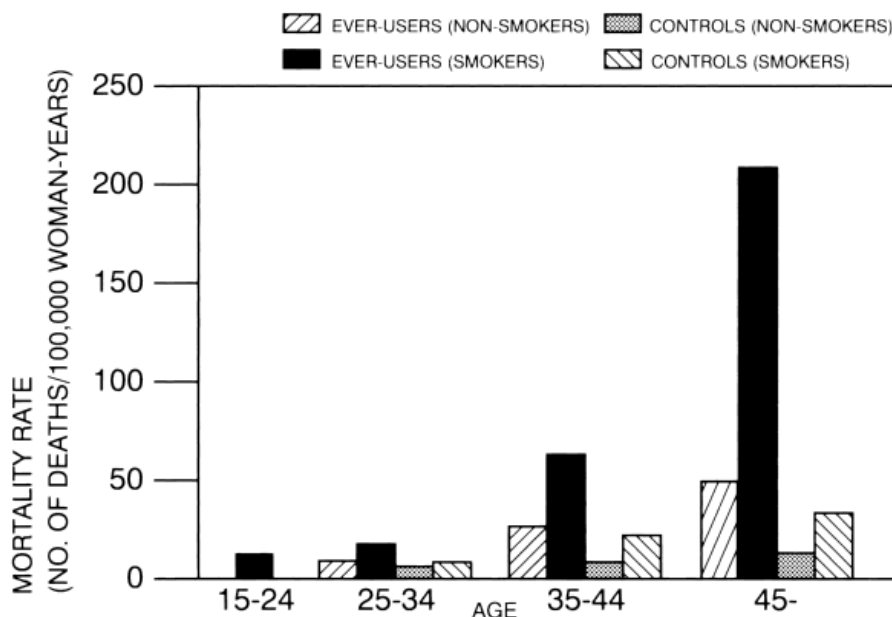
b. Myocardial Infarction

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 six⁴⁻¹⁰ 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 7.)

Figure 7: 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 disease⁷⁰ should be encouraged to use another method of contraception. If these women elect to use ORTHO EVRA[®], they should be monitored closely and if a clinically significant persistent elevation of blood pressure

(BP) occurs (≥ 160 mm Hg systolic or ≥ 100 mm Hg diastolic) and cannot be adequately controlled, ORTHO EVRA[®] should be discontinued. In general, women who develop hypertension during hormonal contraceptive therapy should be switched to a non-hormonal contraceptive. If other contraceptive methods are not suitable, hormonal contraceptive therapy may continue combined with antihypertensive therapy. Regular monitoring of BP throughout hormonal contraceptive therapy is recommended.¹¹² For most women, elevated blood pressure will return to normal after stopping hormonal contraceptives, and there is no difference in the occurrence of hypertension between former and never users.⁶⁸⁻⁷¹

An increase in blood pressure has been reported in women taking hormonal contraceptives⁶⁸ and this increase is more likely in older hormonal contraceptive users⁶⁹ and with extended duration of use.⁶¹ Data from the Royal College of General Practitioners¹² 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 \geq 198 lbs. (90 kg)

Results of clinical trials suggest that ORTHO EVRA[®] may be less effective in women with body weight \geq 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 or diaphragm and spermicide, 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 $\geq 2.5\%$ of ORTHO EVRA[®]-treated subjects in these trials are shown in Table 7.

Table 7. Adverse Drug Reactions Reported by $\geq 2.5\%$ 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 retention¹, malaise
- **Hepatobiliary disorders:** Cholecystitis
- **Investigations:** Blood pressure increased, lipid disorders¹
- **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

¹Represents a bundle of similar terms

Postmarketing Experience

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

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

System Organ Class	Adverse Drug Reactions
Cardiac disorders	Myocardial infarction [†]
Endocrine disorders	Hyperglycemia, insulin resistance
Eye disorders	Contact lens intolerance or complication
Gastrointestinal disorders	Colitis
General disorders and administration site conditions	Application site reaction [†] , edema [†]
Hepatobiliary disorders	Blood cholesterol abnormal, cholelithiasis, cholestasis, hepatic lesion, jaundice cholestatic, low density lipoprotein increased
Immune system disorders	Allergic reaction [†] , urticaria
Investigations	Blood glucose abnormal, blood glucose decreased
Metabolism and nutrition disorders	Increased appetite
Neoplasms benign, malignant and unspecified (Incl cysts and polyps)	Breast cancer [†] , cervix carcinoma, hepatic adenoma, hepatic neoplasm
Nervous system disorders	Dysgeusia, migraine with aura
Psychiatric disorders	Anger, emotional disorder, frustration, irritability

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

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 BOLDDED 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.

HOW TO START USING THE ORTHO EVRA[®] PATCH FOR THE FIRST TIME

The woman has two options for starting the patch and she should choose the option that is right for her:

- **First Day Start**-The woman should apply her first patch during the first 24 hours of her menstrual period.
- **Sunday Start**-The woman should apply her first patch on the first Sunday after her menstrual period begins. With this option, a non-hormonal backup method of birth control, such as a condom or diaphragm and spermicide, is needed for the first 7 days of the first cycle only. If her period starts on a Sunday, the first patch should be applied that day, and no backup contraception is needed.
- **When Switching From the Pill or Vaginal Contraceptive Ring to the Patch**-If the woman is switching from the pill or vaginal contraceptive ring to ORTHO EVRA[®], she should complete her current pill cycle or vaginal ring cycle and apply the first ORTHO EVRA[®] patch on the day she would normally start her next pill or insert her next vaginal ring. If she does not get her period within a week after taking the last active pill or removing the last vaginal ring, she should check with her healthcare professional to be sure that she is not pregnant, but she may go ahead and start ORTHO EVRA[®] for contraception. If the patch is applied more than a week after taking the last

active pill or removal of the last vaginal ring, a non-hormonal contraceptive should be used concurrently for the first 7 days of patch use.

CHOOSING A PLACE ON THE BODY TO PUT THE PATCH






- The patch may be placed on the upper outer arm, abdomen, buttock or back in a place where it won't be rubbed by tight clothing. For example, it should not be placed under the waistband of clothing.
- The patch should not be placed on the breasts, on cut or irritated skin, or on the same location as the previous patch.

Before applying the patch:

- The woman should make sure the skin is clean and dry.
- She should not use lotions, creams, oils, powders, or make-up at the patch site. It may cause the patch to fail to stick properly or to become loose.

HOW TO APPLY THE PATCH

	<ul style="list-style-type: none"> • The woman should tear open the pouch at the top edge. She should peel open the foil pouch that contains the patch and its clear plastic cover. She should gently remove the patch and its plastic cover together from the pouch, being careful not to separate the patch from the clear plastic cover.
	<ul style="list-style-type: none"> • Using a fingernail, the woman should peel away half of the clear plastic. She should avoid touching the sticky surface with her fingers.
	<ul style="list-style-type: none"> • The woman should apply the sticky side of the patch on the skin she has cleaned and dried. She should then remove the other half of the clear plastic and attach the entire patch to her skin.



- The woman should press firmly on the patch with the palm of her hand for 10 seconds, making sure that the whole patch adheres to her skin.
- She should run her fingers over the entire surface area to smooth out any “wrinkles” around the outer edges of the patch.

- The woman should check her patch every day to make sure all edges are sticking correctly.

WHEN TO CHANGE THE ORTHO EVRA[®] PATCH

- The patch works for seven days (one week). The woman applies a new patch on the same day each week (her Patch Change Day) for 3 weeks in a row. She must make sure she has removed her old patch prior to applying the new patch.
- During week 4, she **DOES NOT** wear a patch. She must make sure she removes her old patch. (Her period should begin during this week.)
- Following week 4, she repeats the cycle of three weekly applications followed by a patch-free week.

WHAT IF THE PATCH BECOMES LOOSE OR FALLS OFF?

The patch must stick securely to the skin to work properly. If the ORTHO EVRA[®] patch becomes partially or completely detached and remains detached, insufficient drug delivery occurs. The woman should not try to reapply a patch if it is no longer sticky, if it has become stuck to itself or another surface, or if it has other material stuck to it.

If a patch edge lifts up:

- The woman should press down firmly on the patch with the palm of her hand for 10 seconds, making sure that the whole patch adheres to her skin. She should run her fingers over the entire surface area to smooth out any “wrinkles” around the edges of the patch.
- If her patch does not stick completely, she should remove it and apply a replacement patch.

- She should not tape or wrap the patch to her skin or reapply a patch that is partially adhered to clothing.

If the patch has been off or partially off:

- **For less than 1 Day**, she should try to reapply it. If the patch does not adhere completely, she should apply a new patch immediately. (No backup contraception is needed and her Patch Change Day will stay the same).
- **For more than 1 Day or if she is not sure for how long**, she may not be protected from pregnancy. To reduce this risk, she should apply a new patch and start a new 4-week cycle. She will now have a new Patch Change Day and **MUST USE NON-HORMONAL BACKUP CONTRACEPTION** (such as a condom or diaphragm and spermicide) for the first week of her new cycle.

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 or diaphragm and spermicide, 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 or diaphragm and spermicide, 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 pregnancy 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.

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 or diaphragm and spermicide, for the first seven days. (See Precautions: Nursing Mothers, and Warnings: Thromboembolic and Other Vascular Problems.)

Use After Abortion or Miscarriage¹⁰⁶

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 be 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 50458-192-15); each cycle contains 3 patches.

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

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

Special Precautions for Storage and Disposal

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

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

Do not store in the refrigerator or freezer.

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

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DETAILED PATIENT LABELING

ORTHO EVRA[®] (norelgestromin/ethinyl estradiol transdermal system)

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

DESCRIPTION

The contraceptive patch ORTHO EVRA[®] is a thin, beige, plastic patch that sticks to the skin. The sticky part of the patch contains the following hormones: norelgestromin (progestin) and ethinyl estradiol (estrogen). These hormones are absorbed continuously through the skin and into the bloodstream. On average, the

amount of estrogen delivered through the skin produces estrogen exposure that is higher than the exposure when taking a birth control pill containing 35 micrograms of estrogen. Each patch is sealed in a pouch that protects it until you are ready to wear it.

INTRODUCTION

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

EFFECTIVENESS OF HORMONAL CONTRACEPTIVE METHODS

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

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

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

- Implant: <1%
- Injection: <1%
- IUD: <1-2%
- Diaphragm with spermicides: 20%
- Spermicides alone: 26%
- Female sterilization: <1%
- Male sterilization: <1%
- Cervical Cap with spermicide: 20 to 40%
- Condom alone (male): 14%

Condom alone (female): 21%
Periodic abstinence: 25%
No birth control method: 85%
Withdrawal: 19%

WHO SHOULD NOT USE ORTHO EVRA[®]

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

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

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

- A history of heart attack or stroke
- Blood clots in the legs (thrombophlebitis), lungs (pulmonary embolism), or eyes
- A history of blood clots in the deep veins of your legs
- An inherited problem that makes your blood clot more than normal
- Chest pain (angina pectoris)
- Known or suspected breast cancer or cancer of the lining of the uterus, cervix or vagina
- Unexplained vaginal bleeding (until your doctor reaches a diagnosis)
- Hepatitis or yellowing of the whites of your eyes or of the skin (jaundice) during pregnancy or during previous use of hormonal contraceptives such as ORTHO EVRA[®], NORPLANT[®], or the birth control pill
- Liver tumor (benign or cancerous)
- Known or suspected pregnancy
- Severe high blood pressure
- Diabetes with complications of the kidneys, eyes, nerves, or blood vessels
- Headaches with neurological symptoms

- Use of oral contraceptives (birth control pills)
- Disease of heart valves with complications
- Need for a prolonged period of bed rest following major surgery
- An allergic reaction to any of the components of ORTHO EVRA[®]

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

OTHER CONSIDERATIONS BEFORE USING ORTHO EVRA[®]

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

Like pregnancy, hormonal birth control methods increase the risk of serious blood clots, especially in women who have other risk factors, such as smoking, obesity, or age greater than 35 years. This increased risk is highest when you first start using hormonal birth control. Some studies have reported that women who use ORTHO EVRA[®] have a higher risk of getting a blood clot. **Talk with your healthcare provider about your risk of getting a blood clot before deciding which type of birth control is right for you.**

It is possible to die or be permanently disabled from a problem caused by a blood clot, such as a heart attack or a stroke. Some examples of serious clots are blood clots in the:

- Legs (deep vein thrombosis)
- Lungs (pulmonary embolus)
- Eyes (loss of eyesight)
- Heart (heart attack)
- Brain (stroke)

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

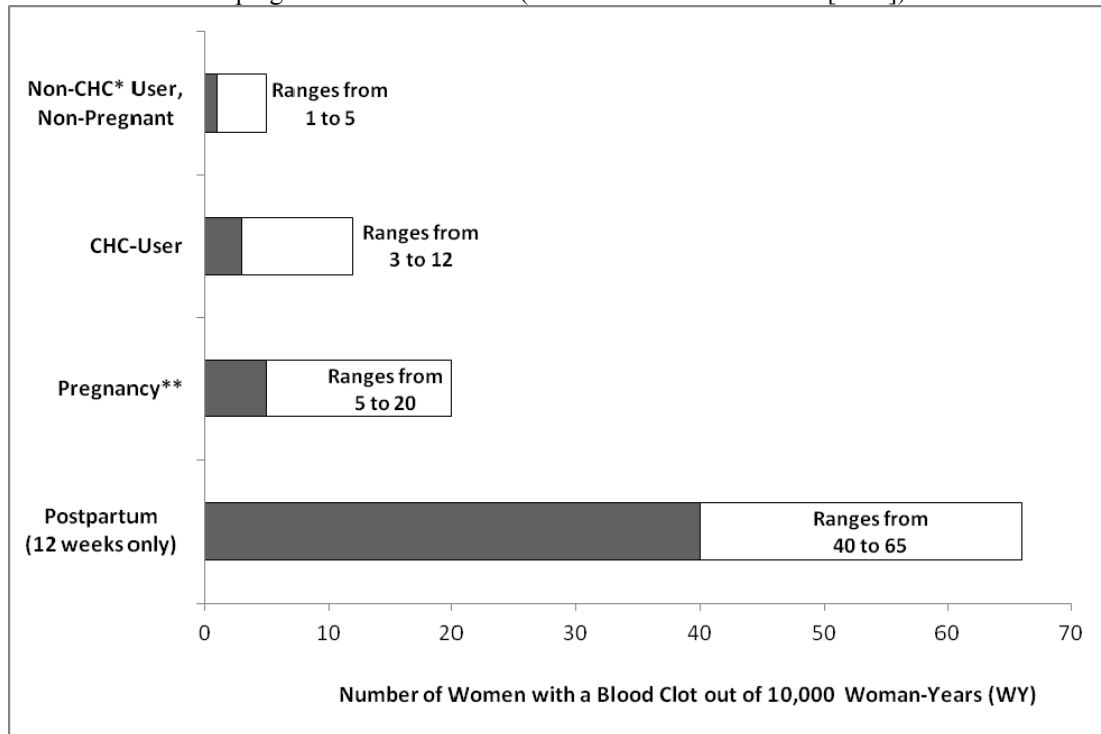
Like pregnancy, hormonal birth control methods increase the risk of serious blood clots, especially in women who have other risk factors, such as smoking, obesity, or age greater than 35 years. This increased risk is highest when you first start using hormonal birth control. Some studies have reported that women who use ORTHO EVRA[®] have a higher risk of getting a blood clot. **Talk with your healthcare provider about your risk of getting a blood clot before deciding which type of birth control is right for you.**

It is possible to die or be permanently disabled from a problem caused by a blood clot, such as a heart attack or a stroke. Some examples of serious clots are blood clots in the:

- Legs (deep vein thrombosis)
- Lungs (pulmonary embolus)
- Eyes (loss of eyesight)
- Heart (heart attack)
- Brain (stroke)

To put the risk of developing a blood clot into perspective: If 10,000 women who are not pregnant and do not use hormonal birth control are followed for one year, between 1 and 5 of these women will develop a blood clot. The figure below shows the likelihood of developing a serious blood clot for women who are not pregnant and do not use hormonal birth control, for women who use hormonal birth control, for pregnant women, and for women in the first 12 weeks after delivering a baby.

Likelihood of Developing a Serious Blood Clot (Venous Thromboembolism [VTE])



*CHC=combination hormonal contraception

**Pregnancy data based on actual duration of pregnancy in the reference studies. Based on a model assumption that pregnancy duration is nine months, the rate is 7 to 27 per 10,000 WY.

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 \geq 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.

HOW TO START USING YOUR ORTHO EVRA[®] PATCH FOR THE FIRST TIME

You have two options for starting the patch. Choose which option is right for you:

- **First Day Start**—Apply your first patch during the first 24 hours of your menstrual period.

- **Sunday Start**—Wait until the first Sunday after your menstrual period begins. With this option, a non-hormonal backup method of birth control, such as a condom or diaphragm and spermicide, is needed for the first 7 days of the first cycle only. If your period starts on a Sunday, the first patch should be applied that day, and no backup contraception is needed.
- **When Switching From the Pill or Vaginal Contraceptive Ring to the Patch**—If you are switching from the pill or vaginal contraceptive ring to ORTHO EVRA[®], complete your current pill cycle or vaginal ring cycle and apply the first ORTHO EVRA[®] patch on the day you would normally start your next pill or insert your next vaginal ring. If you do not get your period within a week after taking the last active pill or removing the last vaginal ring, you may still start the ORTHO EVRA[®] patch. Check with your healthcare professional to be sure that you are not pregnant. If the patch is applied more than a week after taking the last active pill or removal of the last vaginal ring, a non-hormonal method of birth control should be used at the same time as the patch for the first 7 days of patch use.

CHOOSE A PLACE ON YOUR BODY TO PUT THE PATCH







- The patch may be placed on your upper outer arm, abdomen, buttock or back in a place where it won't be rubbed by tight clothing. For example, do not place it under the waistband of clothing.
- Do not put the patch on your breasts, on cut or irritated skin, or on the same location as the previous patch.

Before you apply the patch:

- Make sure your skin is clean and dry.
- Do not use lotions, creams, oils, powders, or make-up at the patch site. It may cause the patch to fail to stick properly or to become loose.

HOW TO APPLY THE PATCH

	<ul style="list-style-type: none"> • Tear open the pouch at the top edge. Peel open the foil pouch that contains the patch and its clear plastic cover. Gently remove the patch and its plastic cover together from the pouch, being careful not to separate the patch from the clear plastic cover.
	<ul style="list-style-type: none"> • Using a fingernail, peel away half of the clear plastic. Avoid touching the sticky surface with your fingers.
	<ul style="list-style-type: none"> • Apply the sticky side of the patch on the skin you have cleaned and dried. Remove the other half of the clear plastic and attach the entire patch to your skin.
	<ul style="list-style-type: none"> • Press firmly on the patch with the palm of your hand for 10 seconds, making sure that the whole patch adheres to your skin. • Run your fingers over the entire surface area to smooth out any “wrinkles” around the outer edges of the patch.

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

Never cut, damage or alter the patch in any way.

WHEN DO I CHANGE MY ORTHO EVRA[®] PATCH?

- The patch works for seven days (one week). Apply a new patch on the same day each week (your Patch Change Day) for 3 weeks in a row. Make sure you have removed your old patch prior to applying the new patch.
- During week 4, **DO NOT** wear a patch. Make sure you removed your old patch. (Your period should begin during this week).
- Following week 4, repeat the cycle of three weekly applications followed by a patch-free week.



WHAT IF MY PATCH BECOMES LOOSE OR FALLS OFF?

The patch must stick securely to your skin to work properly. Do not try to reapply a patch if it is no longer sticky, if it has become stuck to itself or another surface, or if it has other material stuck to it.

If a patch edge lifts up:

- Press down firmly on the patch with the palm of your hand for 10 seconds, making sure that the whole patch adheres to your skin. Run your fingers over the entire surface area to smooth out any “wrinkles” around the edges of the patch.
- If your patch does not stick completely, remove it and apply a replacement patch. (Ask your healthcare professional for a replacement patch prescription so you always have an extra patch available).
- Do not tape or wrap the patch to your skin or reapply a patch that is partially adhered to clothing.

If your patch has been off or partially off:

- **For less than 1 Day**, try to reapply it. If the patch does not adhere completely, apply a new patch immediately. (No backup contraception is needed and your Patch Change Day will stay the same).
- **For more than 1 Day or if you are not sure for how long**, you may become pregnant. To reduce this risk, apply a new patch and start a new 4-week cycle. You will now have a new Patch Change Day and **MUST USE NON-HORMONAL BACKUP CONTRACEPTION** (such as a condom or diaphragm and spermicide) for the first week of your new cycle.

HOW TO PURCHASE A REPLACEMENT PATCH

You can get a replacement patch at the pharmacy where you filled your prescription. You will need a replacement patch prescription from your healthcare professional.

If you have any questions about the extra patch or reimbursement for it, or would like to speak with an ORTHO EVRA[®] Customer Service Representative, please call **1-800-526-7736** or visit us at **www.orthoevra.com**.

WHAT IF I FORGET TO CHANGE MY 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.

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 WITH PATCH USE:**
 - Use a BACK-UP METHOD, such as a condom or diaphragm and spermicide anytime you have sex. Be sure to have one of these non-hormonal birth control methods ready at all times.
 - 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. If you miss TWO PERIODS IN A ROW contact your healthcare professional because you might be pregnant.
7. The amount of drug you get from the ORTHO EVRA[®] patch should not be affected by VOMITING OR DIARRHEA.
8. IF YOU TAKE CERTAIN MEDICINES, ORTHO EVRA[®] may not work as well. Use a non-hormonal back-up method (such as a condom or diaphragm and spermicide) until you check with your healthcare professional.
9. 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.
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. 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.
12. If your patch becomes loose or falls off, single replacement patches are available through your pharmacist. Ask your healthcare professional for a replacement patch prescription so you'll always have an extra patch available if needed. For patch replacement, see "How to Purchase a Replacement Patch."

IF YOU HAVE ANY QUESTIONS OR ARE UNSURE ABOUT THE INFORMATION IN THIS LEAFLET, call your healthcare professional. For further information, you can also log on to www.orthoevra.com or call toll free **1-800-526-7736**.

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.

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Mfd. for:
Janssen Pharmaceuticals, Inc.
Titusville, New Jersey 08560

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

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