

PRODUCT MONOGRAPH

PrEVRA^{®*}

6.0 mg norelgestromin and 0.60 mg ethinyl estradiol

Transdermal System

(Each transdermal system releases approximately 200 µg norelgestromin
and 35 µg ethinyl estradiol per 24 hours)

Hormonal Contraceptive

This Product Monograph is the exclusive property of Janssen Inc.
It may not be copied in whole or in part without the written permission of Janssen Inc.

Janssen Inc.
19 Green Belt Drive
Toronto, Ontario
M3C 1L9

www.janssen.ca

Date of Preparation:
August 8, 2002

Date of Revision:
July 14, 2011

Submission Control No: 147347

* All trademark rights used under license

© 2011 JANSSEN Inc.

Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION.....	3
SUMMARY PRODUCT INFORMATION	3
INDICATIONS AND CLINICAL USE	3
CONTRAINDICATIONS	4
WARNINGS AND PRECAUTIONS.....	5
ADVERSE REACTIONS.....	15
DRUG INTERACTIONS	23
DOSAGE AND ADMINISTRATION	30
OVERDOSAGE	35
ACTION AND CLINICAL PHARMACOLOGY	35
STORAGE AND STABILITY	43
SPECIAL HANDLING INSTRUCTIONS	44
DOSAGE FORMS, COMPOSITION AND PACKAGING	44
PART II: SCIENTIFIC INFORMATION	45
PHARMACEUTICAL INFORMATION.....	45
CLINICAL TRIALS	47
DETAILED PHARMACOLOGY	48
TOXICOLOGY	52
REFERENCES	60
PART III: CONSUMER INFORMATION.....	66

PrEVRA®*

6.0 mg norelgestromin and 0.60 mg ethinyl estradiol

(Each transdermal system releases approximately 200 µg norelgestromin and 35 µg ethinyl estradiol per 24 hours)

Transdermal System

Hormonal Contraceptive

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Transdermal	Each transdermal system contains 6.0 mg norelgestromin (NGMN) and 0.60 mg ethinyl estradiol (EE) and releases approximately 200 µg norelgestromin and 35 µg ethinyl estradiol from the patch every 24 hours	None <i>For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.</i>

INDICATIONS AND CLINICAL USE

The EVRA® (norelgestromin and ethinyl estradiol) transdermal system is indicated for the prevention of pregnancy.

The pharmacokinetic profile for the EVRA® transdermal system is different from that of an oral contraceptive. The clinical relevance of the differences in PK profiles between transdermal and oral delivery is not known. (See **WARNINGS AND PRECAUTIONS – General**, Transdermal versus Oral Contraceptives and **ACTION AND CLINICAL PHARMACOLOGY – Pharmacokinetics**, Transdermal versus Oral Contraceptives.)

CONTRAINDICATIONS

The EVRA[®] (norelgestromin and ethinyl estradiol) transdermal system should not be used in women with:

- a history of or actual thrombophlebitis or thromboembolic disorders;
- known thrombophilic conditions;
- a history of or actual cerebrovascular disorders;
- a history of or actual myocardial infarction or coronary artery disease;
- valvular heart disease with complications;
- active liver disease, or history of or actual benign or malignant liver tumours;
- known or suspected carcinoma of the breast;
- carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia;
- undiagnosed abnormal vaginal bleeding;
- steroid-dependent jaundice, cholestatic jaundice, history of jaundice of pregnancy;
- any ocular lesion arising from ophthalmic vascular disease, such as partial or complete loss of vision, or defect in visual fields;
- known or suspected pregnancy;
- current or history of migraine with focal aura;
- presence of severe or multiple risk factor(s) for arterial or venous thrombosis such as:
 - Persistent blood pressure values of ≥ 160 mm Hg systolic or ≥ 100 mm Hg diastolic¹²
 - hereditary or acquired predisposition for venous or arterial thrombosis, such as Factor V Leiden mutation and activated protein C (APC-) resistance, antithrombin-III-deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinaemia (e.g. due to MTHFR C677T, A1298 mutations), prothrombin mutation G20210A, and antiphospholipid-antibodies (anticardiolipin antibodies, lupus anticoagulant)
 - severe dyslipoproteinemia
 - heavy smoking (>15 cigarettes per day) and over age 35
 - diabetes mellitus with vascular involvement
- major surgery associated with an increased risk of post-operative thromboembolism
- prolonged immobilization
- hypersensitivity to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

The risk of venous thromboembolism (VTE) in users of the ORTHO EVRA[®] patch (the formulation of EVRA[®] marketed in the United States) compared to users of oral contraceptives containing norgestimate and 35µg of EE was assessed in two epidemiological studies with a nested case-control design conducted in women aged 15 to 44 years. One of these studies found an increased risk of VTE for current users of ORTHO EVRA[®] compared to current users of the oral contraceptives [odds ratio 2.46 (95% CI 1.10 – 5.52)]²⁵ The other study did not find an increase in risk of VTE for current users of ORTHO EVRA[®] [odds ratio 0.9 (95% CI 0.5 – 1.6)]³⁰ (see **WARNINGS AND PRECAUTIONS – General, Updated Epidemiologic Data**).

Prescribers are advised to carefully assess a patient's baseline and cumulative risk of thromboembolism before prescribing hormonal contraceptives, including EVRA[®]. Obesity (BMI ≥30 kg/m²) has been identified as a risk factor for venous thromboembolism.^{1,20,64,69} Particular caution should be exercised when prescribing hormonal contraceptives, including EVRA[®], to women who are obese (see **CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS – General, Cardiovascular, Endocrine and Metabolism, Hematologic and ADVERSE REACTIONS**).

Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels. This risk increases with age and becomes significant in hormonal contraceptive users older than 35 years of age. Women should be counselled not to smoke (see **Cardiovascular** section below).

Hormonal contraceptives **DO NOT PROTECT** against sexually transmitted diseases including HIV/AIDS. For protection against STDs, it is advisable to use latex condoms **IN COMBINATION WITH** hormonal contraceptives.

General

The risk of venous thromboembolism (VTE) among women aged 15-44 who used ORTHO EVRA[®] compared to women who used oral contraceptives containing 30-35 µg of ethinyl estradiol (EE) and either norgestimate (NGM) or levonorgestrel (LNG) has been estimated in three case control studies using electronic healthcare claims data derived from users in the USA. These studies (see Table 1.1), which used different study designs, reported odds ratios ranging from 0.9 (indicating no increase in risk) to 2.5 (indicating an approximate doubling of risk). One study (i3 Ingenix) included patient chart review to confirm the VTE occurrence. (see **WARNINGS AND PRECAUTIONS, Serious Warnings and Precautions**).

Table 1.1 Estimates (Odds Ratios) of Venous Thromboembolism Risk in Current Users of ORTHO EVRA[®] compared to Oral Contraceptive Users

Epidemiologic Study	Comparator Product	Odds Ratio (95% C.I.)
i3 Ingenix ^{25,26}	Norgestimate/35 µg Ethinyl Estradiol	2.5* (1.1-5.5) 33 months of data Data Set one ²⁵
		1.4 (0.5-3.7) 24 months of data [€] Data Set two ²⁶
		2.2 (1.2-4.0) Cumulative [¥]
Boston Collaborative Drug Surveillance Program ^{7,29,30} (Norgestimate)	Norgestimate/35 µg Ethinyl Estradiol	0.9 (0.5-1.6) ³⁰ initial 36 months of data 1.1 (0.6-2.1) ²⁹ 17 Month Extension [‡] 2.4* (1.2-5.0) ⁷ 14 Month Extension [‡] 1.2 (0.9-1.8) ⁷ [Pooled odds ratio from 3 datasets above]
Boston Collaborative Drug Surveillance Program ⁶ (Levonorgestrel) Database one	Levonorgestrel/30 µg Ethinyl Estradiol	2.0 (0.9-4.1) 48 Months of data
Boston Collaborative Drug Surveillance Program (Levonorgestrel) Database two ⁸	Levonorgestrel/30 µg Ethinyl Estradiol	1.3 (0.8-2.0) 69 Months of data

* Increase in risk of VTE is statistically significant

‡ New cases not included in the previous estimates

€ Separate estimate from 24 months of data on new cases not included in the previous estimate

¥ Cumulative odds ratio from Data set one and Data set two.

Transdermal versus Oral Contraceptives

Prescribers should be aware of the differences in pharmacokinetic (PK) profiles of transdermal and oral combined hormonal contraceptives and should exercise caution when making a direct comparison between these parameters. In general, transdermal patches are designed to maintain steady delivery of EE and NGMN over a seven-day period while oral contraceptives are administered on a daily basis and produce daily peaks and troughs. Inter-subject variability (%CV) for PK parameters following delivery from the patch is higher relative to the variability determined from the oral contraceptive. The clinical relevance of the differences in PK profiles between transdermal and oral

delivery is not known. (See **ACTION AND CLINICAL PHARMACOLOGY – Pharmacokinetics**, Transdermal versus Oral Contraceptives.)

Sex Hormone Binding Globulin (SHBG)

Published reports have indicated that the mean percent change in concentration of SHBG, a marker of systemic estrogenic activity, is higher following the application of a combined transdermal patch releasing ethinyl estradiol 20 µg and norelgestromin 150 µg per 24 hours than following administration of a daily oral contraceptive. The clinical significance of this finding is not known.^{47, 79}

Discontinue Medication at the Earliest Manifestation of:

- A. Thromboembolic and cardiovascular disorders**, such as thrombophlebitis, pulmonary embolism, cerebrovascular disorders, myocardial ischemia, mesenteric thrombosis and retinal thrombosis;
- B. Conditions that predispose to venous stasis and vascular thrombosis**, such as immobilization after accidents or confinement to bed during long-term illness. Other non-hormonal methods of contraception should be used until regular activities are resumed. For use of hormonal contraceptives when surgery is contemplated, see **Peri-operative Considerations** below;
- C. Visual defects—partial or complete;**
- D. Papilledema or ophthalmic (retinal) vascular lesions;**
- E. Severe headache of unknown etiology or worsening of pre-existing migraine headache.**

Risk of Unintentional Increase in Drug Exposure

(See **Drug-Lifestyle Interactions, PHARMACOKINETICS-Absorption**).

Patients with Fever: Serum estradiol concentrations could theoretically increase in patients with fever. Any clinical consequences due to any increase in temperature are unknown at this time.

External Heat Sources: Due to a theoretical risk of increased exposure to ethinyl estradiol, all patients should be advised to avoid exposing the EVRA[®] application site to direct external heat sources, such as heating pads, electric blankets, heated water beds, heat lamps, hot water bottles, saunas and hot whirlpool spa baths, intensive sunbathing, etc.

The following information is provided from studies of combination oral contraceptives. The use of the EVRA[®] (norelgestromin and ethinyl estradiol) transdermal system is expected to be associated with similar 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 small in healthy women without underlying risk factors. The risk of morbidity and mortality increases significantly if associated with the presence of other risk factors such as hypertension, hyperlipidemias, obesity and diabetes. The excess risk of venous thromboembolism (VTE) is highest during the first year a woman ever uses a combined hormonal contraceptive.

The information contained in this section 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 orally or transdermally remains to be determined.

Carcinogenesis and Mutagenesis

Breast cancer

Increasing age and a strong family history are the most significant risk factors for the development of breast cancer. Other established risk factors include obesity, nulliparity and late age for first full-term pregnancy. The identified groups of women that may be at increased risk of developing breast cancer before menopause are long-term users of hormonal contraceptives (more than eight years) and starters at early age. In a few women, the use of hormonal contraceptives may accelerate the growth of an existing but undiagnosed breast cancer. Since any potential increased risk related to oral contraceptive use is small, there is no reason to change prescribing habits at present.

Women using hormonal contraceptives should be instructed in breast self-examination. Their healthcare providers should be notified whenever any mass is detected. A yearly clinical breast examination is recommended because, if a breast cancer should develop, drugs that contain estrogen may cause a rapid progression.

Hepatocellular carcinoma

Hepatocellular carcinoma may be associated with oral contraceptives. The risk appears to increase with duration of hormonal contraceptive use. However, the attributable risk (the excess incidence) of liver cancers in oral contraceptive users is extremely small. See *Product Monograph Part II: TOXICOLOGY – **Mutagenicity*** and ***Carcinogenicity*** for discussion on animal data.

Cardiovascular

See also **CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS – Boxed Warning, General, Hematologic** and **ADVERSE DRUG REACTIONS**.

In the post-market period there have been cases of myocardial infarction, stroke, deep vein thrombosis and pulmonary embolism associated with use of EVRA[®], with some cases resulting in fatality.

Prescribers are advised to carefully assess a patient's baseline and cumulative risk of thromboembolism and discuss the risk of thromboembolism with all patients before prescribing EVRA[®].

Predisposing Factors for Coronary Artery Disease

Cigarette smoking increases the risk of serious cardiovascular side effects and mortality. Hormonal contraceptives increase this risk, especially with increasing age. Convincing data are available to support an upper age limit of 35 years for hormonal contraceptive use by women who smoke.

Other women who are independently at high risk for cardiovascular disease include those who suffer from hypertension (persistent blood pressure values ≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic)¹², systemic lupus erythematosus^{11,21,42,43,45,78}, an abnormal lipid profile or have a family history of diabetes. Whether hormonal contraceptives accentuate this risk is unclear.

In low-risk, non-smoking women of any age, the benefits of hormonal contraceptive use outweigh the possible cardiovascular risks associated with low-dose formulations. Consequently, hormonal contraceptives may be prescribed for these women up to the age of menopause.

Hypertension

Patients with essential hypertension whose blood pressure is well controlled may be given hormonal contraceptives but only under close supervision. If a significant persistent elevation of blood pressure (≥ 160 mm HG systolic or ≥ 100 mm Hg diastolic) in previously normotensive or hypertensive subjects occurs at any time during the administration of the drug and cannot be adequately controlled, cessation of medication is necessary. 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 anti-hypertensive therapy. Regular monitoring of BP throughout hormonal contraception therapy is recommended¹².

In three clinical trials of EVRA[®] (n = 1530, 819 and 748, respectively), mean changes from baseline in systolic and diastolic blood pressure were less than 1 mm Hg.

Endocrine and Metabolism

Obesity

Obesity (BMI ≥ 30 kg/m²) is generally considered a risk factor for venous thromboembolism.^{1,20,64,69}

There have been a number of post-market cases of thromboembolism reported in overweight (BMI ≥ 25 kg/m²) and obese (BMI ≥ 30 kg/m²) women using EVRA[®]. Particular caution should be exercised when prescribing hormonal contraceptives, including EVRA[®], to women who are obese. (See also **WARNINGS AND PRECAUTIONS-Boxed Warning, Hematologic.**)”

Body Weight ≥ 90 kg

Analyses of Phase III data suggest that the EVRA[®] (norelgestromin and ethinyl estradiol) transdermal system may be less effective in women with body weight ≥ 90 kg (198 lbs.) than in women with lower body weights. Below 90 kg, there was no apparent association

between body weight and pregnancy rate. (See *Product Monograph Part II: CLINICAL TRIALS.*)

Lipid and Other Metabolic Effects

A small proportion of women will have adverse lipid changes while on oral contraceptives. Alternative contraception should be used in women with uncontrolled dyslipidemias. (See also **CONTRAINDICATIONS.**) Elevations of plasma triglycerides may lead to pancreatitis and other complications.

Diabetes

Current low-dose hormonal contraceptives exert minimal impact on glucose metabolism. Diabetic patients, or those with a family history of diabetes, should be observed closely to detect any worsening of carbohydrate metabolism. Patients predisposed to diabetes who can be kept under close supervision may be given hormonal contraceptives. Young diabetic patients whose disease is of recent origin, well controlled and not associated with hypertension or other signs of vascular disease such as ocular fundal changes, should be monitored more frequently while using hormonal contraceptives.

In a 6-cycle clinical trial with EVRA[®], there were no clinically significant changes in fasting blood glucose from baseline to end of treatment.

Genitourinary

Vaginal Bleeding

Persistent irregular vaginal bleeding requires assessment to exclude underlying pathology.

Fibroids

Patients with fibroids (leiomyomata) should be carefully observed. Sudden enlargement, pain or tenderness requires discontinuation of hormonal contraceptive use.

Hematologic

See also **CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS- Boxed Warning, General, Cardiovascular, Peri-operative Considerations and ADVERSE REACTIONS.**

In the clinical trials (n = 3330 subjects with 1704 women years of exposure), two cases of non-fatal pulmonary embolism were reported with use of EVRA[®], one of which was postoperative.

In the post-market period there have been cases of myocardial infarction, stroke, deep vein thrombosis and pulmonary embolism associated with use of EVRA[®], with some cases resulting in fatality.

Prescribers are advised to carefully assess a patient's baseline and cumulative risk of thromboembolism and discuss the risk of thromboembolism with all patients before prescribing EVRA[®].

Post-partum period

There have been post-market cases of thromboembolism reported in women using EVRA[®] up to two months post-partum. Since the immediate postpartum period is 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 breast-feed. If possible, women should be encouraged to use a non-hormonal form of contraception in the three months following delivery. Women who elect to use EVRA[®] in the immediate post-partum period should be carefully monitored for signs and symptoms of thromboembolism.

Post-abortion/post-miscarriage

After an abortion or miscarriage that occurs at or after 20 weeks gestation, hormonal contraceptives may be started either on Day 21 post-abortion or on the first day of the first spontaneous menstruation, whichever comes first. (See **DOSAGE AND ADMINISTRATION.**)

Obesity

Obesity (BMI \geq 30kg/m²) is generally considered a risk factor for venous thromboembolism.^{1,20,64,69}

There have been a number of post-market cases of thromboembolism reported in overweight (BMI \geq 25kg/m²) and obese (BMI \geq 30kg/m²) women using EVRA[®]. Particular caution should be exercised when prescribing hormonal contraceptives, including EVRA[®], to women who are obese (See also **WARNINGS AND PRECAUTIONS-Boxed Warning, Endocrine and Metabolism.**)

Other risk factors for venous thromboembolism (VTE)

Other generalized risk factors for VTE include but are not limited to a personal history of VTE, a family history (the occurrence of VTE in a direct relative at a relatively early age may indicate genetic predisposition), systemic lupus erythematosus and inflammatory bowel disease such as Crohn's disease or ulcerative colitis.^{5,10,17,36,46,67,71} The risk of VTE also increases with age and smoking. The risk of VTE may be temporarily increased with prolonged immobilization, major surgery or trauma. Also, patients with varicose veins and leg cast should be closely supervised.

If a hereditary or acquired predisposition to venous thromboembolism is suspected, the woman should be referred to a specialist for advice before deciding on any hormonal contraception use.

Hepatic/Biliary/Pancreatic

Jaundice

Patients who have had jaundice should be given hormonal contraceptives only with great care and under close observation. Oral contraceptive-related cholestasis has been described in women with a history of pregnancy-related cholestasis. Women with a history of cholestasis may have the condition recur with subsequent hormonal contraceptive use.

The development of severe generalized pruritus or icterus requires that the medication be withdrawn until the problem is resolved.

If a patient develops jaundice that proves to be cholestatic in type, the use of hormonal contraceptives should not be resumed. In patients taking hormonal contraceptives, changes in the composition of the bile may occur and an increased incidence of gallstones has been reported.

Hepatic nodules

Hepatic nodules (adenoma and focal nodular hyperplasia) have been reported, particularly in long-term users of hormonal contraceptives. Although these lesions are extremely rare, they have caused fatal intra-abdominal hemorrhage and should be considered in women with an abdominal mass, acute abdominal pain, or evidence of intra-abdominal bleeding.

Gallbladder disease

Users of oral contraceptives have a greater risk of developing gallbladder disease requiring surgery within the first year of use. The risk may double after four or five years of use.

Neurologic

Migraine and Headache

The onset or exacerbation of migraine or the development of headaches with a new pattern that is recurrent, persistent or severe requires discontinuation of hormonal contraceptives and evaluation of the cause. Women with migraine headache who take hormonal contraceptives may be at increased risk of stroke (see **CONTRAINDICATIONS**).

Epilepsy/seizures

There have been very rare cases of seizure/convulsion reported in patients using EVRA[®] (see **Post-market Adverse Drug Reactions**). Patients with epilepsy or other seizure disorders who are being treated with anticonvulsants should be monitored closely while using hormonal contraceptives. In some patients being treated with anticonvulsants, a method of contraception other than hormonal contraceptives may be recommended. If a woman experiences new onset or exacerbation of seizures while using EVRA[®], the use of EVRA[®] should be re-evaluated.

Ophthalmologic

Ocular Disease

Patients who are pregnant or are taking oral contraceptives may experience corneal edema. This may cause visual disturbances and changes in contact lens tolerance in rigid contact lens users; soft contact lenses do not usually cause disturbances. If visual changes or alterations in lens tolerance occur, temporary or permanent cessation of wear may be advised.

Peri-Operative Considerations

Thromboembolic Complications - Post-surgery

A two- to four-fold increase in relative risk of postoperative thromboembolic complications has been reported with the use of hormonal contraceptives. The relative risk of venous thrombosis in women who have predisposing conditions is twice that of women without such medical conditions.

Hormonal contraceptives should be discontinued and an alternative method substituted at least four weeks prior to elective surgery of a type associated with an increase in risk of thromboembolism and during prolonged immobilization. Hormonal contraceptives should not be resumed until the first menstrual period after hospital discharge following surgery or following prolonged immobilization.

Psychiatric

Emotional Disorders

Patients with a history of emotional disturbances, especially the depressive type, may be more prone to have a recurrence of depression while using hormonal contraceptives. In cases of a serious recurrence, a trial of an alternative method of contraception should be made, which may help to clarify the possible relationship. Women with premenstrual syndrome (PMS) may have a varied response to hormonal contraceptives, ranging from symptomatic improvement to worsening of the condition.

Renal

Fluid Retention

Hormonal contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention.

Sexual Function/Reproduction

Return to Fertility

After discontinuing hormonal contraceptive therapy, the patient should delay pregnancy until at least one normal spontaneous cycle has occurred in order to date the pregnancy. An alternative contraceptive method should be used during this time. There may be some delay in the patient becoming pregnant following discontinuation of the contraceptive patch, particularly if the patient had irregular menstrual cycles before using the contraceptive patch.

Amenorrhea

In the event of amenorrhea, pregnancy should be ruled out.

Women with a history of oligomenorrhea, secondary amenorrhea or irregular cycles may remain anovulatory or become amenorrheic following discontinuation of estrogen-progestin combination therapy.

Amenorrhea, especially if associated with breast secretion, that continues for six months or more after withdrawal warrants a careful assessment of hypothalamic-pituitary function.

Special Populations

Pregnant Women

Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy.

Hormonal contraceptives should not be taken by pregnant women. However, if conception accidentally occurs while hormonal contraceptives are being used, there is no conclusive evidence that the hormones contained in the contraceptive will harm the developing child. The majority of recent studies also do not indicate a teratogenic effect, particularly insofar as cardiac anomalies and limb reduction defects are concerned, when taken inadvertently during early pregnancy.⁵⁹

Nursing Women

In breast-feeding women, the use of hormonal contraceptives results in the hormonal components being excreted in breast milk and may reduce its quantity and quality. If the use of oral contraceptives is initiated after the establishment of lactation, there does not appear to be any effect on the quantity and quality of the milk.

A few adverse effects on the child have been reported, including jaundice and breast enlargement.¹⁷ The nursing mother should be advised not to use combination hormonal contraceptives, but to use other forms of contraception until she has completely weaned her child.

Pediatrics (<18 years of age)

The safety and efficacy of EVRA[®] have not been established in women younger than 18 years of age. Use of this product before menarche is not indicated.

Geriatrics

EVRA[®] is not indicated for use in post-menopausal women.

Renal Impairment

EVRA[®] has not been studied in women with renal impairment. There is a suggestion in the literature that the unbound fraction of ethinyl estradiol is higher.⁵¹ EVRA[®] should be used with supervision in this population.

Hepatic Impairment

EVRA[®] is contraindicated in this population (see **CONTRAINDICATIONS**).

Monitoring and Laboratory Tests

Physical Examination and Follow-up

Before hormonal contraceptives are used, a thorough history and physical examination should be performed, including a blood pressure determination. Breasts, liver, extremities and pelvic organs should be examined. A Papanicolaou smear should be taken if the patient has been sexually active.

The first follow-up visit should be three months after the initiation of hormonal contraceptive therapy. Thereafter, examinations should be performed at least once a

year, or more frequently if indicated. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care. At each visit, examination should include those procedures that were done at the initial visit, as outlined above or as per the recommendations of the Canadian Task Force on the Periodic Health Examination.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Listed below are adverse events that have been associated with the use of combination hormonal contraceptives. These are also likely to apply to combination transdermal hormonal contraceptives such as EVRA[®].

An increased risk of the following serious adverse reactions has been associated with the use of hormonal contraceptives:

- Thrombophlebitis and venous thrombosis with or without embolism
- Arterial thromboembolism
- Pulmonary embolism
- Mesenteric thrombosis
- Myocardial infarction
- Cerebral hemorrhage
- Cerebral thrombosis
- Hypertension
- Gallbladder disease
- Hepatic adenomas or benign liver tumours
- Neuro-ocular lesions (e.g. Retinal thrombosis)
- Congenital anomalies

The following adverse reactions have also been reported in patients receiving hormonal contraceptives:

- Nausea
- Vomiting
- Gastrointestinal symptoms (such as abdominal cramps and bloating)
- Breakthrough bleeding
- Spotting
- Change in menstrual flow
- Amenorrhea during and after treatment
- Temporary infertility after discontinuation of treatment
- Edema
- Chloasma or melasma that may persist
- Breast changes (tenderness, enlargement, secretion)
- Change in weight (increase or decrease)
- Change in cervical erosion and secretion
- Diminution in lactation when given immediately postpartum

- Cholestatic jaundice
- Migraine
- Rash (allergic)
- Depression
- Reduced tolerance to carbohydrates
- Vaginal candidiasis
- Change in corneal curvature (steepening)
- Intolerance to contact lenses
- Administration-site reaction (transdermal, sub-dermal or intramuscular administration only)
- Premenstrual-like syndrome
- Cataracts
- Optic neuritis
- Retinal thrombosis
- Chorea
- Changes in appetite
- Cystitis-like syndrome
- Rhinitis
- Headache
- Nervousness
- Dizziness
- Hirsutism
- Loss of scalp hair
- Erythema multiforme
- Erythema nodosum
- Hemorrhagic eruption
- Vaginitis
- Porphyria
- Impaired renal function
- Hemolytic uremic syndrome
- Raynaud's phenomenon
- Auditory disturbances
- Pancreatitis
- Dysmenorrhea
- Increase in size of uterine leiomyomata
- Endocervical hyperplasia
- Change in libido

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Two adequate and well-controlled trials demonstrated that the incidence of breakthrough bleeding and spotting with EVRA[®] is statistically and clinically comparable to that seen with CYCLEN[®] (norgestimate/ethinyl estradiol) and TRIPHASIL[®] (levonorgestrel/ethinyl estradiol) tablets.

Presented in the following table are the most common treatment-emergent adverse events reported with the use of EVRA[®] in three clinical studies (n=3330), two comparing EVRA[®] to an oral contraceptive, and a third evaluating EVRA[®] alone, occurring in $\geq 1\%$ of subjects. Treatment-emergent adverse events are all adverse events reported in three clinical studies in subjects receiving EVRA[®] regardless of whether they were deemed by the Investigator to be causally related to EVRA[®] use.

Table 1.2 Incidence (% of patients) of Treatment-Emergent Adverse Events in Three Studies

Body System	EVRA[®] (n = 3330) (%)
Gastrointestinal disorders	nausea (17%), abdominal pain (9%), vomiting (5%), diarrhea (4%), dyspepsia (2%), flatulence (2%), gastroenteritis (2%), toothache (1%)
General disorders and administration site conditions	application site reaction (17%), Influenza-like symptoms (7%), fatigue (3%), injury (3%), fever (2%), malaise (1%)
Immune system disorders	allergy (1%)
Infections and infestations	monoliasis (3%), otitis media (1%)
Investigations	weight increase (3%), cervical smear test positive (1%)
Musculo-skeletal and connective tissue disorders	back pain (5%), myalgia (2%), tendon disorder (1%)
Nervous system disorders	headache (21%), dizziness (3%), migraine (3%)
Psychiatric disorders	emotional lability (4%), depression (3%), libido decreased (1%)
Renal and urinary disorders	urinary tract infection (2%), cystitis (1%)

Body System	EVRA [®] (n = 3330) (%)
Reproductive system and breast disorders	breast discomfort, (17%), dysmenorrhea (10%), vaginitis (5%), breast pain female (4%), intermenstrual bleeding (3%), menorrhagia (3%), breast engorgement (2%), breast enlargement (2%), leukorrhea (2%), breast fibroadenosis (1%), menstrual disorder (1%)
Respiratory, thoracic and mediastinal disorders	upper respiratory tract infection (10%), pharyngitis (5%), sinusitis (5%), bronchitis (2%), coughing (1%), rhinitis (1%)
Skin and subcutaneous tissue disorders	pruritus (4%), acne (3%), rash (2%), pruritus genital (1%)

Less common Clinical Trial Treatment-Emergent Adverse Events occurring in <1% of Subjects

Blood and lymphatic system disorders: anemia, granulocytopenia, leucopenia, leukocytosis, lymphadenopathy, monocytosis, platelets abnormal, thrombocytopenia

Cardiac disorders: angina pectoris, bradycardia, edema dependent, hypertension, hypotension, palpitation, tachycardia

Ear and labyrinth disorders: ear disorder nos, earache, tinnitus, vestibular disorder

Endocrine disorders: goitre, hyperprolactinaemia, hypothyroidism

Eye disorders: conjunctival discolouration, conjunctivitis, corneal ulceration, exophthalmos, eye abnormality, eye pain, eyelid retraction, myopia, retinal detachment, vision abnormal, xerophthalmia

Gastrointestinal disorders: abdomen enlarged, colitis, constipation, enanthema, enteritis, gastritis, gastro-intestinal disorder nos, gastroesophageal reflux, gingival bleeding, gingivitis, glossitis, hemorrhoids, mouth dry, periodontal destruction, rectal disorder, saliva increased, stomatitis ulcerative, taste perversion, tenesmus, tooth caries, tooth disorder

General disorders and administration site conditions: asthenia, chest pain, application site cellulitis, face edema, hot flushes, edema, edema generalized, edema peripheral, pain, rigors, syncope, thirst, tolerance decreased

Hepatobiliary disorders: cholecystitis, cholelithiasis, hepatic function abnormal

Immune system disorders: allergic reaction, vasculitis allergic

Infections and infestations: abscess, herpes simplex, herpes zoster, infection, infection bacterial, infection fungal, infection viral

Investigations: globulins increased, SGOT increased, SGPT increased, weight decrease

Metabolism and nutrition disorders: alcohol intolerance, anorexia, appetite increase, dehydration, diabetes mellitus, fat disorder, hypercholesterolemia, hyperglycemia, hypertriglyceridemia, hypoglycaemia, oedema legs, obesity

Musculoskeletal and connective tissue disorders: arthralgia, arthritis, arthrosis, bursitis, cramps legs, leg pain, muscle weakness, myositis, osteoma, skeletal pain, tendonitis, torticollis

Neoplasms benign, malignant and unspecified: breast neoplasm benign female, cervical uterine polyp, cervix carcinoma in situ, lipoma, melanoma malignant, neoplasm nos, neuroma, ovarian cyst, phaeochromocytoma, skin neoplasm malignant, thyroid cyst, uterine fibroid

Nervous System disorders: convulsions, coordination abnormal, dysphonia, hemiplegia, hypertonia, hypoesthesia, hypotonia, meningitis, migraine aggravated, neuralgia, paraesthesia, stupor, tremor, vertigo

Psychiatric disorders: amnesia, anxiety, apathy, crying abnormal, depersonalization, depression aggravated, dyspareunia, insomnia, libido increased, nervousness, paroniria, psychosis manic-depressive, sleep disorder, somnolence, suicide attempt

Renal and urinary disorders: dysuria, micturition frequency, pyelonephritis, renal calculus, renal pain, strangury, urethral disorder, urinary incontinence, urine abnormal

Reproductive system and breast disorders: breast atrophy, cervical dysplasia, cervicitis, cervix lesion, endometriosis, genital ulceration, lactation nonpuerperal, mastitis, ovarian disorder, pelvic inflammation, perineal pain female, uterine disorder nos, uterine spasm, vaginal hemorrhage, vulva disorder, withdrawal bleeding

Respiratory, thoracic and mediastinal disorders: asthma, bronchospasm, dyspnoea, laryngitis, pleurisy, pneumonia, stridor

Skin and subcutaneous tissue disorders: alopecia, bullous eruption, chloasma, dermatitis, dermatitis contact, eczema, folliculitis, furunculosis, hypertrichosis, melanosis, nail disorder, paronychia, photosensitivity allergic reaction, photosensitivity reaction, pigmentation abnormal, psoriasis, purpura, rash erythematous, rash maculopapular, seborrhoea, skin cold clammy, skin depigmentation, skin discolouration, skin disorder, skin dry, sweat gland disorder, sweating increased, urticaria, vasculitis allergic, verruca

Social Circumstance: drug abuse

Vascular disorders: aneurysm, epistaxis, flushing, hematoma, peripheral ischaemia, phlebitis, pulmonary embolism, purpura allergic, thrombophlebitis, thrombophlebitis superficial, vascular disorder, thrombosis arterial leg, vasculitis, vein disorder, vein distended, vein pain, vein varicose

Post-Market Adverse Drug Reactions

In addition to the adverse events observed in clinical trials listed above, the following other serious and unexpected adverse events have been reported in users of EVRA[®] in the post-marketing period. These adverse events are compiled from spontaneous reports and

are listed regardless of frequency and whether or not a causal relationship with EVRA[®] has been established:

Blood and lymphatic system disorders: hemolytic uremic syndrome, idiopathic thrombocytopenic purpura, iron deficiency anemia

Cardiac disorders: acute coronary syndrome, arrhythmia, atrial tachycardia, cardiac failure, coronary artery atherosclerosis, coronary artery dissection (with fatal outcome), intracardiac thrombus, myocardial infarction, myocarditis (with fatal outcome), pericardial effusion, sinus tachycardia, supraventricular tachycardia

Congenital, familial and genetic disorders: atrial septal defect, cleft lip, cleft palate, congenital musculoskeletal anomaly, dermoid cyst of ovary, Fallot's tetralogy, limb malformation, skull malformation, ventricular septal defect

Ear and labyrinth disorders: motion sickness, otosclerosis

Endocrine disorders: thyroid disorder

Eye disorders: amaurosis fugax, blindness, blindness transient, blindness unilateral, cataract, contact lens intolerance, corneal neovascularisation, diplopia, dry eye, eye disorder, eye irritation, eye haemorrhage, eye swelling, iritis, mydriasis, ocular discomfort, ocular hyperaemia, ocular icterus, optic nerve disorder, papilloedema, photophobia, retinal vascular thrombosis, vision blurred, visual acuity reduced, visual disturbance

Gastrointestinal disorders: abdominal discomfort, abdominal distension, ascites, colitis ulcerative, edema mouth, gastric disorder gastrointestinal edema, gastrointestinal hemorrhage, gastrointestinal pain, gastroesophageal reflux disease, hypoaesthesia oral, intestinal ischemia, intestinal obstruction, irritable bowel syndrome, oral mucosal blistering, pancreatic disorder, pancreatitis, rectal hemorrhage, stomach discomfort, umbilical hernia

General disorders and administration site conditions: abasia, application site burn, application site dermatitis, application site discolouration, application site erythema, application site irritation, application site pain, application site photosensitivity reaction, application site pruritus, application site swelling, application site urticaria, chest discomfort, chills, cyst rupture, death, difficulty in walking, disease progression, drug ineffective, drug interaction, drug withdrawal syndrome, dysplasia, feeling abnormal, feeling cold, feeling hot and cold, feeling jittery, feeling of body temperature change, gait disturbance, hernia, hunger, irritability, local swelling, swelling, temperature intolerance, therapeutic response delayed

Hepatobiliary disorders: cholestasis, gallbladder disorder, hepatic cirrhosis, hepatic failure, hepatic pain, hepatitis, hepatocellular damage, hepatomegaly, jaundice, liver disorder, portal vein thrombosis

Immune system disorders: anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, autoimmune disorder, food allergy, hypersensitivity, sarcoidosis

Infections and infestations: alpha haemolytic streptococcal infection, appendicitis, breast abscess, cavernous sinus thrombosis, cellulitis, ear infection, encephalitis viral (with fatal outcome), Escherichia urinary tract infection, gastroenteritis viral, gastrointestinal infection, infectious mononucleosis, influenza, joint abscess, nasopharyngitis, osteomyelitis, pelvic inflammatory disease, pneumonia, respiratory tract infection, septic embolus, septic shock, skin infection, staphylococcal infection, streptococcal infection, tonsillitis, vaginal candidiasis, vaginal infection, vaginitis bacterial, vulvovaginal mycotic infection

Injury, poisoning and procedural complications: brachial plexus injury, closed head injury, collapse of lung, concussion, contusion, drug administration error, drug exposure during pregnancy, drug exposure via breast milk, fall, inappropriate schedule of drug administration, incision site complication, intentional misuse, joint sprain, limb injury, medication error, overdose, road traffic accident, stress fracture, wrist fracture

Investigations: alanine aminotransferase increased, anti-thyroid antibody positive, aspartate aminotransferase increased, blood cholesterol increased, blood creatine phosphokinase increased, blood glucose increased, blood lactate dehydrogenase increased, blood pressure increased, blood test abnormal, blood triglycerides increased, cardiac enzymes increased, electrocardiogram abnormal, electrocardiogram T wave abnormal, fetal heart rate decreased, hemoglobin abnormal, haemoglobin decreased, heart rate decreased, heart rate increased, heart rate irregular, hepatic enzyme increased, intraocular pressure increased, liver function test abnormal, red blood cell sedimentation rate increased, smear cervix abnormal, thyroid function test abnormal

Metabolism and nutrition disorders: anorexia, decreased appetite, diabetes mellitus non-insulin-dependent, fluid retention, food intolerance, gestational diabetes, hypokalemia, increased appetite, iron deficiency

Musculoskeletal and connective tissue disorders: bone pain, flank pain, groin pain, joint effusion, joint swelling, muscle spasms, muscle tightness, muscle twitching, pain in extremity, rhabdomyolysis, rotator cuff syndrome, sensation of heaviness, shoulder pain

Neoplasms benign, malignant and unspecified: benign hydatidiform mole, brain neoplasm, cervix carcinoma, colon cancer Stage II, colon neoplasm, fibroadenoma of breast, fibromatosis, focal nodular hyperplasia, gastrointestinal carcinoma, hepatic neoplasm, neoplasm malignant, ovarian cancer, peritoneal neoplasm, renal neoplasm, teratoma benign, thyroid gland cancer

Nervous system disorders: amnesia, basilar artery thrombosis, benign intracranial hypertension, burning sensation, carotid artery stenosis, cerebral artery occlusion, cerebral hemorrhage, cerebral infarction, cerebral thrombosis, cerebral venous thrombosis (with fatal outcome), cerebrovascular accident (with fatal outcome), coma, depressed level of consciousness, dysarthria, dysgeusia, dyskinesia, encephalitis, facial

palsy, facial paresis, formication, grand mal convulsion, hemiparesis, hemorrhagic stroke, intracranial aneurysm, intracranial venous sinus thrombosis, ischemic stroke, lethargy, loss of consciousness, mental impairment, migraine with aura, monoparesis, multiple sclerosis, multiple sclerosis relapse, nervous system disorder, optic neuritis, petit mal epilepsy, polyneuropathy, sinus headache, somnolence, speech disorder, subarachnoid haemorrhage, superior sagittal sinus thrombosis, syncope, thrombotic stroke, transient ischemic attack, transverse sinus thrombosis, tunnel vision, visual field defect

Pregnancy, puerperium and perinatal conditions: abnormal product of conception, abortion, abortion incomplete, abortion missed, abortion spontaneous, abortion threatened, antepartum hemorrhage, blighted ovum, ectopic pregnancy, fetal disorder, fetal growth retardation, intra-uterine death, oligohydramnios, placenta previa, placental insufficiency, postpartum haemorrhage, preeclampsia, pregnancy, pregnancy-induced hypertension, premature labour, premature separation of placenta, ruptured ectopic pregnancy, twin pregnancy, unintended pregnancy

Psychiatric disorders: abnormal behaviour, acute psychosis, affect lability, aggression, anger, attention deficit/hyperactivity disorder, bipolar disorder, completed suicide, confusional state, decreased interest, depressed mood, expressive language disorder, hallucination (auditory, visual), homicidal ideation, mood altered, mood swings, nightmare, panic attack, personality change, stress, suicidal ideation

Renal and urinary disorders: chromaturia, renal disorder, renal failure, renal failure acute, urethral cyst

Reproductive system and breast disorders: adenomyosis, amenorrhea, breast discharge, breast disorder, breast dysplasia, breast mass, breast swelling, breast tenderness, galactorrhea, genital discharge, genital rash, hypertrophy breast, hypomenorrhea, infertility, menometrorrhagia, oligomenorrhea, ovulation pain, pelvic discomfort, pelvic pain, polymenorrhea, premenstrual syndrome, reproductive tract disorder, uterine cyst, uterine hemorrhage, vaginal disorder, vaginal lesion, withdrawal bleeding irregular

Respiratory, thoracic and mediastinal disorders: acute respiratory distress syndrome, dyspnea, lung consolidation, neonatal respiratory distress syndrome, pharyngeal edema, pharyngolaryngeal pain, pharynx discomfort, pulmonary alveolar hemorrhage (with fatal outcome), pulmonary congestion, pulmonary edema (with fatal outcome), pulmonary alveolar hemorrhage, pulmonary congestion, pulmonary embolism (with fatal outcome), pulmonary hypertension, pulmonary infarction, pulmonary thrombosis, respiratory disorder, respiratory failure, sinus disorder, sleep apnea syndrome, tonsillar disorder

Skin and subcutaneous tissue disorders: angioneurotic edema, dermatitis allergic, erythema nodosum, hyperhidrosis, night sweats, pigmentation disorder, pruritus generalized, pyoderma gangrenosum, rash generalized, rash papular, rash pruritic, seborrheic dermatitis, skin irritation, skin reaction, swelling face, urticaria generalized, yellow skin

Surgical and medical procedures: abortion induced, appendectomy, dental operation, foot operation, gallbladder operation, hospitalization, hysterectomy, lipectomy, plastic surgery, renal stone removal, salpingo-oophorectomy, surgery, sympathectomy

Vascular disorders: angiopathy, arterial thrombosis, cavernous sinus thrombosis, circulatory collapse, deep vein thrombosis (with fatal outcome), diastolic hypertension, embolism, hemorrhage, iliac artery thrombosis, jugular vein thrombosis, malignant hypertension, orthostatic hypotension, pallor, Raynaud's phenomenon, thrombosis (with fatal outcome), vasculitis necrotizing (with fatal outcome), venous thrombosis, venous thrombosis limb

DRUG INTERACTIONS

Overview

The concurrent administration of oral contraceptives with other drugs may result in an altered response to either agent (Tables 1.3 and 1.4). Similar drug interactions are likely with the transdermal system. It is important to ascertain all drugs that a patient is taking, both prescription and non-prescription, before hormonal contraceptives are prescribed.

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, she should be counselled 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
 - griseofulvin
 - modafinil
 - 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[®] (the formulation of EVRA[®] marketed in the United States) did not significantly affect the pharmacokinetics of norelgestromin or EE.

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 and fluconazole)
- grapefruit juice
- HMG-CoA reductase inhibitors (including atorvastatin and rosuvastatin)

Changes in Plasma Levels of Co-administered Drugs:

Data from the literature concerning 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 increase (due to CYP inhibition) include:

- cyclosporine
- omeprazole
- prednisolone
- theophylline
- voriconazole

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

- acetaminophen
- lamotrigine
- morphine
- salicylic acid
- temazepam

Physicians are advised to consult the labelling of concurrently-used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.

Refer to *Oral Contraceptives 1994* (Chapter 8), Health Canada, for possible drug interactions with hormonal contraceptives.

Table 1.3: Drugs that May Decrease the Efficacy of Oral Contraceptives

Class of Compound	Drug	Proposed Mechanism	Suggested Management
Anticonvulsants	Carbamazepine Oxcarbazepine Ethosuximide Lamotrigine Phenobarbital Phenytoin Primidone Topiramate	Induction of hepatic microsomal enzymes. Rapid metabolism of estrogen and increased binding of progestin and ethinyl estradiol to SHBG.	Use higher dose OCs (50 µg ethinyl estradiol), another drug or another method.
Antibiotics	Ampicillin Cotrimoxazole Penicillin	Enterohepatic circulation disturbance, intestinal hurry.	For short course, use additional method or use another drug. For long course, use another method.
	Rifampin	Increased metabolism of progestins. Suspected acceleration of estrogen metabolism.	Use another method.
	Chloramphenicol Metronidazole Neomycin Nitrofurantoin Sulfonamides Tetracyclines	Induction of hepatic microsomal enzymes. Also disturbance of enterohepatic circulation.	For short course, use additional method or use another drug. For long course, use another method.
	Troleandomycin	May retard metabolism of OCs, increasing the risk of cholestatic jaundice.	
Antifungals	Griseofulvin	Stimulation of hepatic metabolism of contraceptive steroids may occur.	Use another method.
Sedatives and Hypnotics	Benzodiazepines Barbiturates Chloral Hydrate Glutethimide Meprobamate	Induction of hepatic microsomal enzymes.	For short course, use additional method or another drug. For long course, use another method or higher-dose OCs.
Antacids		Decreased intestinal absorption of progestins.	Dose two hours apart.
Other Drugs	Phenylbutazone Antihistamines Analgesics Antimigraine Preparations Vitamin E Modafinil	Reduced OC efficacy has been reported. Remains to be confirmed.	
	Bosentan	Induction of hepatic microsomal enzymes	Consider switching to a non-hormonal contraceptive method or adding a barrier method to oral contraceptive therapy.

Table 1.4: Modification of Other Drug Action by Oral Contraceptives

Class of Compound	Drug	Modification of Drug Action	Suggested Management
Alcohol		Possible increased levels of ethanol or acetaldehyde.	Use with caution.
Alpha-II Adrenoreceptor Agents	Clonidine	Sedation effect increased.	Use with caution.
Anticoagulants	All	OCs increase clotting factors, decrease efficacy. However, OCs may potentiate action in some patients.	Use another method.
Anticonvulsants	All	Estrogens may increase risk of seizures.	Use another method.
	Lamotrigine	Significantly decreased lamotrigine levels (due to induction of lamotrigine glucuronidation) may lead to breakthrough seizures.	Adjust dose of drug if necessary. ¹³
Antidiabetic Drugs	Oral Hypoglycemics and Insulin	OCs may impair glucose tolerance and increase blood glucose.	Use low-dose estrogen and progestin OC or another method. Monitor blood glucose.
Antihypertensive Agents	Guanethidine and Methyldopa	Estrogen component causes sodium retention, progestin has no effect.	Use low-dose estrogen OC or use another method.
	Beta Blockers	Increased drug effect (decreased metabolism).	Adjust dose of drug if necessary. Monitor cardiovascular status.
Antipyretics	Acetaminophen	Increased metabolism and renal clearance.	Dose of drug may have to be increased.
	Antipyrine	Impaired metabolism.	Decrease dose of drug.
	ASA	Effects of ASA may be decreased by the short-term use of OCs.	Patients on chronic ASA therapy may require an increase in ASA dosage.
Aminocaproic Acid		Theoretically, a hypercoagulable state may occur because OCs augment clotting factors.	Avoid concomitant use.
Betamimetic Agents	Isoproterenol	Estrogen causes decreased response to these drugs.	Adjust dose of drug as necessary. Discontinuing OCs can result in excessive drug activity.
Caffeine		The actions of caffeine may be enhanced as OCs may impair the hepatic metabolism of caffeine.	Use with caution.

Table 1.4: Modification of Other Drug Action by Oral Contraceptives (cont'd)

Class of Compound	Drug	Modification of Drug Action	Suggested Management
Corticosteroids	Prednisone Prednisolone	Markedly increased serum levels.	Possible need for decrease in dose.
Cyclosporine		May lead to an increase in cyclosporine levels and hepatotoxicity.	Monitor hepatic function. The cyclosporine dose may have to be decreased.
Folic Acid		OCs have been reported to impair folate metabolism.	May need to increase dietary intake, or supplement.
Meperidine		Possible increased analgesia and CNS depression due to decreased metabolism of meperidine.	Use combination with caution.
Phenothiazine Tranquilizers	All Phenothiazines, Reserpine and similar drugs	Estrogen potentiates the hyperprolactinemia effect of these drugs.	Use other drugs or lower dose OCs. If galactorrhea or hyperprolactinemia occurs, use other method.
Sedatives and Hypnotics	Chlordiazepoxide Lorazepam Oxazepam Diazepam	Increased effect (increased metabolism).	Use with caution.
Theophylline	All	Decreased oxidation, leading to possible toxicity.	Use with caution. Monitor theophylline levels.
Tricyclic Antidepressants	Clomipramine (possibly others)	Increased side effects; i.e. depression.	Use with caution.
Vitamin B ₁₂		OCs have been reported to reduce serum levels of Vitamin B ₁₂ .	May need to increase dietary intake, or supplement.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

A possible interaction has been suggested with hormonal contraceptives and the herbal supplement St. John's Wort based on some reports of oral contraceptive users experiencing breakthrough bleeding shortly after starting St. John's Wort. Pregnancies have been reported by users of combined hormonal contraceptives who also used some form of St. John's Wort.

Drug-Laboratory Test Interactions

Laboratory Test Interactions

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

Coagulation Tests

Factors II, VII, IX, X, XII and XIII	Increased
Factor VIII	Mild increase
Platelet aggregation and adhesiveness	Mild increase in response to common aggregating agents
Fibrinogen	Increased
Plasminogen	Mild increase
Antithrombin III	Mild decrease
Prothrombin time	Increased

Thyroid Function Tests

Protein-Bound Iodine (PBI)	Increased
Total serum thyroxine (T ₄)	Increased
Thyroid Stimulating Hormone (TSH)	Unchanged
Free T ₃ resin uptake	Decreased, reflecting the elevated TBG
Free T ₄ concentration	Unchanged

Miscellaneous Tests

Other binding proteins	May be elevated in serum
Sex Hormone Binding Globulins	Increased and resulted in elevated levels of total circulating endogenous sex steroids and corticoids; however, free or biologically active levels either decrease or remain unchanged
High-Density Lipoprotein (HDL-C)	May increase
Total Cholesterol (Total-C)	May increase
Low-Density Lipoprotein (LDL-C)	May increase
Triglycerides	May increase
LDL-C/HDL-C ratio	May remain unchanged
Glucose tolerance	May be decreased

Serum folate levels	May be depressed by hormonal contraceptive therapy. This may be of clinical significance if a woman becomes pregnant shortly after discontinuing hormonal contraceptives.
Insulin response	Mild to moderate increase
c-Peptide response	Mild to moderate increase

Tissue Specimens

Pathologists should be advised of hormonal contraceptive use when specimens from surgical procedures and/or Pap smears are submitted for examination.

Drug-Lifestyle Interactions

When use of EVRA[®] was studied under conditions encountered in a health club (sauna, whirlpool and treadmill), there were slight increases in both steady state concentration (C_{ss}) and area under the curve (AUC) of ethinyl estradiol; however, the C_{ss} values following these treatments were within the reference range. The clinical significance of this finding is not known. Due to a theoretical risk of increased exposure to ethinyl estradiol, all patients should be advised to avoid exposing the EVRA[®] application site to direct external heat sources, such as heating pads, electric blankets, heated water beds, heat lamps, hot water bottles, saunas and hot whirlpool spa baths, intensive sunbathing, etc. (See **WARNINGS AND PRECAUTIONS –General and PHARMACOKINETICS- Absorption.**)

NON-CONTRACEPTIVE BENEFITS OF HORMONAL CONTRACEPTIVES

Several health advantages other than contraception have been reported.

1. Combination hormonal contraceptives reduce the incidence of cancer of the endometrium and ovaries.
2. Hormonal contraceptives reduce the likelihood of developing benign breast disease and, as a result, decrease the incidence of breast biopsies.
3. Hormonal contraceptives reduce the likelihood of development of functional ovarian cysts.
4. Users of hormonal contraceptives have less menstrual blood loss and have more regular cycles, thereby reducing the chance of developing iron-deficiency anemia.
5. The use of hormonal contraceptives may decrease the severity of dysmenorrhea and premenstrual syndrome, and may improve acne vulgaris, hirsutism, and other androgen-mediated disorders.

6. Hormonal contraceptives decrease the incidence of acute pelvic inflammatory disease and, thereby, reduce as well the incidence of ectopic pregnancy.
7. Hormonal contraceptives have potential beneficial effects on endometriosis.

DOSAGE AND ADMINISTRATION

Dosing Considerations

To achieve maximum contraceptive effectiveness, the EVRA[®] (norelgestromin and ethinyl estradiol) transdermal system must be used exactly as directed. Complete instructions to facilitate patient counselling on proper system usage may be found in ***Product Monograph Part III: CONSUMER INFORMATION.***

Recommended Dose and Dosage Adjustment

Transdermal Contraceptive System Overview

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.

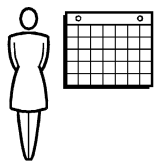
This means that every new patch will be applied on the same day of the week. This day is known as the “Patch Change Day.” For example, if the first patch is applied on a Monday, all subsequent patches should be applied on a Monday. Only one patch should be worn at a time.


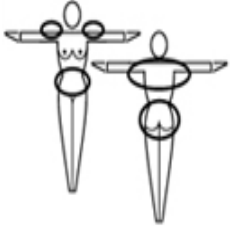
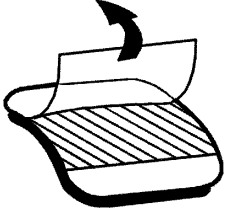


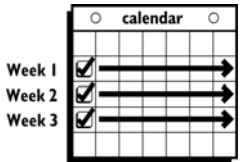
The patch should not be cut, damaged or altered in any way. If the patch is cut, damaged or altered in size, contraceptive efficacy may be impaired.


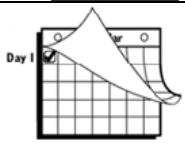
On the day after Week Four ends, a new four-week cycle is started by applying a new patch. Under no circumstances should there be more than a 7-day patch-free interval between dosing cycles.

Clinical trials demonstrated that subjects randomized to EVRA[®] were able to adhere to the weekly dosing regimen better than with daily dosing of oral contraceptives (see ***Product Monograph Part II: CLINICAL TRIALS.***)

Administration

1		<p>If the patient is starting EVRA[®] for the first time, she should wait until the day she begins her menstrual period. Either a First Day start or Sunday start may be utilized (see below). The day she applies her first patch will be Day 1. Her “Patch Change Day” will be on this day every week.</p>
---	---	---

<p>2</p> <p>CHOOSE ONE OPTION:</p>  <p><input type="checkbox"/> First Day Start or <input type="checkbox"/> Sunday Start</p>	<ul style="list-style-type: none"> for First Day start: the patient should apply her first patch during the first 24 hours of her period. <p>OR</p> <ul style="list-style-type: none"> for Sunday start: the patient should apply her first patch on the first Sunday after her period starts. She must use back-up contraception for the first week of her first cycle only. If the menstrual period begins on a Sunday, the first patch should be applied on that day. No back-up contraception is needed. <p>For both a First Day start and a Sunday start: A non-hormonal contraceptive (such as a condom or diaphragm) should be used concurrently for the first 7 consecutive days of the first treatment cycle.</p>
<p>3</p> 	<p>Where to apply the patch. The patch should be applied to clean, dry, intact healthy skin on the buttock, abdomen, upper outer arm or upper torso, in a place where it won't be rubbed by tight clothing. EVRA[®] should not be placed on skin that is red, irritated or cut, nor should it be placed on the breast.</p> <p>To prevent interference with the adhesive properties of EVRA[®], no make-up, creams, lotions, powders or other topical products should be applied to the skin area where the EVRA[®] patch is currently placed or will be applied shortly.</p>
<p>4</p> 	<p>Application of the EVRA[®] patch</p> <p>The foil pouch is opened by tearing it along the edge using the fingers. A corner of the patch is grasped firmly and gently removed from the foil pouch. Sometimes patches can stick to the inside of the pouch – the patient should be careful not to accidentally remove the clear liner as she removes the patch. Then half of the clear protective liner is peeled away. The patient should avoid touching the sticky surface of the patch.</p>
<p>5</p> 	<p>The patch is positioned on the skin and the other half of the liner is removed. The patient should press down firmly on the patch with the palm of her hand for 10 seconds, making sure that the edges stick well. She should check her patch every day to make sure it is sticking.</p>
<p>6</p> 	<p>The patch is worn for 7 days (one week). On the "Patch Change Day," Day 8, the used patch is removed and a new one is applied immediately. The used patch still contains some active hormones – it should be thrown away by carefully folding it in half so that it sticks to itself.</p>
<p>7</p> 	<p>A new patch is applied on Week Two (Day 8) and again on Week Three (Day 15), on the usual "Patch Change Day." Patch changes may occur at any time on the Change Day. Consecutive EVRA[®] patches should be applied to a new spot on the skin to help avoid potential irritation, although they may be kept within the same anatomic site.</p>

<p>8</p> 	<p>Week Four is patch-free (Day 22 through Day 28), thus completing the four-week contraceptive cycle. Bleeding is expected during this time.</p>
<p>9</p> 	<p>The next four-week cycle is started by applying a new patch on the usual “Patch Change Day,” the day after Day 28, no matter when the menstrual period begins or ends.</p> <p>Under no circumstances should there be more than a 7-day patch-free interval between dosing cycles.</p>

Patch adhesion was assessed indirectly by replacement rates for complete and partial patch detachment. Experience with more than 70,000 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 EVRA[®] patch becomes partially or completely detached and remains detached, insufficient drug delivery occurs.

If the patch remains even partly detached

- **for less than one day** (up to 24 hours), try to reapply it to the same place or replace with a new patch immediately. No back-up contraception is needed. The woman’s “Patch Change Day” will remain the same.
- **for more than one day (> 24 hours) OR if the patient 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 putting on a new patch. There is now a new “Day 1” and a new “Patch Change Day.” Back-up contraception must be used for the first week of the new cycle only.

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-attached, a new patch should be applied immediately. Supplemental adhesives or wraps should not be used to hold the EVRA[®] patch in place.

If the patient 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 patient must use back-up contraception for the first week of her 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), **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 patient must use back-up contraception for one week.
- **at the end of the patch cycle (Week Four/Day 22):**
if the patient 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 7-day patch-free interval between dosing cycles. If there are more than 7 patch-free days, **the patient may not be protected from pregnancy** and back-up contraception must be used concurrently for 7 days. As with combined oral contraceptives, the risk of ovulation increases with each day beyond the recommended contraceptive-free period. If coital exposure has occurred during the patch-free interval, the possibility of fertilization should be considered.

Change Day Adjustment

If the patient wishes to move her “Patch Change Day” she should complete her current cycle, removing the third EVRA[®] patch on the correct day. During the patch-free week, a new “Patch Change Day” may be selected by applying a new EVRA[®] patch on the first occurrence of the desired day. In no case should there be more than 7 consecutive patch-free days.

The shorter the patch-free interval, the higher the risk of breakthrough bleeding and spotting replacing the expected withdrawal bleeding. **This practice is for a one-time only change and should not be used as a standard dosing regimen, as there are no long term safety data available on the continuous use of EVRA[®].**

Switching from an Oral Contraceptive

Treatment with EVRA[®] should begin on the first day of withdrawal bleeding. If there is no withdrawal bleeding within 5 days of the last active (hormone-containing) tablet, pregnancy must be ruled out prior to start of treatment with EVRA[®]. If therapy starts after the first day of withdrawal bleeding, a non-hormonal contraceptive should be used concurrently for 7 days. If more than 7 days elapse after taking the last active oral contraceptive tablet, the patient may have ovulated. The patient should be instructed to consult her physician before initiating treatment with EVRA[®].

Use after Childbirth

Women who elect not to breast-feed should start contraceptive therapy with EVRA[®] no sooner than 4 weeks after childbirth (see **WARNINGS AND PRECAUTIONS - Hematologic**).

Use after Abortion or Miscarriage

After an abortion or miscarriage that occurs before 20 weeks gestation, EVRA[®] may be started immediately. An additional method of contraception is not needed if EVRA[®] is started immediately. Be advised that ovulation may occur within 10 days of an abortion or miscarriage.

After an abortion or miscarriage that occurs at or after 20 weeks gestation, EVRA[®] may be started either on Day 21 post-abortion or on the first day of the first spontaneous menstruation, whichever comes first. The incidence of ovulation on Day 21 post-abortion (at 20 weeks gestation) is not known.

In Case of Vomiting or Diarrhea

Unlike oral contraceptives, dose delivery by transdermal application should be unaffected by vomiting. Dose delivery is also expected to be unaffected by diarrhea.

In Case of Skin Irritation

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

Additional Instructions for All Dosing Regimens

Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing hormonal contraceptives.

Breakthrough Bleeding or Spotting

In the event of breakthrough bleeding or spotting (bleeding that occurs during EVRA[®] usage), treatment should be continued. This type of bleeding usually disappears after the first few cycles. Non-functional causes should be considered, however, and in cases 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 formulation may solve the problem. Changing to a hormonal contraceptive with a higher estrogen content, while potentially useful in minimizing menstrual irregularity, should be done only if necessary since this may increase the risk of thromboembolic disease.

Amenorrhea

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 ruled out at the time of the first missed period.

2. If EVRA[®] has been used correctly, the absence of withdrawal bleeding (bleeding that should occur during the patch-free week) is not necessarily an indication of pregnancy. If the woman has adhered to the prescribed regimen and misses one period, she should continue using her contraceptive patches on the next scheduled Change Day. If the woman has adhered to the prescribed regimen and misses two consecutive periods, pregnancy should be ruled out before continuing hormonal contraceptive use.

OVERDOSAGE

For management of suspected drug overdose, contact your regional Poison Control Centre.

Serious ill effects have not been reported following accidental ingestion of large doses of hormonal contraceptives. Overdosage may cause nausea and vomiting. Withdrawal bleeding may occur in females. In case of suspected overdose, all transdermal contraceptive systems should be removed and symptomatic treatment given. Liver function tests should be conducted, particularly transaminase levels, 2 to 3 weeks after overdosage.

ACTION AND CLINICAL PHARMACOLOGY

The EVRA[®] (norelgestromin and ethinyl estradiol) transdermal system, with a contact surface area of 20 cm², is a thin, matrix-type transdermal system consisting of three layers. Each transdermal system contains 6.0 mg norelgestromin and 0.60 mg ethinyl estradiol (EE). Each transdermal system releases an average of approximately 200 µg of NGMN and 35 µg of EE every 24 hours (see **PART II: DETAILED PHARMACOLOGY, Residual Analysis Study**). Drug exposure is more appropriately characterized by the pharmacokinetic profile. Systemic exposures (as measured by area under the curve [AUC] and steady state concentration [C_{ss}]) of NGMN and EE during use of EVRA[®] are comparable to those produced by an oral contraceptive containing norgestimate 250 µg / EE 35 µg, and peak concentrations (C_{max}) are lower than those produced by this oral contraceptive.

Each EVRA[®] transdermal system consists of three layers.

1. 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.
2. 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 EE.

3. The third layer is the release liner, which is a transparent polyethylene terephthalate (PET) film with a polydimethylsiloxane coating on the side that is in contact with the middle adhesive layer. The release liner protects the adhesive layer during storage and is removed just prior to application.

The outside of the backing layer is heat-stamped “EVRA™”.

Pharmacodynamics

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

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 norgestimate and norelgestromin exhibit high progestational activity with minimal intrinsic androgenicity. 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.

Pharmacokinetics

Absorption: Following application of EVRA[®], both norelgestromin and EE rapidly appear in the serum, reach a plateau by approximately 48 hours, and are maintained at an approximate steady-state throughout the wear period. C_{SS} concentrations for norelgestromin and EE during one week of patch wear are approximately 0.8 ng/mL and 50 pg/mL, respectively, and are generally consistent from all studies and application sites. These C_{SS} concentrations are well within the reference ranges for norelgestromin (0.6 to 1.2 ng/mL) and EE (25 to 75 pg/mL) established based upon the C_{ave} concentrations in 90% of the individual subjects taking CYCLEN[®]. This was computed from AUC_{0-t} for these analytes from steady-state data following administration of the NGM/EE oral contraceptives.

The absorption of norelgestromin and EE following application of EVRA[®] to the abdomen, buttock, upper outer arm and upper torso (excluding breast) was evaluated in a crossover design study. The results of this study indicated that C_{SS} and AUC for the buttock, upper arm and torso for each analyte were equivalent. While C_{SS} values for the abdomen were within reference ranges for EE 35 µg/NGM 250 µg oral contraceptive users, strict bioequivalence requirements for AUC were not met in this study for the abdomen. However, in a separate parallel-group multiple-application pharmacokinetic

study, C_{SS} and AUC for the buttock and abdomen were not statistically different. In a dose-ranging study, EVRA[®] caused effective ovulation suppression when applied to the abdomen. Therefore, all four sites are therapeutically equivalent.

The absorption of norelgestromin and EE following application of 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 norelgestromin there were no significant treatment effects on C_{SS} or AUC when compared to normal wear. For EE, slight increases were observed due to sauna, whirlpool and treadmill; however, the C_{SS} values following these treatments were within the reference range. There was no significant effect of cold water on these parameters. Serum estradiol concentrations could theoretically increase in patients with fever. Any clinical consequences due to an increase in temperature are unknown at this time. Due to a theoretical risk of increased exposure to ethinyl estradiol, all patients should be advised to avoid exposing the EVRA[®] application site to direct external heat sources, such as heating pads, electric blankets, heated water beds, heat lamps, hot water bottles, saunas and hot whirlpool spa baths, intensive sunbathing, etc. See **WARNINGS AND PRECAUTIONS – General and Drug-Lifestyle Interactions.**

In multiple dose studies, C_{SS} and AUC for norelgestromin and EE were found to increase slightly over time when compared to Week 1 of Cycle 1. In a three-cycle study, these pharmacokinetic parameters reached steady-state conditions during all three weeks of Cycle 3 (see Table 1.5, Figures 1.1 and 1.2).

Table 1. 5: Mean (SD) Pharmacokinetic Parameters of Norelgestromin and EE Following Three Consecutive Cycles of EVRA[®] Wear on the Buttock

Analyte	Parameter	Cycle 1 Week 1	Cycle 3 Week 1	Cycle 3 Week 2	Cycle 3 Week 3
Norelgestromin	C _{SS} ^a	0.70 (0.28)	0.70 (0.29)	0.80 (0.23)	0.70 (0.32)
	AUC ₀₋₁₆₈ ^b	107 (44.2)	105 (45.5)	132 (57.1)	120 (52.8)
	t _{1/2} ^c	nc	nc	nc	32.1 (12.9)
EE	C _{SS} ^d	46.4 (17.9)	47.6 (17.3)	59.0 (25.1)	49.6 (27.0)
	AUC ₀₋₁₆₈ ^e	6796 (2673)	7160 (2893)	10054 (4205)	8840 (5176)
	t _{1/2} ^c	nc	nc	nc	21.0 (9.07)

^a ng/mL ^b ng·h/mL ^c h ^d pg/mL ^e pg·h/mL nc = not calculated

Figure 1.1: Mean Norelgestromin (NGMN) Serum Concentrations (ng/mL) in Healthy Female Volunteers Following Application of EVRA[®] on the Buttock for Three Consecutive Cycles (Dotted horizontal lines indicate the reference range. Dotted vertical arrow indicates time of patch removal.)

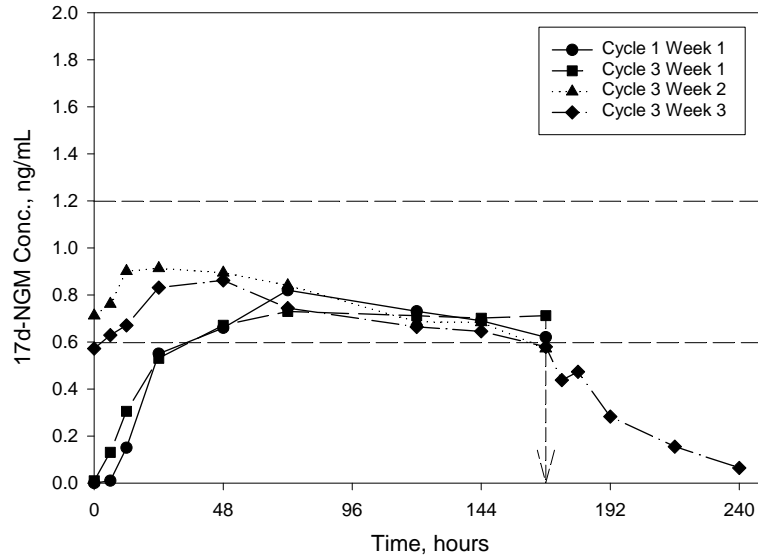
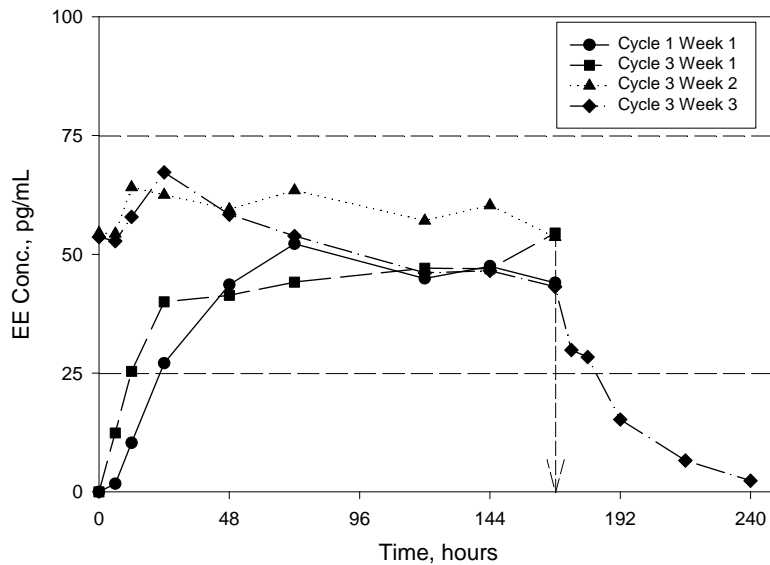


Figure 1.2: Mean Ethinyl Estradiol (EE) Serum Concentrations (pg/mL) in Healthy Female Volunteers Following Application of EVRA[®] on the Buttock for Three Consecutive Cycles (Dotted horizontal lines indicate the reference range. Dotted vertical arrow indicates time of patch removal.)



Results from a study of consecutive EVRA[®] wear for 7 days and 10 days indicated that target C_{ss} of norelgestromin and EE were maintained during a 3-day extended wear of EVRA[®]. These findings suggest that clinical efficacy would be maintained even if a scheduled change is missed for as long as 2 full days (see Figures 1.3 and 1.4).

Figure 1.3: Mean Norelgestromin (NGMN) Serum Concentrations (ng/mL) Following Application of EVRA[®] to the Abdomen for 7 Days and 10 Days (Dotted horizontal lines indicate the reference range. Solid vertical arrows indicate actual time of patch removal. Dotted vertical arrow indicates theoretical time of patch removal under normal use.)

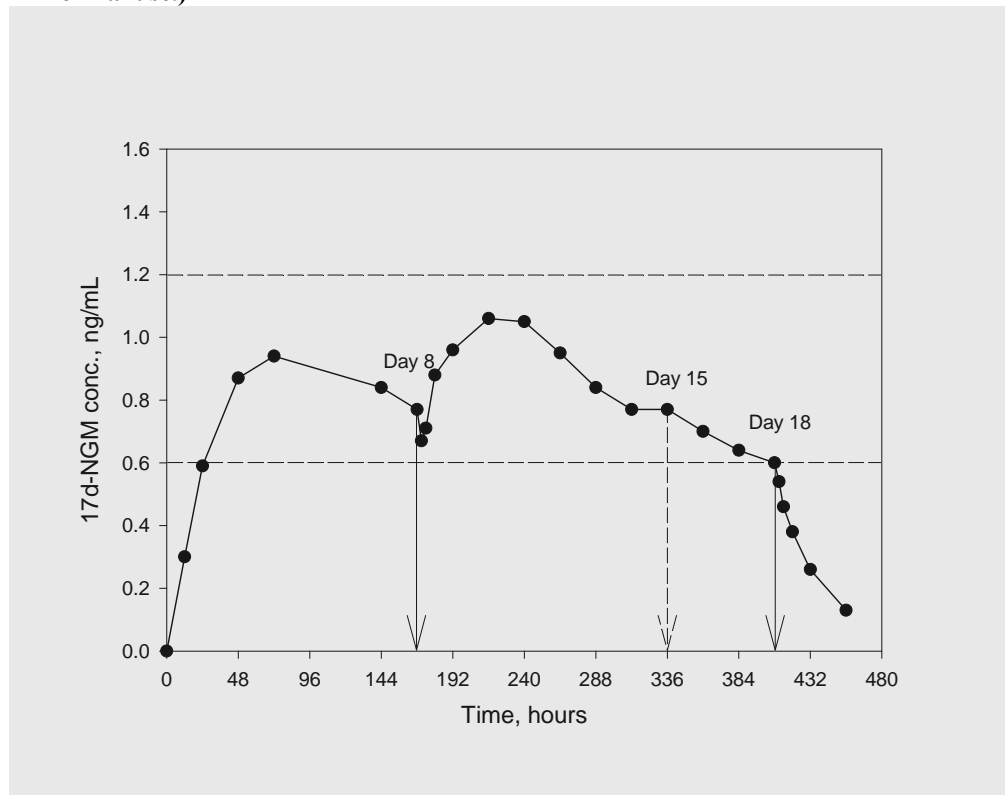
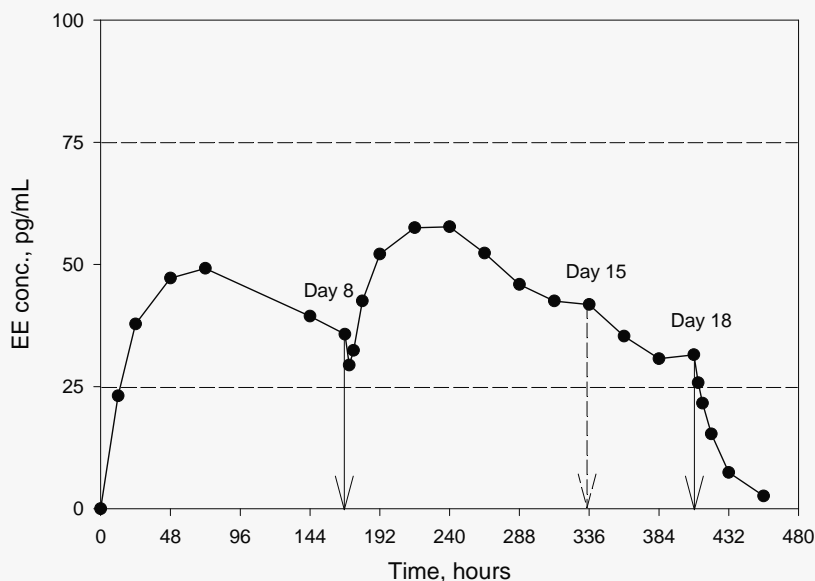


Figure 1.4: Mean Ethinyl Estradiol (EE) Serum Concentrations (pg/mL) Following Application of EVRA[®] to Abdomen for 7 Days and 10 Days (Dotted horizontal lines indicate reference range. Solid vertical arrows indicate actual time of patch removal. Dotted vertical arrow indicates theoretical time of patch removal under normal use.)



Distribution: Norelgestromin and norgestrel (a serum metabolite of norelgestromin) are highly bound (> 97%) to serum proteins. Norelgestromin 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.

Metabolism: Since EVRA[®] is applied transdermally, first-pass metabolism (via the gastrointestinal tract and/or liver) of norelgestromin and ethinyl estradiol that would be expected with oral administration is avoided. Hepatic metabolism of norelgestromin 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.

Excretion: Following removal of transdermal systems, the elimination kinetics of norelgestromin and ethinyl estradiol were consistent for all studies with half-life values of approximately 28 hours and 17 hours, respectively. The metabolites of norelgestromin and ethinyl estradiol are eliminated by renal and fecal pathways.

Transdermal versus Oral Contraceptives

The pharmacokinetic profiles of transdermal and oral combined hormonal contraceptives are different and caution should be exercised when making a direct comparison of these PK parameters.

The EVRA[®] transdermal patch was designed to deliver EE and NGMN over a seven-day period while oral contraceptives (containing NGM 250 µg / EE 35 µg) are administered on a daily basis. Figures 1.5 and 1.6 present mean pharmacokinetic (PK) profiles for EE and NGMN following administration of an oral contraceptive (containing NGM 250 µg / EE 35 µg) compared to the 7-day transdermal EVRA[®] patch (containing NGMN 6.0 mg / EE 0.60 mg) in 54 healthy female volunteers.

Figure 1.5: Mean Serum Concentration-Time Profiles of NGMN Following Once-Daily Administration of an Oral Contraceptive for 7 days or Application of EVRA[®] to the Buttock in Healthy Female Volunteers

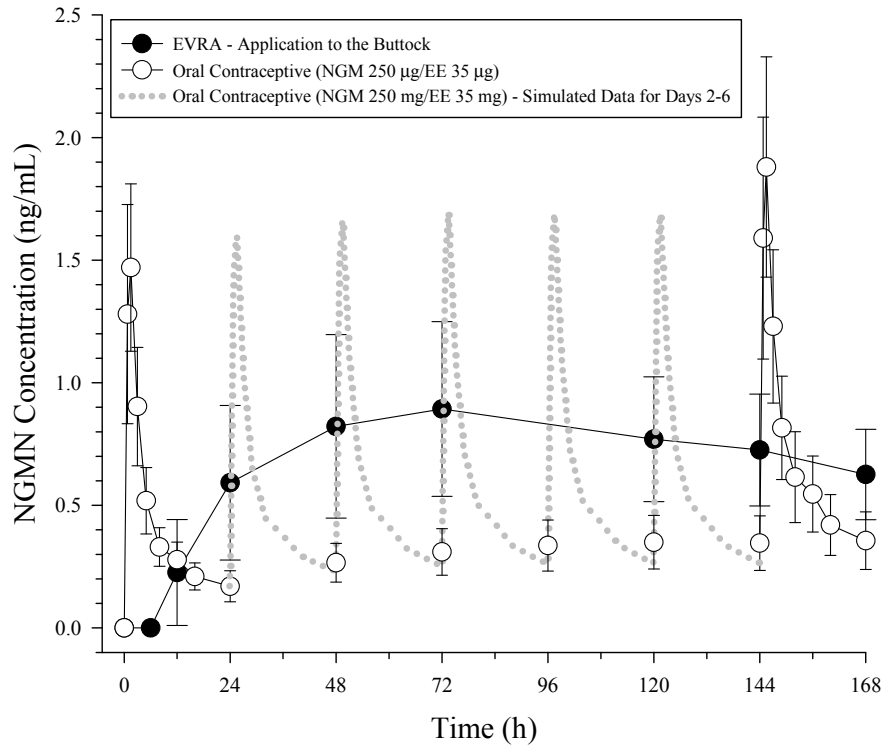


Figure 1.6: Mean Serum Concentration-Time Profiles of EE Following Once-Daily Administration of an Oral Contraceptive for 7 days or Application of EVRA[®] to the Buttock in Healthy Female Volunteers

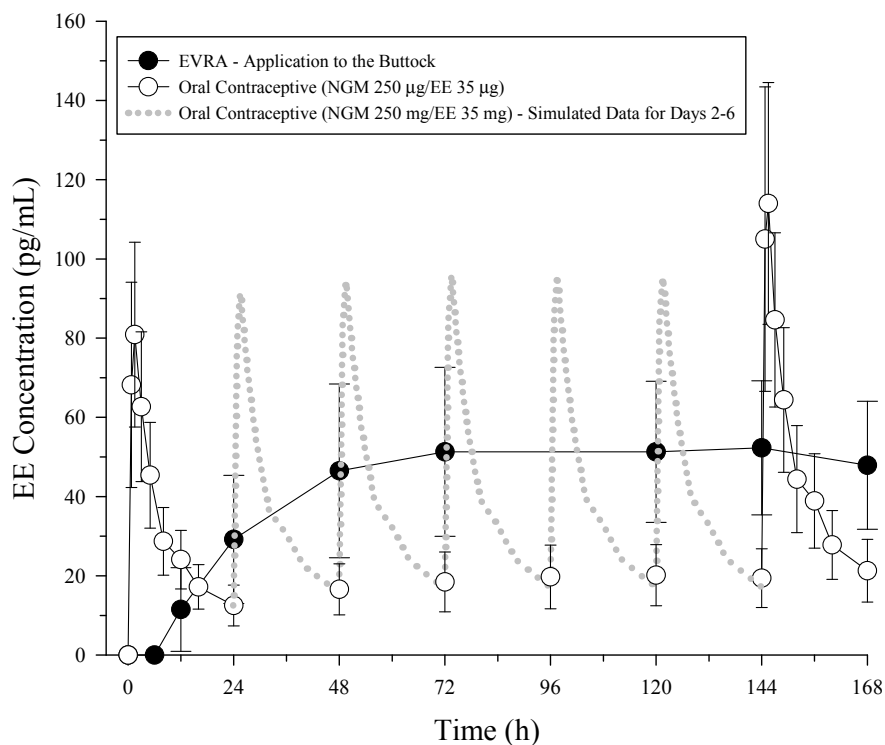


Table 1.6 provides the mean (%CV) for NGMN and EE pharmacokinetic (PK) parameters.

Table 1.6: Mean (%CV) NGMN and EE Steady State Pharmacokinetic Parameters Following Application of EVRA[®] and Once-daily Administration of an Oral Contraceptive (containing NGM 250 µg / EE 35 µg) in Healthy Female Volunteers

Parameter	EVRA ^{®d}	ORAL CONTRACEPTIVE ^e
<u>NGMN^a</u>		
C _{max} (ng/mL)	0.934 (37.7)	1.95 (21.3)
AUC ₀₋₁₆₈ (ng·h/mL)	118 (36.9)	108 (21.5) ^b
C _{ss} (ng/mL)	0.768 (34.0)	0.663 (25.1) ^c
<u>EE</u>		
C _{max} (pg/mL)	58.5 (38.1)	118 (28.7)
AUC ₀₋₁₆₈ (pg·h/mL)	7289 (35.8)	7226 (28.3) ^b
C _{ss} (ng/mL)	49.9 (34.8)	45.2 (27.8) ^c

^aNGM is rapidly metabolized to NGMN following oral administration

^bAverage weekly exposure, calculated as AUC₂₄ × 7

^cC_{avg}

^dDays 1-7

^eWeek 1

In general, C_{max} values were 2-fold higher for NGMN and EE in subjects administered the oral contraceptive compared to EVRA[®], while overall exposure (AUC and C_{ss}) was comparable in subjects treated with EVRA[®]. Inter-subject variability (%CV) for the PK parameters following delivery from 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.

The clinical relevance of the difference in PK profile and pharmacodynamic (PD) response between transdermal and oral delivery is not known. (See **WARNINGS AND PRECAUTIONS – General**).

Special Populations and Conditions

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 norelgestromin and ethinyl estradiol were evaluated in 230 healthy women from nine pharmacokinetic studies of single 7-day applications of EVRA[®]. For both norelgestromin and ethinyl estradiol, 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 (10-20%) of the overall variability in the pharmacokinetics of norelgestromin and ethinyl estradiol following application of 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.

Hepatic Insufficiency: No studies with EVRA[®] have been conducted in women with hepatic impairment. EVRA[®] is contraindicated in patients with hepatic dysfunction (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS**).

Renal Insufficiency: No studies with EVRA[®] have been conducted in women with renal impairment.

STORAGE AND STABILITY

Store between 15°C - 30°C. Do not refrigerate or freeze. Store patches in their protective pouches inside the original box. Apply patch immediately upon removal from its packaging.

Keep new and used transdermal systems out of the reach of children and pets.

SPECIAL HANDLING INSTRUCTIONS

Disposal of EVRA[®]

Used transdermal systems still contain some active hormones. Used transdermal systems should be carefully folded in half so the adhesive side sticks to itself. The folded patch should be placed in a sturdy container, preferably with a child-resistant cap, and disposed of in the garbage out of the reach of children and pets. Remaining active hormonal ingredients of the patch may have harmful effects if reaching the aquatic environment. Used or unused patches should not be flushed down the toilet or placed in liquid waste disposal systems.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms and Packaging

The EVRA[®] (norelgestromin and ethinyl estradiol) transdermal system is available in cartons containing 3 systems each. Each system is sealed within a protective pouch and heat-stamped “EVRA[™].”

Composition

Backing Layer:	low-density pigmented polyethylene outer layer and a polyester inner layer.
Middle Layer:	Active components - 6.00 mg norelgestromin and 0.60 mg ethinyl estradiol releasing approximately 200 µg norelgestromin and 35 µg ethinyl estradiol every 24 hours. Inactive components - polyisobutylene/ polybutene adhesive, crospovidone, non-woven polyester fabric, lauryl lactate.
Release Liner:	polyethylene terephthalate film with polydimethylsiloxane coating on one side.

The EVRA[®] transdermal system does not contain any metal components.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

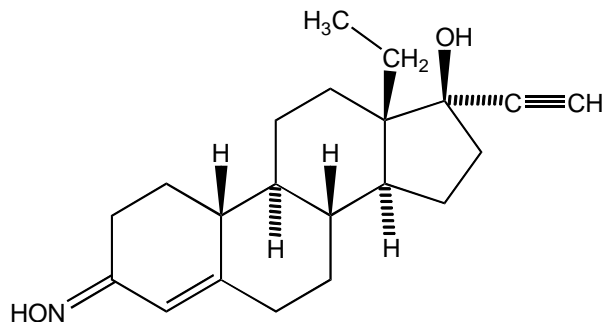
Drug Substance

Proper name: norelgestromin

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

Molecular formula and molecular mass: C₂₁H₂₉NO₂
327.47

Structural formula:



Physicochemical properties: norelgestromin is a white or off-white crystalline powder

Partition coefficient: 2.70

Solubility: Practically insoluble in water, freely soluble in ethanol and acetone, and sparingly soluble in methylene chloride.

Melting point: As 17d-NGM is a mixture of the *syn*- and *anti*-isomers, its melting point varies between 174°C and 185°C.

Proper name: ethinyl estradiol

INN: Ethinylestradiol

Ph. Eur.: Ethinylestradiol, Ethinylestradiolum

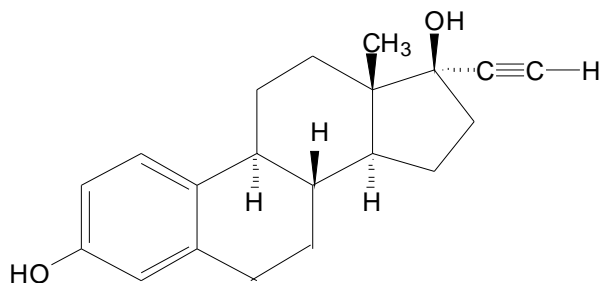
USP, USAN: Ethinyl Estradiol

BAN: Ethinyloestradiol

Chemical name: 19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17 α)-
19-Nor-17 α -pregna-1,3,5(10)-trien-20-yne-3,17-diol
(17)- α Ethinyl-1,3,5(10)-estratrien-3,17-diol
19-Ethinyl-estra-1,3,5(10)-triene-3,17 β -diol

Molecular formula and molecular mass: $C_{20}H_{24}O_2$
296.41

Structural formula:



Physicochemical properties: ethinyl estradiol is a white or slightly yellowish-white, crystalline powder

Partition coefficient: 1.69

Solubility: Practically insoluble in water, freely soluble in ethanol, acetone, dioxane, and diethyl ether.
Soluble in chloroform.

Melting point: 180°C to 186°C; EE forms a stable hemihydrate, characterized by a melting range of approximately 140°C to 150°C.

CLINICAL TRIALS

Three Phase III contraceptive trials (CONT-002, CONT-003 and CONT-004) involving 4578 women for 31,026 cycles were conducted worldwide. Overall, 3319 women received EVRA[®]. The overall Pearl Index for EVRA[®] from these trials was 0.88. Analyses were performed to determine whether in the Phase III studies (n = 3319) the population characteristics of age, race and weight were associated with pregnancy. The analyses indicated no association of age and race with pregnancy. With respect to weight, 5 of the 15 pregnancies reported with EVRA[®] were among women with a baseline body weight \geq 90 kg (198 lbs.), which constituted < 3% of the study population. Below 90 kg, there was no apparent association between body weight and pregnancy rate. Although only 10 – 20% of the variability in pharmacokinetic data can be explained by weight (see **ACTION AND CLINICAL PHARMACOLOGY - Special Populations**), the greater proportion of pregnancies among women at or above 90 kg was statistically significant and suggests that EVRA[®] may be less effective in these women (see **WARNINGS AND PRECAUTIONS - Body Weight \geq 90 kg**).

In the North American comparative trial, 811 women received EVRA[®] and 605 women received TRIPHASIL[®] (levonorgestrel/ethinyl estradiol), an oral contraceptive containing a triphasic regimen. Phase 1 consisted of 50 μ g levonorgestrel and 30 μ g EE for 6 days, phase 2 consisted of 75 μ g levonorgestrel and 40 μ g of EE for 5 days and phase 3 consisted of 125 μ g of levonorgestrel and 30 μ g EE for 10 days. In this trial, the Pearl Index for EVRA[®] was 1.24 and the Pearl Index for TRIPHASIL[®] was 2.18.

Adherence to the EVRA[®] dosing regimen was shown to be superior to that for oral contraceptives in two (CONT-001 and CONT-004) adequate and well-controlled comparative trials (89% vs. 79%, respectively).

Among more than 3000 women who used EVRA[®] for up to 13 cycles, the mean change in body weight from baseline to the end of treatment was an increase less than 1 lb. In a 9-cycle, placebo-controlled trial there was no difference between EVRA[®] and placebo in the mean change in body weight from baseline to the end of treatment.

The following table gives reported pregnancy rates for various forms of birth control, including no birth control. The reported rates represent the number of women out of 100 who would become pregnant in one year.

Reported Pregnancies per 100 Women per Year:

Combination pill	less than 1 to 2
Intrauterine device (IUD)	less than 1 to 6
Condom with spermicidal foam or gel	1 to 6
Mini-pill	3 to 6
Condom	2 to 12

Diaphragm with spermicidal foam or gel	3 to 18
Spermicide	3 to 21
Sponge with spermicide	3 to 28
Cervical cap with spermicide	5 to 18
Periodic abstinence (rhythm), all types	2 to 20
No birth control	60 to 85

DETAILED PHARMACOLOGY

Nonclinical Pharmacology

Norelgestromin is the primary active metabolite produced following oral administration of norgestimate (NGM). Extensive in vivo and in vitro pharmacology studies have been conducted with oral norelgestromin, NGM and EE, alone or in combination. Tables 2.1 and 2.2 present results for norelgestromin (17d-NGM), and NGM and EE in combination.

Table 2.1: Pharmacological Effects of 17-Deacetylnorgestimate (17d-NGM)

Pharmacological Effects	Test Methods	Results								
Progestational Activity	<p>Clauberg progestational assay: Measured ability to stimulate the endometrium of immature estrogen-primed rabbits.</p> <p>Progestin receptor binding: Measured displacement of ³H-R50200 (a synthetic progestin ligand) from isolated progestin receptors of rabbit uteri. 0.01 or 0.1% bovine serum albumin (BSA) was added to the test solutions to prevent binding of test substances to glassware.</p>	The response and potency of 17d-NGM was similar to that of norgestimate (NGM). 3-Keto-norgestimate and levonorgestrel were 3.39 and 4.92 times more potent than NGM, respectively.								
		<u>Test substance</u>	<u>IC₅₀</u>	<u>(nM)</u>						
		17d-NGM ^a	2.82*	-						
		NGM	5.01*	4.72**					*In presence of 0.1% BSA	
		3-Keto-norgestimate ^a	0.83*	-					**In presence of 0.01% BSA	
		Levonorgestrel ^a	0.71*	0.84**						
Progesterone	-	1.87**								
Androgenic	<p>Measured stimulation of ventral prostate growth in groups of castrated rats dosed orally and subcutaneously for 7 days.</p> <p>Androgen receptor binding: Measured displacement of radiolabeled 5α-dihydrotestosterone from isolated androgen receptors from rat ventral prostates. 0.1% BSA was added to the test solutions to prevent binding of test substances to glassware.</p>	Androgenic activity of 17d-NGM was not significantly different from that of NGM. 3-Keto-norgestimate and levonorgestrel were significantly more androgenic than NGM.								
		<u>Test substance</u>	<u>IC₅₀ (nM)</u>							
		17d-NGM ^a	156							
		NGM	857							
		3-Keto-norgestimate ^a	78							
		Levonorgestrel ^a	11							
Dihydrotestosterone	2.2									
Antioviulatory	<p>Examined oviducts for presence of ova of rats dosed orally or subcutaneously with 17d-NGM or NGM. The rats were dosed on the mornings of metestrus, diestrus, and proestrus.</p>	<u>Number of rats ovulating/10 rats treated</u>								
			mg/kg:	1010	0.062	0.126	0.2589	0.053	1.0	
		Oral	17d-NGM:	-						3
			NGM:	-						2
		s.c.	17d-NGM:	8						-
	NGM:	10						-		

^a Metabolite of NGM

IC₅₀ = the concentration of test substance corresponding to 50% inhibition on the linear regression response curve; s.c. = subcutaneous

Table 2.2: Pharmacological Effects of Norgestimate/Ethinyl Estradiol (NGM/EE)

Pharmacological Effects	Test Methods	Results
Antiovarulatory Activity	Examination of oviducts for ova	EE alone had no inhibitory effect on the number of rats ovulating. NGM alone and NGM/EE at 0.5 mg/kg totally inhibited ovulation. Doses of 0.25 mg/kg showed partial inhibition of ovulation.
	Examination of oviducts for ova	NGM alone at 250, 500, and 1000 µg/kg inhibited ovulation in 30, 60 and 100% of the rats, respectively. EE alone had no effect at 140 µg/kg. At some doses NGM/EE caused a greater inhibition of ovulation than NGM alone.
	Examination of oviducts for ova. Vaginal cytology of rats monitored.	NGM given alone inhibited ovulation in 20, 30, 60 and 100% of animals at 0.25, 0.5, 1.0 and 2.0 mg/kg, respectively. EE alone inhibited ovulation by 50% at 270 µg/kg, but had no effect at lower doses. NGM/EE was approximately 2.8 times more potent than NGM alone at dose levels of 30, 90, and 270 mg/kg EE.
Progestational Activity	Uterine contents of rats and guinea pigs examined for number of implants following oral administration (10:1 NGM/EE ratio).	The NGM/EE combination caused implantation failure at 2.0 mg/kg in the rat and 0.1 mg/kg in the guinea pig. NGM alone at the equivalent dose had no effect, confirming that the antifertility effects were due to EE.
	Clauberg progestational assay: measured ability to stimulate the endometrium of immature rabbits (10:1 NGM/EE ratio).	Endometrial proliferation observed at a total dose as low as 0.2 mg NGM alone. When in combination with EE, NGM was less potent.

Other Clinical Experience

In a multi-centre dose selection study for EVRA[®], 615 subjects were randomized to receive either one of 3 patch sizes or CYCLEN[®] (norgestimate/ethinyl estradiol), an oral contraceptive comparator containing 250 µg NGM/ 35 µg EE, for 4 cycles. This study demonstrated that the 20 cm² patch (EVRA[®]) inhibits ovulation to the same extent as CYCLEN[®] (norgestimate/ethinyl estradiol).

Pharmacokinetic studies with EVRA[®] demonstrated consistent elimination kinetics for norelgestromin and EE with half-life values of approximately 28 hours and 17 hours, respectively. 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. Therefore, it is anticipated that following discontinuation of EVRA[®] treatment, return to fertility will be rapid, approximately that seen with oral contraceptives.

Residual Analysis Study

Study NRGEEP-CON-1013, a single center, randomized, open-label, 2-way crossover study in 50 healthy women, was designed to estimate the average daily release rate of ethinyl estradiol (EE) and norelgestromin (NGMN) from the EVRA[®] transdermal patch after single 7-day applications to the abdomen and buttock. Subjects were randomly assigned to one of two treatment sequence groups and wore the EVRA[®] patch on the abdomen or the buttock during separate treatment periods for 7 days each. At the end of each 7-day application period, the worn patches were removed and the skin area under the patch was swabbed to collect any EE and NGMN sitting on the surface of the skin. The worn patches and skin swabs were analyzed for residual drug content. Differences in the drug content between worn and unworn patches were used to estimate average daily release rates of drug from the patch.

Table 2.3: Descriptive Statistics for Amounts of EE and NGMN Released Daily from the Worn Patches (With and Without Swab Data) (Study NRGEEP-CON-1013: Pharmacokinetic Analysis Set)

-- DRUG RELEASE / DAY --				
Analyte	Application Site	N	Mean	90% CI
<u>Amount of drug contained in worn patch only</u>				
EE (µg)	Abdomen	50	31.6	(29.4; 33.8)
	Buttock	49	36.1	(34.4; 37.9)
	Combined	99	33.9	(32.4; 35.3)
NGMN (µg)	Abdomen	50	190.2	(179.3; 201.1)
	Buttock	49	215.4	(204.9; 226.0)
	Combined	99	202.7	(194.6; 210.8)
<u>Amount of drug contained in combination worn patch/swab</u>				
EE (µg)	Abdomen	50	30.9	(28.7; 33.2)
	Buttock	49	35.5	(33.7; 37.2)
	Combined	99	33.2	(31.7; 34.6)
NGMN (µg)	Abdomen	50	183.4	(172.4; 194.3)
	Buttock	49	209.2	(198.6; 219.7)
	Combined	99	196.1	(188.0; 204.3)

Table 2.3 summarizes the average daily release rate of EE and NGMN from EVRA[®]. The mean amounts of EE released from the patch following application to the abdomen and buttock, averaged over the 7-day wear period, were 31.6 µg/day and 36.1 µg/day, respectively. Similarly, the mean amounts of NGMN released were 190 µg/day from the abdomen and 215 µg/day from the buttock. The overall mean amounts of EE and NGMN released from the patch when combining data from both the application sites were approximately 35 µg/day and 200 µg/day, respectively.

TOXICOLOGY

The toxicology program for EVRA[®] 17d-NGM/EE with 17d-NGM, NGM and EE alone or in combination includes acute toxicity, long-term toxicity, mutagenicity, reproductive and special toxicity studies. The majority of subchronic and chronic toxicity studies conducted in support of EVRA[®] are conducted with oral formulations of NGM/EE or NGM alone. Since 17d-NGM is the primary metabolite of NGM in most laboratory animal species, the pharmacological activity of 17d-NGM is equivalent to NGM, and the metabolism, distribution, and excretion of 17d-NGM in women following dermal administration of 17d-NGM and oral administration of NGM are comparable. Studies have also been conducted for the patch excipient, dermal lauryl lactate (LL).

Acute Toxicology

Table 2.4: Summary of the Acute Toxicity Studies Conducted with NGM and EE Alone and in Combination.

Species	Route	Test Article	Dose Levels (mg/kg)	Lethality	LD (mg/kg)	Summary of Observations
Mouse	Oral	NGM	5000	0/10 males 0/10 females	>5000	No clinical signs; necropsy – 3/10 with slight hyperemia of uterus.
Mouse	Oral	EE	5000	0/10 males 0/10 females	>5000	Depression, laboured breathing, males only; 10/10 – slightly enlarged uterus.
Mouse	Oral	NGM/EE 5:1 ratio	5000	0/10 males 1/10 females	>5000	Intermittent hyperactivity up to first 3 days; necropsy – enlarged periovarian sac in 7/10 and distended uterus in 3/10; fatty metamorphosis of liver in most females and some males.
Rat	Oral	NGM	5000	0/10 males 0/10 females	>5000	No clinical signs; small testes – 1/10.
Rat	Oral	NGM	6200	0/5 females	>6200	No clinical signs.
Rat	Oral	EE	3200 4000 5000	1/10 males 5/10 females 0/10 males 7/10 females 5/10 males 9/10 females	Males 5300 Females 3200	Dose-related depression, ataxia, and exophthalmos.
Rat	Oral	NGM/EE, 5:1 ratio	5000	0/10	>5000	No clinical signs; reduced size of testes, prostate and seminal vesicles; spermatogenic arrest in 2 males examined microscopically.
Dog	Oral	NGM	1000 2500 5000	0/2 0/2 0/2	>5000	No remarkable findings.
Dog	Oral	EE	1000 2500 5000	0/2 0/2 0/2	>5000	No remarkable findings.
Dog	i.v.	NGM/EE 7:1 ratio	16.3 0 (vehicle)	0/2 males 0/3 females 0/1 males 0/1 females	>16.3	Signs of ethanol intoxication (prostration, decreased response to stimuli and coordination, increased respiration); meiosis and salivation in females. Necropsy-prominence of corticomedullary junction of kidney and reddened areas at base of papillary muscle in each treated animal.

Long-term Toxicology

Table 2.5: Summary of the Repeated-dose Toxicity Studies Conducted with 17d-NGM/EE, NGM and EE.

Species	No./Sex/Group Duration	Test Article Ratio	Dosage (mg/kg/day)	Results
Rabbit	5 females 28 days	17d-NGM/EE (EVRA [®])	3/0.375; 4.5/0.56; 6/0.75 mg applied once weekly (10, 15, or 20 cm ² patch)	Mild signs of irritation at the patch site were unrelated to 17d-NGM/EE and caused in part by difficulty of patch removal. Some rabbits had decreased erythrocyte values and increases and decreases in serum liver enzyme concentrations, increased glucose, and decreased triglyceride and phosphorus. These effects were dose-related and considered secondary to hormonally-induced metabolic changes. Other dose-related hormonal changes included increased ovarian weights, smooth muscle hypertrophy in the vagina and cervix, and mammary gland development with secretory activity; uterine enlargement, multifocal decidualization (stromal thickening, increased vascularity of myometrium and endometrium, myometrial hypertrophy, glandular hyperplasia, and luminal dilation). Uterine epithelial, myometrial and endometrial necrosis were observed in one high dose rabbit and another had foci of decidualization in the spleen. Thymic lymphoid depletion and deposits of amyloid-like material in the spleen.
Rat	15 females 3 mo	NGM NA	0, 0.5, 1.0, 2.5, 10	There were no deaths and no remarkable findings observed in the clinical signs. There was a dose-related decrease in cholesterol levels. Dose-related decrease in uterine and ovary weights; increase in liver weight were seen at 10 mg/kg. There were no remarkable microscopic observations.
Rat	15 females 3 mo	NGM/EE 10:1	0, 0.55, 1.1, 2.75, 11.0	Decreased body weight gain in all treated groups. Lower erythrocyte counts, hemoglobin and hematocrit in all groups but within normal range. Dose-related decrease in cholesterol and weights of pituitary, thyroid, ovaries, and kidney. Adrenal, liver and heart weight were increased. There were no remarkable microscopic observations and no deaths.
Rat	110 females (Controls) 70 females (NGM/EE dosed groups) 24 mo	NGM/EE 5:1	0, 0.15, 0.6, 3.0	Lethality at 24 mo: Control 44/75; low 20/50; mid 17/50; high 24/50 (35 controls and 20 per treated group were sacrificed at 1 yr). Slight decrease in body weight gain in all groups; greater incidence of lenticular opacities in treated groups than controls. Slight decrease in red blood cell parameters in all groups; slight increase in neutrophils and decrease in lymphocytes. At high dose; decrease in cholesterol for all groups at 12 and 24 mo. Increased alkaline phosphatase in all treated groups at 12 mo. Dose-related decreases in uterine and ovarian weights and increases in adrenal weight in all treated groups and liver weight in mid- and high-dose groups at 24 mo. Increased incidence of liver cell hyperplasia/hypertrophy, telangiectasis and hematocyst formation; increased incidence of endometrial hyperplasia. Significantly increased incidence of mammary adenocarcinoma in high-dose group.
Rat	100 females in carboxymethyl-cellulose (CMC) control group; 50 females in treated groups and food only group 24 mo	NGM/EE 5:1 NG/EE 5:1 NG EE NGM	0, 0, 0.01875, 0.0375, 0.075, 0.15 0.0375, 0.075, 0.15 0.125 0.025 0.125	Lethality: Vehicle control 49/100; food control 27/50; low 22/50; ^a low-mid 28/50; mid 30/50; high 26/50. Minor transient body weight and food consumption changes early in study. Cumulative incidence of lenticular opacities comparable between controls and NGM/EE groups, time of onset shorter but not statistically different for NGM/EE compared to controls; slight decrease in hematocrit in high-dose NGM/EE; decreased cholesterol in high-dose NGM/EE and EE alone and increased triglycerides in all groups given progestin/EE combinations. Organ weight changes comparable to previous study; no significant differences in mammary tumours between control and treated groups.

Table 2.5: Summary of the Repeated-dose Toxicity Studies Conducted with 17d-NGM/EE, NGM and EE (cont'd)

Species	No./Sex/Group Duration	Test Article Ratio	Dosage (mg/kg/day)	Results
Dog	4 females 3 mo	NGM/EE 10:1	0, 0.28, 1.65, 5.5	Decreased incidence of estrus, enlarged vulva and mammary glands seen in all treated groups. Increased uterine weight and decreased ovarian weight in all treated groups. Increased leukocytes in mid- and high-dose groups. Increased liver and kidney weights in mid- and high-dose groups. Similar microscopic changes noted as reported for NGM alone. There were no deaths.
Dog	20 females (control, low- and mid- dose) 16 females (high dose) 24 mo	NGM/EE 5:1	0, 0.06, 0.15, 0.6 (cyclically)	Lethality: None. Observations similar to those for NGM. Decreased erythrocytes, hemoglobin, and hematocrit at high-dose; increased leukocytes related to neutrophils in high and mid-dose groups. Decreased ovarian and increased uterine weights seen in all treated groups. Dose-related genital and mammary changes as described above. Benign ductal adenoma in one high-dose dog.
Dog	15 females 84 mo	NGM/EE 5:1 during Mo 1 to 46 7:1 during Mo 47 to 84	0, 0.003, 0.03, 0.075 (cyclically) 0, 0.0057, 0.057, 0.1425 (cyclically)	Lethality: Control – 2; low – 1; mid – 4; high – 2. Enlarged uteri at high- and mid-dose; decreased incidence of estrus in mid- and high-dose, posterior polar lenticular opacities in one control, 4 low-, 3 mid-, and 3 high-dose dogs at 84 mo. Decreased erythrocyte parameters primarily at high dose; sporadic increases in serum glutamic pyruvic transaminase in all groups; decreased cholesterol and triglyceride levels and increased T ₄ in high-dose group. Ovarian suppression, cystic endometrial hyperplasia and hepatic nodular tissue. Benign smooth muscle and connective tissue tumours in one each of control, low- and mid-dose dogs and in five high-dose dogs; leiomyosarcoma in one high-dose dog.
Monkey	4 females 3 mo	NGM	0, 0.25, 1.5, 5.0	Decreased duration of menses at 5.0 mg/kg. Increased liver to body weight ratio at 0.25 and 5 mg/kg and increased heart:body weight ratios at 1.5 and 5 mg/kg. No changes seen under microscopy or in clinical pathology and there were no deaths.
Monkey	4 females 3 mo	NGM/EE 10:1	0, 0.275, 1.65, 5.5	Decreased duration of menses at 5.5 mg/kg. Increased absolute heart weight in 0.275 and 5.5 mg/kg. Stimulation of cervical mucus secretion and mammary gland activity at 5.5 mg/kg. Endometrial hyperplasia and sloughing; increased size and number of mammary gland acini. No changes seen in clinical pathology were observed and there were no deaths.
Monkey	4 females 6 mo	NGM EE NGM/EE 7:1	0, 0.005 0, 0.0007 0, 0.0057 0.0285 (cyclically)	There were neither deaths nor changes in clinical signs except effects on menstrual cycle. Menstruation clearly regulated by NGM alone and high-dose NGM/EE and to a lesser extent by low-dose NGM/EE. Decreased progesterone levels were observed in all treated groups except EE alone. Decreased ovarian weights in all treated groups with an increase in uterine weight in the EE group. No change was seen in liver microscopy in any group. Microscopy of reproductive organs showed all individuals in luteal phase, all groups except EE alone. One case of epithelial plaque seen in the high-dose NGM/EE group.
Monkey	20 females in the control, low- and mid- dose groups 16 females in the high-dose group 24 mo	NGM/EE 5:1	0, 0.06, 0.3, 0.6 (cyclically)	Lethality: Control – 1; 0.06 mg/kg – 0; 0.3 mg/kg – 4; 0.6 mg/kg – 1. Decreased body weight gain (0.6 mg/kg) and menses primarily during withdrawal (0.3 and 0.6 mg/kg). Increased degree of hypopigmented spots in the macula of treated groups. Transient decrease in erythrocyte parameters and platelets; increased triglyceride and decreased serum alkaline phosphatase; transient increase in prothrombin time and cholesterol. Decreased ovarian and uterine weights; ovarian, vaginal and mammary gland changes as described above; increased vacuolization of pigmented epithelium of retina; isolated cases of focal capsular sinusoidal dilation, congestion and/or hemorrhages in the liver.

Table 2.5: Summary of the Repeated-dose Toxicity Studies Conducted with 17d-NGM/EE, NGM and EE (cont'd)

Species	No./Sex/Group Duration	Test Article Duration	Dosage (mg/kg/day)	Results
Monkey	16 females 120 mo	NGM/EE 5:1 (Mo 1 to 48) 7:1 (Mo 49 to 120)	0, 0.003, 0.03, 0.15 (cyclically) 0, 0.0057, 0.057, 0.285 (cyclically)	Lethality: Control – 3; low – 1; mid – 0; high – 2. Transient decrease in body weight gain (mid- and high-dose) and menses primarily during withdrawal (mid- and high-dose); decreased number menses in latter part of study (control and high dose); dose-related sex skin changes; mammary nodules in 1 mid- and 1 high-dose monkey; increased incidence mammary secretion (mid- and high-dose); increased intensity of macular hypopigmentation in mid- and low-doses; no differences in visual acuity. Increased neutrophils, APTT, platelets (mid- and high-dose), dose-related increase in globulin, serum glutamic pyruvic transaminase, triglycerides and T3 and T4; decreased albumin, T3 uptake and cholesterol. Increased liver and pituitary weights (mid- and high-dose) and decreased ovarian weight (all groups); increased incidence and amount cervical mucus (mid- and high-dose); increased ovarian size (all doses); decreased thickness and keratinization of vaginal mucosa, ovarian atrophy associated with absence of corpora luteum; decreased maturing follicles, endometrial atrophy with stromal proliferation and/or decidualization, villous elongation and crypt dilation of cervical mucosa, mucosal atrophy and columnar metaplasia of vaginal mucosa, atrophy of oviducts and lobular hyperplasia of some mammary glands – mid- and high-dose; mucoepidermoid carcinoma of cervix and leiomyoma – one high dose; mammary gland carcinoma in situ and intraductal papilloma – one high dose; few other miscellaneous tumours.

Special Toxicity Studies

Table 2.6: Summary of Special Toxicity Studies with 17d-NGM/EE

Study type	No./Group/Species/Duration	Test Article/Dose/Route	Results
Primary Irritation	6 female rabbits 24-h exposure	6 mg 17d-NGM/ 0.75 mg EE patches, dermal	Rabbits observed for 72 h after patch removal. Slight to well-defined erythema observed. Patches and mineral oil (control) were mildly irritating.
Sensitization	10 female guinea pigs	17d-NGM/EE (estimated 3.0/0.49 mg disk form EVRA [®]) dermal	Induction: 6 h exposure, 3 times weekly over 18 days. Challenge: 14 days after induction with patch applied for 6 h. No indication of sensitization. Dinitrochlorobenzene (positive control) induced sensitization.

Mutagenicity

The mutagenic potentials of 17d-NGM, NGM, and NGM/EE have been extensively tested in bacterial and mammalian cell point mutation assays, chromosome aberration assay, in vivo sister chromatid exchange assay, and in vivo micronucleus assays. There were no indications of mutagenic activity in any of the assays with these compounds.

Carcinogenicity

An initial carcinogenicity study of NGM/EE (5:1 ratio) was conducted in rats at dosages of 0.15 to 3.0 mg/kg/day. A significant increase in the incidence of malignant mammary tumours, especially adenocarcinomas in the high-dose group, was observed. A second rat oral carcinogenicity study was conducted with lower dosages of NGM/EE (5:1 ratio) that ranged from 0.01875 to 0.15 mg/kg/day. In this study, the incidence of mammary tumours was comparable between the control and treated groups supporting a dose-response relationship.

In a 7-year dog study with NGM/EE, oral dosages of 0.003, 0.03, and 0.075 mg/kg/day (5:1 ratio) were given for 46 months followed by 0.0057, 0.057, and 0.1425 mg/kg/day (7:1 ratio) for the remaining half of the study. A cyclic dosing regimen was used. An increased incidence over controls in leiomyomas and leiomyosarcomas, tumours of smooth muscle origin, occurred in the high-dose group. Hepatic nodular hyperplasia also occurred in a few NGM/EE-dosed dogs.

A 10-year study of NGM/EE was conducted with rhesus monkeys. The monkeys were given oral dosages of 0.003, 0.03, and 0.15 mg/kg/day (5:1 ratio) for 4 years followed by 0.0057, 0.057, and 0.285 mg/kg/day (7:1 ratio) for the remaining 6 years of the study using a cyclic dosing regimen. Single occurrences of tumours were noted in the vagina and cervix of one high-dose monkey, the lobular and ductal mammary tissue of one high-dose monkey, and the urinary bladder of a mid-dose monkey. Other less noteworthy tumours occurred without predilection for treated groups.

Reproduction and Teratology

All studies conducted with NGM/EE use the oral formulation while the 17d-NGM study uses a subcutaneous route of administration.

Table 2.7: Summary of the Fertility and Reproductive Performance Studies Conducted with 17d-NGM and NGM/EE.

Species Test article/Ratio Dosage, Duration	Maternal Toxicity	Summary of Reproduction Parameters
Female Fertility		
Female rats, NGM/EE, 5:1 ratio 0.03, 0.05, 0.06, 0.0833, 0.120 mg/kg/day for 14 days pre-mating to termination; treated females mated to untreated males	Minimal body weight reduction at all doses during first pre-mating week; weight reduction during gestation due to increased resorptions and decreased litter size; dose-related decrease in fertility.	Dose-related decreased implantation and litter size and increased resorptions and stillbirths; decreased neonatal survival at ≥ 0.06 mg/kg; Similar findings but to lesser degree in F ₁ generation.
Embryo/Fetal Toxicity		
Rabbit, 17d-NGM 1, 2, 4, 6 mg/kg/day Gestation Days 7 to 19	Reduced food consumption at 6 mg/kg and thickened placentae firmly adhered to the uterine wall at 4 mg/kg and above.	Reduced ossification of pubis bone (fetal variation) was observed at 1 mg/kg and above. Decreased fetal body weights occurred at 2 mg/kg and above. Malformations were observed at higher dose levels, including paw hyperflexion at 4 mg/kg and above and cleft palate and paw hyperextension at 6 mg/kg. An increased number of resorptions and a decrease in live fetuses were also observed at the 6 mg/kg dose level.
Rats, NGM/EE 5:1 ratio 0.012, 0.06, 0.3 mg/kg/day on Days 6 through 15 gestation	Dose-related decreases in body weight and body weight gains.	Decreased implantations and increased resorptions at the high dose. Increase in incidence of wavy rib variations at the mid- and high-doses. No malformations were observed.
Rabbit, NGM/EE, 5:1 ratio 0.012, 0.060, 0.3 mg/kg/day on Days 7 through 19 of gestation	Mean body weight loss observed in all treated groups.	Resorptions in 65.5 and 100% of mothers in mid- and high-dose. No malformations or variations.
Peri-/Postnatal Toxicity		
Rats, NGM/EE 5:1 ratio, 0.03, 0.18, 0.3, 0.6 mg/kg/day on Day 15 of gestation through lactation	Some lactation insufficiency at the high dose.	Dose-related decrease in female fertility of F ₁ generation at ≥ 0.18 mg/kg/day; decreased offspring viability and pup weight at high dose; no significant effects on F ₂ generation.

Excipient: Dermal LL

Dermal LL is > 70% lauryl lactate and < 30% lauryl alcohol and lauryl lactoyl lactate. Lauryl lactate (LL) with empirical formula C₁₅H₃₀O₃ is an ester of lauryl alcohol and the alpha-hydroxy acid, lactic acid.

Lauryl lactate was not toxic when given orally to five male and five female rats at a dose of 5 mL/kg. The animals were observed over a 14-day period for pharmacological and toxicological activity.

Lauryl lactate was found to have no apparent potential to cause significant eye irritation when a 10% w/w solution was tested with six New Zealand white rabbits. In studies with face cream formulations containing 5% lauryl lactate, minimal or mild irritation was observed. Minimal eye irritation was caused by 15% lauryl lactate in propylene glycol in rabbits. Ocular irritation determined in the Eytex in vitro assay was reported as being minimal (0.1% in eye cream formulations) to moderate (3.2% in a face cream).

The potential of lauryl lactate to cause dermal irritation was investigated in one study in which six New Zealand white rabbits were dosed with 0.5 mL of a 10% w/w solution in propylene glycol. It was found that at 10%, lauryl lactate caused minimal irritation. Primary dermal irritation studies in rabbits of two cosmetic products containing lauryl lactate applied on an occlusive patch had caused minimal (1% concentration) or mild (5% concentration) irritation.

A contact sensitization assay was conducted in female guinea pigs. The animals were induced with 2 doses of lauryl lactate and challenged with 5% or 25% lauryl lactate. Signs of mild irritation were only observed in the high-dose group. This study suggests that lauryl lactate has little potential to cause contact sensitization.

The mutagenic potential of lauryl lactate has been extensively tested in bacterial and mammalian cell point mutation assays, and an *in vivo* micronucleus assay. There were no indications of mutagenic activity in any of the assays with lauryl lactate.

REFERENCES

1. Abdollahi M, Cushman M, Rosendaal FR. Obesity: risk of venous thrombosis and the interaction with coagulation factor levels and oral contraceptive use. *Thromb Haemost* 2003 Mar;89(3):493-498.
2. Alton KB, Hetyei NS, Shaw C, Patrick JE. Biotransformation of Norgestimate in Women. *Contraception* 1984;29(1):19-29.
3. Anderson FD. Selectivity and minimal androgenicity of norgestimate in monophasic and triphasic oral contraceptives. *Acta Obstet Gynecol Scand* 1992; 156 (Supplement):15-21.
4. Back DJ, Orme M.L'E. Pharmacokinetic drug interactions with oral contraceptives. *Clin Pharmacokinet* 1990;18:472-484.
5. Bernstein CN, Blanchard JF, Houston DS, et al. The incidence of deep venous thrombosis and pulmonary embolism among patients with inflammatory bowel disease: A population-based cohort study. *Thromb Haemost* 2001;85:430-434.
6. Boston Collaborative Drug Surveillance Program. Post-marketing study of ORTHO EVRA[®] and levonorgestrel oral contraceptives with 30 µg of EE in relation to non-fatal venous thromboembolism, ischemic stroke and myocardial infarction. EDMS-USRA-10436025.
7. Boston Collaborative Drug Surveillance Program. Report on the 2007 Update on Postmarketing Study of ORTHO EVRA[®] in Relation to Non-Fatal Venous Thromboembolism, Ischemic Stroke, Acute Myocardial Infarction, and Cerebral Vascular Sinus Thrombosis. May 2008. EDMS-USRA-10827326.
8. Boston Collaborative Drug Surveillance Program. Postmarketing Study of ORTHO EVRA[®] and Levonorgestrel-Containing Oral Hormonal Contraceptives with 30 µg of EE in Relation to Non-Fatal Venous Thromboembolism. Final Report. 03 April 09.
9. Brinton LA, Huggins GR, Lehman HF, Malli K, Savitz DA, Trapido E, Rosenthal J, Hoover R. Long-term use of oral contraceptives and risk of invasive cervical cancer. *Int J Cancer* 1986;38:339-344.
10. Cattaneo M, Vecchi M, Zighetti ML, et al. High prevalence of hyperhomocysteinemia in patients with inflammatory bowel disease: a pathogenic link with thromboembolic complications? *Thromb Haemost* 1998;80:542-545.
11. Chang ER, Pineau CA, Bernatsky S, Neville C, Clarke AE, Fortin PR. Risk for incident arterial or venous vascular events varies over the course of systemic lupus erythematosus. *J Rheumatol* 2006;33(9):1780-1784.
12. Chobanian et al. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension* 2003;42:1206-1252.

13. Christensen J, Petrenaite V, Atterman J, et al. Oral contraceptives induce lamotrigine metabolism: evidence from a double-blind, placebo-controlled trial. *Epilepsia* 2007;48(3):484-489.
14. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53,297 women with breast cancer and 100,239 women without breast cancer from 54 epidemiological studies. *Lancet* 1996;347:1713-1727.
15. Crawford P. Interactions between antiepileptic drugs and hormonal contraceptives. *CNS Drugs* 2002;16(40):263-272.
16. FDA Labelling Guidance for Combination Oral Contraceptives. August 1994.
17. Freilinger T, Riedel E, Holtmannspötter M, Dichgans M, Peters N. Ischemic stroke and peripheral arterial thromboembolism in a patient with Crohn's disease: A case presentation. *J Neurol Sci* 2007.
18. Gaffield ME, Curtis KM, Mohllajee AP and Peterson HB. Medical eligibility criteria for new contraceptive methods: combined hormonal patch, combined hormonal vaginal ring and the etonogestrel implant. *Contraception*. 2006;73:134-144.
19. Goldbaum GM, Kendrick JS, Hogelin GC, Gentry EM. The relative impact of smoking and oral contraceptive use on women in the United States. *JAMA* 1987;258:1339-1342.
20. Grimes DA, Shields WC. Family planning for obese women: challenges and opportunities. *Contraception* 2005 Jul;72(1):1-4.
21. Haque S, Bruce IN. Therapy insight: systemic lupus erythematosus as a risk factor for cardiovascular disease. *Nat Clin Pract Cardiovasc Med* 2005;2:423-430.
22. Hennekens CH, Speizer FE, Lipnick RJ, Rosner B, Bain C, Belanger C, Stampfer MJ, Willett W, Peto R. A case-control study of oral contraceptive use and breast cancer. *JNCI* 1984;72:39-42.
23. Henney JE. Risk of drug interactions with St. John's wort. *JAMA* 2000;283(13).
24. Holdich T, Whiteman P, Orme M, et al. Effect of lamotrigine on the pharmacology of the combined oral contraceptive pill. *Epilepsia* 1991;32(1):96.
25. i3 Drug Safety. The Risk of Venous Thromboembolism, Myocardial Infarction, and Ischemic Stroke Among Women Using the Transdermal Contraceptive System Compared to Women Using Norgestimate-Containing Oral Contraceptives With 35 µg Ethinyl Estradiol. Revised Final Report. January 2009.
26. i3 Drug Safety. The Risk of Venous Thromboembolism, Myocardial Infarction and Ischemic Stroke Among Women Using the Transdermal Contraceptive System Compared to Women Using Norgestimate-Containing Oral Contraceptives with 35 µg Ethinyl Estradiol. Final Report. 23 June 2009.

27. Janaud A, Rouffy J, Upmalis D, Dain M-P. A comparison study of lipid and androgen metabolism with triphasic oral contraceptive formulations containing norgestimate or levonorgestrel. *Acta Obstet Gynecol Scand* 1992; 156 (Supplement):34-38.
28. Janerich DT, Piper JM, Glebatis DM. Oral contraceptives and birth defects. *Am J Epidemiol* 1980; 112:73-79.
29. Jick SS, Kaye JA, Jick H. Further results on the risk of nonfatal venous thromboembolism in users of the contraceptive transdermal patch compared to users of oral contraceptives containing norgestimate and 35 µg of EE. *Contraception* 2007;76:4-7.
30. Jick SS, Kaye JA, Russmann S, Jick H. Risk of nonfatal venous thromboembolism in women using a contraceptive transdermal patch and oral contraceptives containing norgestimate and 35 micrograms of ethinyl estradiol. *Contraception*. 2006 Mar;73(3):223-8. Epub 2006 Jan 26.
31. Jick SS, Walker AM, Stergachis A, Jick H. Oral contraceptives and breast cancer. *Br J Cancer* 1989; 59:618-621.
32. Karjalainen M, Neovonen P, Backman J. In vitro inhibition of CYP1A2 by model inhibitors, anti-inflammatory analgesics and female sex steroids: predictability of in vivo interactions. *Basic & Clinical Pharmacology & Toxicology*. 2008;103,157-165
33. Kay CR, Hannaford PC. Breast cancer and the pill - A further report from the Royal College of General Practitioners' oral contraception study. *Br J Cancer* 1988;58:675-680.
34. Korhonen T, Turpeinen M, Tolonen A, Laine K, Pelkonen O. Identification of the cytochrome P450 enzymes involved in the in vitro biotransformation of lynestrenol and norethindrone. *J of Steroid Biochem & Mol etiology*. 2008;110:56-66.
35. Laine K, Yasar U, Widen J, Tybring G. A screening study on the liability of eight different female sex steroids to inhibit CYP2C9, 2C19 and 3A4 activities in human liver microsomes. *Pharmacology & Toxicology*.2003;93:77-81.
36. Lee LC, Spittell JA Jr, Sauer WG, et al. Hypercoagulability associated with chronic ulcerative colitis: changes in blood coagulation factors. *Gastroenterology* 1968;54:76-85.
37. Lewis M, Spitzer WO, Heinemann LAJ, MacRae KD, Bruppacher R, Thorogood M on behalf of Transnational Research Group on Oral Contraceptives and Health of Young Women. Third generation oral contraceptives and risk of myocardial infarction: an international case-control study. *Br Med J* 1996;312:88-90.
38. London RS, Chapdelaine A, et al. Comparative contraceptive efficacy and mechanism of action of the norgestimate-containing triphasic oral contraceptive. *Acta Obstet Gynecol Scand* 1992; 71, Suppl 156:9-14.

39. McPherson K, Drife JO. The pill and breast cancer: why the uncertainty? *Br Med J* 1986;293:709-710.
40. Meade TW, Greenberg G, Thompson SG. Progestogens and cardiovascular reactions associated with oral contraceptives and a comparison of the safety of 50- and 35-mcg oestrogen preparations. *Br Med J* 1980;280(6224):1157-1161.
41. Miller DR, Rosenberg L, Kaufman DW, Schottenfeld D, Stolley PD, Shapiro S. Breast cancer risk in relation to early oral contraceptive use. *Obstet Gynecol* 1986;68:863-868.
42. Mok CC. Accelerated atherosclerosis, arterial thromboembolism, and preventive strategies in systemic lupus erythematosus. *Scand J Rheumatol* 2006;35:85-95.
43. Molad R, Levin-Iaina N, Vaturi M, Sulkes J, Sagie A. Heart valve calcification in young patients with systemic lupus erythematosus: a window to premature atherosclerotic vascular morbidity and a risk factor for all-cause mortality. *Atherosclerosis* 2006;185:406-412.
44. Murphy PA, Kern SE, Stanczyk FZ, Westhoff CL. Interaction of St. John's Wort with oral contraceptives: effects on the pharmacokinetics of norethindrone and ethinyl estradiol, ovarian activity and breakthrough bleeding. *Contraception* 2005;71:402-408.
45. Nikpour M, Urowitz MB, Gladman DD. Premature atherosclerosis in systemic lupus erythematosus. *Rheum Dis Clin North Am* 2005;31:329-354.
46. Novotny DA, Rubin RJ, Slezak FA, Porter JA. Arterial thromboembolic complications of inflammatory bowel disease. *Dis Colon Rectum* 1992;35(2):193-196.
47. Odland V, Milsom I, Persson I, Victor A. Can changes in sex hormone binding globulin predict the risk of venous thromboembolism with combined oral contraceptive pills? A discussion based on recent recommendations from the European agency for evaluation of medicinal products regarding third generation oral contraceptive pills. *Acta Obstet Gynecol Scand* 2002;81(6):482-490.
48. Oral Contraceptives and the Risk of Cardiovascular Disease. *The Medical Letter* 1983;25 (640):69-70.
49. Orme ME, Back DJ. Interactions between oral contraceptive steroids and broad-spectrum antibiotics. *Clin Expl Derm* 1968;11:327-331.
50. Ouellet D, Hsu A, Qian J, Locke CS, Eason CJ, Cavanaugh JH, Leonard JM, Granneman GR. Effect of ritonavir on the pharmacokinetics of ethinyl oestradiol in healthy female volunteers. *Br J Clin Pharmacol* 1998;46(2):111-116.
51. Pacifici GM., Viani A, Rizzo G, Carrai M. Plasma Protein Binding of Ethinyloestradiol: Effect of Disease and Interaction with Drugs. *Int J Clin Pharmacol Ther Toxicol* 1989; 27(7): 362-65.
52. Palmer JR, Rosenberg L, Kaufman DW, Warshauer ME, Stolley P, Shapiro S. Oral Contraceptive Use and Liver Cancer. *Am J Epidemiol* 1989;130:878-882.

53. Paul C, Skegg DG, Spears GFS, Kaldor JM. Oral contraceptives and breast cancer: A national study. *Br Med J* 1986;293:723-725.
54. Phillips A, Demarest K, Hahn DW, Wong F, McGuire JL. Progestational and androgenic receptor binding affinities and in vivo activities of norgestimate and other progestins. *Contraception* 1989; 41(4):399-409.
55. Phillips A, Hahn DW, Klimek S, McGuire JL. A comparison of the potencies and activities of progestogens used in contraceptives. *Contraception* 1987;36(2): 181-192.
56. Pike MC, Henderson BE, Krailo MD, Duke A, Roy S. Breast cancer in young women and use of oral contraceptives: possible modifying effect of formulation and age at use. *Lancet* 1983; 2:926-929.
57. Progestogens and the Cardiovascular System. *Am J Obstet Gynecol* 1982;142 (B Part 2):717-816.
58. Royal College of General Practitioners: Oral Contraceptives, venous thrombosis, and varicose veins. *J Royal Coll Gen Pract* 1978;28:393-399.
59. Savolainen E, Saskela E, Saxen L. Teratogenic hazards of oral contraceptives analyzed in a national malformation register. *Am J Obstet Gynecol* 1981; 140:521-524.
60. Schlesselman J, Stadel BV, Murray P, Lai S. Breast cancer in relation to early use of oral contraceptives. *JAMA* 1988;259:1828-1833.
61. Schlesselman JJ. Cancer of the breast and reproductive tract in relation to use of oral contraceptives. *Contraception* 1989;40:1-38.
62. Shenfield GM. Oral Contraceptives. Are drug interactions of clinical significance? *Drug Saf* 1993 Jul;9(1):21-37.
63. Sidhu J, Job S, Singh S, et al. The pharmacokinetic and pharmacodynamic consequences of the co-administration of lamotrigine and combined oral contraceptive in healthy female subjects. *Br J Clin Pharmacol* 2005;61(2):191-199.
64. Sidney S, Petitti DB, Soff GA, Cundiff DL, Tolan KK, Quesenberry CP Jr. Venous thromboembolic disease in users of low-estrogen combined estrogen-progestin oral contraceptives. *Contraception* 2004 Jul;70(1):3-10.
65. Skolnick JL, Stoler BS, Katz DG, Anderson WH. Rifampicin, oral contraceptives and pregnancy. *J Am Med Assoc* 1976;236:1382.
66. Slone D, Shapiro S, Kaufman DW, Rosenberg L, Miettinen OS, Stolley PD. Risk of myocardial infarction in relation to current and discontinued use of oral contraceptives. *N Engl J Med* 1981;305:420-424.
67. Solem CA, Loftus EV Jr, Tremaine WJ, Sandborn WJ. Venous thromboembolism in inflammatory bowel disease. *Am J Gastroenterol* 2003;99:97-101.

68. Stadel BV, Lai S, Schlesselman JJ, Murray P. Oral contraceptives and premenopausal breast cancer in nulliparous women. *Contraception* 1988;38: 287-299.
69. Stein PD, Beemath A, Olson RE. Obesity as a risk factor in venous thromboembolism. *Am J Med* 2005 Sep;118(9):978-980.
70. Stein PD, Goldman J. Obesity and thromboembolic disease. *Clin Chest Med*. 2009;30(3):489-493.
71. Talbot RW, Heppell J, Dozois RR, Beart RW Jr. Vascular complications of inflammatory bowel disease. *Mayo Clin Proc* 1986;61(2):140-145.
72. The Cancer and Steroid Hormone Study of the Centers for Disease Control and the National Institute of Child Health and Human Development: Oral contraceptive use and the risk of breast cancer. *N Engl J Med* 1986;315:405-411.
73. The UK National Case-Control Study Group. Oral contraceptive use and breast cancer risk in young women. *Lancet* 1989;1:973-982.
74. Trussel J. Contraceptive efficacy. In Hatcher RA, Trussel J, Stewart F, Cates W, Stewart GK, Kowal D, Guest F, *Contraceptive Technology: Seventeenth Revised Edition*. New York NY: Irvington Publishers, 1998, in press.
75. Van Giesbergen PLM, Halabi A, Dingemase J. Pharmacokinetic Interaction between bosentan and the oral contraceptives norethisterone and ethinyl estradiol. *Int J Clin Pharmacol* 2006;44:113-118.
76. Vessey M, Painter R, Yeates D. Oral contraception and epilepsy: findings in a large cohort study. *Contraception* 2002; 66:77-79.
77. Vessey MP, Smith MA, Yeates D. Return of fertility after discontinuation of oral contraceptives: influence of age and parity. *Brit J Fam Plan* 1986;11:120-124.
78. Ward MM. Premature morbidity from cardiovascular and cerebrovascular diseases in women with systemic lupus erythematosus. *Arthritis Rheum* 1999;42:338-346.
79. White T, Jain JK, Stanczyk FZ. Effect of oral versus transdermal steroidal contraceptives on androgenic markers. *Am J Obstet Gynecol* 2005;192(6): 2055-2059.
80. WHO Collaborative Study of Neoplasia and Steroid Contraceptives: Invasive cervical cancer and combined oral contraceptives. *Br Med J* 1985;290:961-965.
81. Zhang H, Cui D, Wang B, Han YH, BalimaneP, Yang Z, Sinz M, Rogrigues AD. Pharmacokinetic drug interactions involving 17 α -ethinyl estradiol. A new look to an old drug. *Clin Pharmacokinet* 2007;46(2):133-157.

PART III: CONSUMER INFORMATION

PrEVRA[®]*
 norelgestromin and ethinyl estradiol
 Transdermal System

This leaflet is Part III of a three-part "Product Monograph" published when EVRA[®] was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about EVRA[®]. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

- prevention of pregnancy

What it does:

EVRA[®] is a hormonal contraceptive patch that contains two female sex hormones (norelgestromin and ethinyl estradiol). The EVRA[®] patch sticks to the skin and continuously releases the hormones through the skin and into the blood stream. The EVRA[®] patch produces a hormone exposure pattern that is different from that of the birth control pill. Talk to your health professional about how this relates to your use of EVRA[®].

Hormonal contraceptives, including EVRA[®], have been shown to be highly effective in preventing pregnancy when taken as prescribed by your doctor. Pregnancy is always more risky than taking hormonal contraceptives, except in smokers older than age 35.

Hormonal contraceptives like EVRA[®] work in two ways:

1. they inhibit the monthly release of an egg by the ovaries
2. they change the mucus produced by the cervix. This slows the movement of the sperm through the mucus and through the uterus (womb).

Effectiveness of Hormonal Contraceptive Methods:

When EVRA[®] is used correctly, the chance of becoming pregnant is comparable to that of combination birth control pills, which are more than 99 percent effective in preventing pregnancy (when the pills are **taken as directed**, and the amount of estrogen is 20 µg or more).

A 99 percent effectiveness rate means that if 100 women used the contraceptive patch for one year, one woman in the group would get pregnant.

The chance of becoming pregnant increases with incorrect use.

Other Ways to Prevent Pregnancy:

Other methods of birth control are available to you. They are usually less effective than hormonal contraceptive methods such as the birth control pill or EVRA[®]. When used properly, however, other methods of birth control are effective enough for many women.

The following table gives reported pregnancy rates for various forms of birth control, including no birth control. The reported rates represent the number of women out of 100 who would become pregnant in one year.

Reported Pregnancies per 100 Women per Year:

Combination pill	less than 1 to 2
Intrauterine device (IUD)	less than 1 to 6
Condom with spermicidal foam or gel	1 to 6
Mini-pill	3 to 6
Condom	2 to 12
Diaphragm with spermicidal foam or gel	3 to 18
Spermicide	3 to 21
Sponge with spermicide	3 to 28
Cervical cap with spermicide	5 to 18
Periodic abstinence (rhythm), all types	2 to 20
No birth control	60 to 85

Pregnancy rates vary widely because people differ in how carefully and regularly they use each method. (This does not apply to IUDs since they are implanted in the uterus.) Regular users may achieve pregnancy rates in the lower ranges. Others may expect pregnancy rates more in the middle ranges.

The effective use of birth control methods other than the contraceptive patch may require more effort than replacing a single patch every week for three out of four weeks. It is an effort that many couples undertake successfully.

When it should not be used:

EVRA[®] is not suitable for every woman. In a small number of women, serious side effects may occur. Your doctor can advise you if you have any conditions that would pose a risk to you. The use of EVRA[®] should always be supervised by your doctor.

You should not use EVRA[®] if you have or have had any of the following conditions:

- blood clots in the legs, lungs, eyes, or elsewhere, or thrombophlebitis (inflammation of the veins)
- stroke, heart attack, or coronary artery disease (e.g. angina pectoris)
- disease of the heart valves with complications
- severe high blood pressure
- diabetes with complications
- known abnormalities of the blood clotting system that increase your risk for developing blood clots
- very high blood cholesterol or triglyceride levels
- heavy smoking (>15 cigarettes per day) and over age 35
- migraine headache
- you are scheduled for major surgery
- prolonged bed rest
- jaundice (yellowing of the eyes or skin), liver disease or liver tumour
- known or suspected cancer of the breast or uterus (womb) or other estrogen-dependent cancer
- unusual vaginal bleeding without a known reason
- loss of vision due to blood vessel disease of the eye
- you are pregnant or suspect you may be pregnant
- allergy (hypersensitivity) to ethinyl estradiol, norelgestromin or to any of the other ingredients in EVRA[®] (see **What the medicinal ingredients are** and **What the nonmedicinal ingredients are**)

What the medicinal ingredients are:

norelgestromin; ethinyl estradiol

What the nonmedicinal ingredients are:

Backing layer: polyethylene outer layer and a polyester inner layer.

Middle layer: polyisobutylene/polybutene adhesive, crospovidone, non-woven polyester fabric, lauryl lactate.

Release liner: polyethylene terephthalate film with polydimethylsiloxane coating on one side.

The EVRA[®] patch does not contain any metal components.

What dosage forms it comes in:

The EVRA[®] transdermal system is available as a thin, beige plastic patch, that sticks to the skin, containing 6.0 mg norelgestromin and 0.60 mg ethinyl estradiol. The sticky part of the patch contains the hormones norelgestromin and ethinyl estradiol, which are released continuously through the skin and into the bloodstream. The EVRA[®] transdermal system releases approximately 35 micrograms of ethinyl estradiol and 200 micrograms of norelgestromin every 24 hours.

The EVRA[®] transdermal system is available in cartons containing 3 systems each. Each system is sealed within a protective pouch and stamped "EVRA[™]."

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

The results of a recent study indicate that women using the ORTHO EVRA[®] contraceptive patch (the formulation of EVRA[®] marketed in the United States) had an increased risk of blood clots in the legs and lungs compared to women using an oral contraceptive. A different study indicated no difference in the risk of blood clots in the legs and lungs in women using ORTHO EVRA[®] compared to women using an oral contraceptive. Women who are obese are at particularly high risk of blood clots.

Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels. This risk increases with age and becomes significant in hormonal contraceptive users older than 35 years of age. Women should not smoke.

The contraceptive patch DOES NOT PROTECT against sexually transmitted diseases (STDs), including HIV/AIDS.

For protection against STDs, it is advisable to use latex condoms IN COMBINATION WITH the contraceptive patch.

Updated Information on risk of blood clots:

There have now been several studies conducted that have assessed the risk of blood clots in the legs and lungs in women using ORTHO EVRA[®] compared to women using oral contraceptives. These studies reported results ranging from no increase in risk of blood clots to an approximate doubling of risk of blood clots in women using ORTHO EVRA[®].

BEFORE you use EVRA[®] talk to your doctor or pharmacist if you:

- smoke
- weigh more than 90 kg (198 lbs)
- have a history of breast disease (e.g. breast lumps) or a family history of breast cancer
- have high blood pressure
- have high cholesterol
- have diabetes
- have heart or kidney disease
- have a history of seizures/epilepsy
- have a history of depression
- have a history of liver disease or jaundice
- wear contact lenses
- have uterine fibroids (benign tumours of the uterus)
- may be pregnant or are breast-feeding

You should also inform your doctor about a family history of blood clots, heart attacks or strokes.

While wearing EVRA[®] you should not expose the patch area to **sources of heat** such as heating pads, electric blankets, heated waterbeds, heat lamps, saunas and hot tubs, intensive sunbathing, etc., as this may increase the drug's ability to go through the skin and therefore result in too much exposure to the estrogen in the patch. This may also occur if you develop a fever. Contact your doctor for advice if you develop a fever.

If you see a different doctor, inform him or her that you are using the EVRA[®] contraceptive patch.

Tell your doctor if you are scheduled for any laboratory tests since certain blood tests may be affected by hormonal contraceptives.

Also tell your doctor if you are scheduled for **MAJOR** surgery. You should consult your doctor about stopping the use of the contraceptive patch four weeks before surgery and not using the contraceptive patch for a time period after surgery or during bed rest.

EVRA[®] should be used only under the supervision of a doctor, with regular follow-up to identify side effects associated with its use. Your visits may include a blood pressure check, a breast exam, an abdominal exam and a pelvic exam, including a Pap smear. Visit your doctor three months or sooner after the initial examination. Afterward, visit your doctor at least once a year. Use EVRA[®] only on the advice of your doctor and carefully follow all directions given to you. You must use the contraceptive patch exactly as prescribed. Otherwise, you may become pregnant.

If you and your doctor decide that, for you, the benefits of the EVRA[®] contraceptive patch outweigh the risks, you should be aware of the following:

THE RISKS OF USING EVRA[®]

1. Circulatory disorders (including blood clots in legs, lungs, heart, eyes or brain)

There have been cases of heart attack, stroke and blood clots in the legs, lungs and eyes in women using EVRA[®]. Blood clots are the most common serious side effects of hormonal contraceptives, including the contraceptive patch. The risk of developing blood clots is especially high during the first year a woman ever uses a hormonal contraceptive. Clots can occur in many parts of the body.

Be alert for the following symptoms and signs of serious adverse effects. Call your doctor immediately if they occur:

- sharp pain in the chest, coughing blood, or sudden shortness of breath. These symptoms could indicate a possible blood clot in the lung.
- pain and/or swelling in the calf. These symptoms could indicate a possible blood clot in the leg.
- crushing chest pain or heaviness. These symptoms could indicate a possible heart attack.
- sudden severe or worsening headache or vomiting, dizziness or fainting, disturbances of vision or speech, or weakness or numbness in an arm or leg. These symptoms could indicate a possible stroke.
- sudden partial or complete loss of vision. This symptom could indicate a blood clot in the eye.

Any of these conditions can cause death or disability. Clots also occur rarely in the blood vessels of the eye, resulting in blindness or impaired vision, or in a blood vessel leading to an arm or leg, resulting in damage to or loss of a limb.

Women who use hormonal contraceptives have a higher incidence of blood clots. The risk of clotting seems to increase with higher estrogen doses. **It is important, therefore, to use as low a dosage of estrogen as possible.**

2. Breast cancer

The most significant risk factors for breast cancer are increasing age and a strong history of breast cancer in the family (mother or sister). Other established risk factors include obesity, never having children, and having your first full-term pregnancy at a late age.

Some women who use hormonal contraceptives may be at increased risk of developing breast cancer before menopause, which occurs around age 50. These women may be long-term users of hormonal contraceptives (more than eight years) or women who start using hormonal contraceptives at an early age. In a few women, the use of hormonal contraceptives may accelerate the growth of an existing but undiagnosed breast cancer. Early diagnosis, however, can reduce the effect of breast cancer on a woman's life expectancy. The potential risks related to hormonal contraceptives seem to be small, however.

A yearly breast examination by a health care professional is recommended for all women.

ASK YOUR DOCTOR FOR ADVICE AND INSTRUCTIONS ON REGULAR SELF-EXAMINATION OF YOUR BREASTS.

3. Cervical cancer

Some studies have found an increase 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.

4. Liver tumours

The short- and long-term use of birth control pills also has been linked with the growth of liver tumours. Such tumours are **extremely** rare. Since the contraceptive patch contains hormones similar to those in birth control pills, this association may also exist with the contraceptive patch.

Contact your doctor immediately if you experience severe pain or a lump in the abdomen.

5. Gallbladder disease

Users of hormonal contraceptives, including the contraceptive patch, have a greater risk of developing gallbladder disease requiring surgery within the first year of use. The risk may double after four or five years of use.

6. Seizures (convulsions)

There have been rare cases of seizures (convulsions) in women using EVRA[®]. It is important to contact your doctor immediately if you experience a new seizure or worsening of a previous seizure disorder (e.g. epilepsy).

7. Body weight >90 kg (198 lbs)

The effectiveness of EVRA[®] may be reduced in women weighing more than 90 kg (198 lbs). If you weigh more than 90 kg (198 lbs) you should talk to your doctor to determine which method of birth control may be right for you.

8. Use in pregnancy

Hormonal contraceptives, including the EVRA[®] contraceptive patch, should not be taken if you think you are pregnant. They will not prevent the pregnancy from continuing. There is no evidence, however, that hormonal contraceptives can damage a developing child. You should check with your doctor about risks to your unborn child from any medication taken during pregnancy.

9. Use after pregnancy, miscarriage or an abortion

Your doctor will advise you of the appropriate time to start the use of EVRA[®] after childbirth, miscarriage, or therapeutic abortion.

10. Pregnancy after stopping EVRA[®]

You will have a menstrual period when you stop using EVRA[®]. There may be some delay in becoming pregnant after you stop using the contraceptive patch, especially if you had irregular menstrual cycles before you used the contraceptive patch.

There is no evidence that the use of hormonal contraceptives immediately before a pregnancy will adversely affect a baby's development. When a woman stops taking the contraceptive patch to become pregnant, however, her doctor may recommend a different form of contraception until she has a period on her own. In this way the pregnancy can be more accurately dated.

11. Use while breast-feeding

If you are breast-feeding, consult your doctor before starting the contraceptive patch. 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 hormonal contraceptives are not resumed until nursing is established, however, the quantity and quality of breast milk does not seem to be affected. You should use a barrier method of contraception since breast-feeding only provides partial protection from becoming pregnant and this partial protection decreases significantly as you breast-feed for longer periods of time. It is recommended that you do not use combination hormonal contraceptives while breast-feeding. You should consider starting the contraceptive patch only after you have weaned your child completely.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist if you are taking, or have been taking, any other medicines, even medicines you buy without a prescription, and herbal products. Certain drugs may interact with hormonal contraceptives, including the contraceptive patch, to make them less effective in preventing pregnancy or cause unexpected bleeding (spotting or breakthrough bleeding). EVRA[®] may also interfere with how other drugs work. Talk to your doctor or pharmacist about when you may need to use an additional back-up, non-hormonal method of birth control (such as condoms, foam or sponge).

Drugs that may interact with EVRA[®] include:

- drugs used for the treatment of epilepsy (e.g. carbamazepine, oxcarbazepine, ethosuximide, phenobarbital, phenytoin, primidone, topiramate, lamotrigine)
- antibiotics (e.g. penicillins, metronidazole, cotrimoxazole, nitrofurantoin, sulfonamides, rifampin).

Tetracycline has been shown not to interact with EVRA[®].

- certain drugs used in the treatment of HIV or AIDS (e.g. indinavir, ritonavir)
- antifungals (e.g. griseofulvin, itraconazole, ketoconazole, voriconazole, fluconazole)
- salicyclic acid
- anticoagulants (blood thinners)
- the herbal remedy St. John's wort (pregnancies and breakthrough bleeding have been reported by users of combined oral contraceptives who also used St. John's wort)
- blood pressure medications
- bronchodilators (drugs used for the treatment of asthma, chronic obstructive pulmonary disease, chronic bronchitis e.g. theophylline)
- diabetic medications
- prednisone, prednisolone
- lipid lowering drugs (e.g. atorvastatin, rosuvastatin)
- sedatives (e.g. benzodiazepines, barbiturates, chloral hydrate, glutethimide, meprobamate)
- stimulants (e.g. modafinil)
- antacids
- acetaminophen
- bosentan
- grapefruit juice
- vitamin C
- vitamin B₁₂
- folic acid

This is not a complete list of possible drug interactions with EVRA[®]. Talk to your doctor for more information about drug interactions.

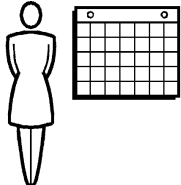

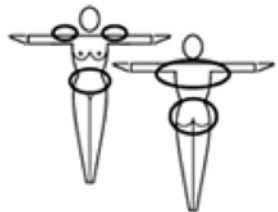
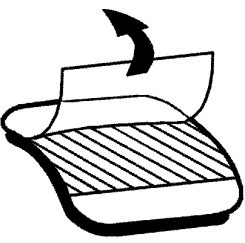
PROPER USE OF THIS MEDICATION



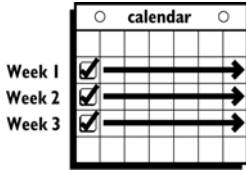

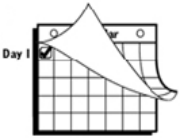
How to Use EVRA[®]

The transdermal contraceptive system 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 system uses a 28-day, four-week cycle. You will apply a new patch each week for three weeks - 21 total days. You will not apply a patch during week four. You will have your period this week. This means that every new patch will be applied on the same day of the week. This 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 will wear only one patch at a time.

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

Save these instructions.

<p>1.</p> 	<p>If this is the first time you are using the birth control patch, wait until the day you get your menstrual period. <i>The day you apply your first patch will be Day 1. Your "Patch Change Day" will be on this day every week.</i></p>
<p>2.</p> <p>CHOOSE ONE OPTION:</p>  <p><input type="checkbox"/> First Day Start or <input type="checkbox"/> Sunday Start</p>	<p>For First Day start: apply your first patch during the first 24 hours of your period.</p> <p><i>OR</i></p> <ul style="list-style-type: none"> • For Sunday start: apply your first patch on the first Sunday after your period starts. <i>For both a First Day start and a Sunday start, you must use back-up contraception for the first week of your first cycle only.</i>
<p>3.</p> 	<p>Choose a place on your body to apply the patch.</p> <p>Put the patch on your buttock, abdomen, upper outer arm or upper torso, in a place where it won't be rubbed by tight clothing. Never put the patch on your breasts. <i>To avoid irritation, apply each new patch to a different place on your skin.</i></p>
<p>4.</p> 	<p>Using your fingers, open the foil pouch by tearing it along the edge. Firmly grasp a corner of the patch and gently remove it from the foil pouch. <i>Sometimes patches can stick to the inside of the pouch - be careful not to accidentally remove the clear liner as you remove the patch.</i> Then, as indicated above, peel away half of the clear protective liner. Avoid touching the sticky surface.</p>

<p>5.</p> 	<p>Position the patch on your skin and then remove the other half of the liner. Press down firmly on the patch with the palm of your hand for 10 seconds, making sure that the edges stick well. <i>Check your patch every day to make sure it is sticking.</i></p>
<p>6.</p> 	<p>Wear the patch for 7 days (one week). On the “Patch Change Day,” Day 8, remove the used patch. Apply a new patch immediately. <i>The used patch still contains some medicine – throw it away by carefully folding it in half so that it sticks to itself.</i></p>
<p>7.</p> 	<p>You will apply a new patch on week two (Day 8) and again on week three (Day 15), on your “Patch Change Day”. <i>To avoid irritation, do not apply the new patch to the exact same place on your skin.</i></p>
<p>8.</p> 	<p>Do not wear a patch on week four (Day 22 through Day 28). You should have your period during this week.</p>
<p>9.</p> 	<p>Begin your next four-week cycle by applying a new patch on your normal “Patch Change Day”, the day after Day 28 - no matter when your period begins or ends.</p>

If your patch has become loose or has fallen off

- **for less than one day**, try to re-apply it or apply a new patch immediately. No back-up contraception is needed. *Your “Patch Change Day” will remain the same.*

- **for more than one day, OR if you are not sure for how long, YOU MAY BECOME PREGNANT.** Start a new **four-week cycle immediately** by putting on a new patch. *You now have a new Day 1 and a new “Patch Change Day”. You must use back-up contraception for the first week of your new cycle.*
- do not try to re-apply a patch 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 has fallen off before. No tapes or wraps should be used to keep the patch in place. If you cannot re-apply a patch, apply a new patch immediately.

Overdose

Overdose may cause nausea and vomiting. Vaginal bleeding may occur in women. In case of suspected overdose, remove all patches and contact your doctor, your hospital or your local Poison Control Centre.

If you forget to change your patch

- **at the start of any patch cycle,**
Week one (Day 1): if you forget to apply your patch, **you may 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 may 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 may become pregnant** - apply the first patch of your new cycle as soon as you remember. *You now have a new “Patch Change Day” and a new Day 1. You must use back-up contraception for the first week of your new cycle.*
- **you should never have the patch off for more than seven days.**

Other Information:

- Always apply your patch to clean, dry skin. Avoid skin that is red, irritated or cut. Do not use creams, oils, powder or makeup on your skin where you will put a patch or near a patch you are wearing. It may cause the patch to become loose.
- Do not cut, damage or alter the patch in any way.
- If patch use results in uncomfortable irritation, a new patch may be applied to a new location until the next change day. Only one patch should be worn at a time.
- Some medicines may change the way the transdermal contraceptive system works. If you are taking any medication, you must talk to your health professional BEFORE you use the patch. *You may need to use back-up contraception.*

Disposal of EVRA®:

Used patches still contain some active hormones. Throw away the used patch by carefully folding in half so the adhesive side sticks to itself, place the folded patch in a sturdy container, preferably with a child-resistant cap, and dispose of in the garbage out of the reach of children and pets. Remaining active hormonal ingredients of the patch may have harmful effects if they reach the aquatic environment. Used patches should not be flushed down the toilet or placed in liquid waste disposal systems.

When You Switch From the Pill to EVRA®:

If you are switching from the pill to the contraceptive patch, wait until you get your menstrual period. If you do not get your period within five days of taking the last active pill, check with your doctor or clinic before starting EVRA®.

Important Points to Remember:

1. It is important to use the contraceptive patch exactly as directed in this leaflet. Dosing errors increase your chances of becoming pregnant. This includes starting your contraceptive cycle late or missing your scheduled Change Day.
2. 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.
3. 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 sexual intercourse during this time, you may be at risk of pregnancy. Check with your doctor or clinic.

4. **If you are not sure what to do about dosing errors:**
 - Use a **back-up method** of birth control any time you have sex.
 - Contact your health professional for instructions.
5. Do not skip patches even if you do not have sex very often.
6. **Many women have spotting or light bleeding, breast tenderness or may feel sick to their stomach during the first three cycles.** 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 doctor or clinic.
7. **Mistakes in using your patches can also cause spotting or light bleeding.**
8. Unlike the pill, the amount of drug you get from the EVRA® patch should not be affected by **vomiting or diarrhea.**
9. **If you want to move your "Patch Change Day"** to a different day of the week, contact your doctor.
10. **Be sure to have ready at all times:**
 - **A non-hormonal birth control** (such as condoms, foam, or sponge) to use as a back-up in case of dosing errors.
11. **If you have trouble remembering to change your contraceptive patch,** talk to your doctor or clinic about how to make patch-changing easier or about using another method of birth control.
12. **There is no need to stop taking the EVRA® contraceptive patch for a rest period.**
13. For patch replacement, see **How to Use EVRA®.**

If you have any questions or are unsure about the information in this leaflet, call your doctor or clinic.

Missed Periods:

There may be times when you may not menstruate regularly during your patch-free week. If you have used your contraceptive patches correctly and miss one menstrual period, continue using your contraceptive patches for the next cycle, but be sure to inform your health professional before doing so. If you have not used your contraceptive patches as instructed and missed a menstrual period, or if you missed two consecutive menstrual periods, you may be pregnant. Check with your health professional immediately to determine whether you are pregnant. Stop using the contraceptive patch and use a non-hormonal method of birth control until you are sure you are not pregnant.

Pregnancy Due to Contraceptive Patch 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 occurs, the risk to the fetus is minimal.

Non-contraceptive Benefits of Hormonal Contraceptives:

Several health advantages have been linked to the use of hormonal contraceptives:

- Reduction in the incidence of cancer of the uterus and ovaries.
- Reduction in the likelihood of developing benign (non-cancerous) breast disease and ovarian cysts.
- Less menstrual blood loss and more regular cycles. The risk of developing iron-deficiency anemia is thus reduced.
- There may be a decrease in painful menstruation and premenstrual syndrome (PMS).
- Acne, excessive hair growth and male hormone-related disorders may also be improved.
- Ectopic (tubal) pregnancy may occur less frequently.
- Acute pelvic inflammatory disease may occur less frequently.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The following side effects have been observed in studies of women taking EVRA®:

Skin irritation

Skin irritation, redness or rash may occur at the site of application. If this occurs, a new patch may be applied to a new location until the next Change Day.

Vaginal bleeding

Unexpected vaginal bleeding or spotting usually disappears after the first few cycles of contraceptive patch use and is not usually a reason to stop using the contraceptive patch. If the bleeding persists for more than one cycle or lasts for more than a few days, talk to your doctor.

Other

Very Common: breast discomfort, nausea, headache, painful menstrual periods

Common (frequent): abdominal pain/discomfort, acne, allergy, back pain, bleeding between periods, breast enlargement, breast pain, bronchitis, coughing, diarrhea, dizziness, fatigue, fever, flatulence, flu-like symptoms, genital itching, heavier menstrual flow, inflammation, migraine, muscle pain, rash, runny or stuffy nose, sore throat, urinary tract infection, vaginal discharge, vaginal discomfort/infection, vomiting, weight gain

Uncommon: blood clots in the lung

The following additional symptoms have been reported in women taking hormonal contraceptives in general:

Abdominal cramps/bloating

- Breast changes (tenderness, enlargement)
- Change in appetite
- Change in menstrual flow, spotting, amenorrhea (lack of menstrual period)
- Change in skin pigmentation
- Depression
- Excessive hair growth or loss of scalp hair
- Fluid retention/swelling of the extremities
- Increase in size of uterine fibroids (benign growths in the uterus/womb)
- Jaundice (yellowing of the skin or eyes)
- Nervousness
- Weight change (increase or decrease)

Infrequently, there is a need to change contact lens prescription or an inability to use contact lenses.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom/effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Un-common	Abdominal pain, nausea or vomiting or lump in the abdomen		✓	
	Breast lump		✓	
	Convulsions or seizure			✓
	Crushing chest pain or heaviness			✓
	Pain or swelling in the leg			✓
	Persistent sad mood			✓
	Sharp pain in the chest, coughing blood, or sudden shortness of breath			✓
	Sudden partial or complete loss of vision or double vision			✓

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Un-common	Sudden severe headache or worsening of headache, vomiting, dizziness, fainting, disturbance of vision or speech, or weakness or numbness in the face, arm or leg			✓
	Unexpected vaginal bleeding		✓	
	Unusual swelling of the extremities		✓	
	Yellowing of the skin or eyes (jaundice)			✓

This is not a complete list of side effects. For any unexpected effects while taking EVRA[®], contact your doctor or pharmacist.

HOW TO STORE IT

Store between 15°C - 30°C. Do not refrigerate or freeze. Store patches in their protective pouches inside the original box. Apply patch immediately upon removal from its packaging.

Keep new and used transdermal systems out of the reach of children and pets.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report online at www.healthcanada.gc.ca/medeffect

Call toll-free at 1-866-234-2345

Complete a Canada Vigilance Reporting Form and:

- Fax toll-free to 1-866-678-6789, or
- Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701D
Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on www.healthcanada.gc.ca/medeffect.

NOTE: *Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.*

MORE INFORMATION

This document plus the full Product Monograph, prepared for health professionals, can be found at:
<http://www.janssen.ca>
or by contacting the sponsor, Janssen Inc., at:
1-800-567-3331

This leaflet was prepared by
Janssen Inc.
Toronto, Ontario M3C 1L9

Last revised: January 2011