Approval Package for:

APPLICATION NUMBER:

21-180/S-008

Trade Name: Ortho Evra

Generic Name: norelgestromin/ethinyl estradiol transdermal system

Sponsor: Ortho-McNeil Pharmaceutical, Inc.

Approval Date: February 04, 2004

Indications: For the prevention of pregnancy.
Reviews / Information Included in this NDA Review.

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APPROVAL LETTER
Ortho-McNeil Pharmaceutical, Inc.
Attention: Patricia Capaccione, R.Ph.
Senior Associate, Regulatory Affairs
920 Route 202 South, P.O. Box 300
Raritan, New Jersey 08869-0602

Dear Ms. Capaccione:

Please refer to your supplemental new drug application dated October 7, 2003, received October 8, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ortho Evra® (norelgestromin and ethinyl estradiol transdermal system).

This supplemental new drug application provides for specific disposal instructions for the patient of the used transdermal contraceptive system.

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, this supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted labeling dated October 7, 2003.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).
If you have any questions, please call Karen Anderson, N.P., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
Daniel A. Shames
2/4/04 06:49:39 PM
APPLICATION NUMBER:
21-180/S-008

LABELING
DESCRIPTION
ORYHO EVRA® is a combination transdermal contraceptive patch with a contact surface area of 30 cm². It contains 6.00 mg norelgestromin and 0.75 mg ethinyl estradiol (EE), and releases 100 micrograms of norelgestromin and 20 micrograms of EE to the bloodstream per 24 hours.

ORTH0 EVRA® is a thin, matrix-type transdermal contraceptive patch consisting of three layers. The backing layer is composed of a beige flexible film consisting of a low-density pigmented polyethylene outer layer and a polyester inner layer. It provides structural support and protects the middle adhesive layer from the environment. The middle layer contains polyethylene terephthalate (PET) film with a polydimethylsiloxane coating on the side that is in contact with the middle adhesive layer. The outside of the backing layer is heat-stamped "ORTH0 EVRA® 150/20:2.

The structural formulas of the components are:

![Molecular Structures](image)

Molecular weight, norelgestromin: 327.47
Molecular weight, ethinyl estradiol: 258.41

Chemical name for norelgestromin: 18, 19-dinorpregn-4-en-20-yn-3-one,
13-ethyl-17-hydroxy-, 3-oxime, (17a)
Chemical name for ethinyl estradiol: 19-Norethynodrel-1, 3, 5 (10)-triene-20-pyridin-1-ylmethyl ether, (Teva)

CLINICAL PHARMACOLOGY

Pharmacodynamics
Norelgestromin is the active progestin largely responsible for the progestational activity that occurs in women following application of ORTH0 EVRA®. Norelgestromin is also the primary active metabolite produced following oral administration of noregestrol (Alesse), the progestin component of the oral contraceptive product ORTHO CYCLIC® and ORTHO TRI-CYCLEN®. Combination oral contraceptives act by suppression of gonadotropins. Although the primary mechanism of this action is Inhibition of ovulation, other alterations Include changes in the cervical mucus (which increases the difficulty of sperm entry into the uterus) and the endometrium (which reduces 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 norelgestromin 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 BHBG, resulting in lower levels of free testosterone in serum compared to baseline.

Pharmacokinetic studies with ORTH0 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-treatment and found that FSH, LH, and Estradiol mean

estriol is extensively bound to serum albumin.

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

Special Populations
Effects of Age, Body Weight, Body Surface Area and Race: The effects of age, body weight, body surface area and race on the pharmacokinetics of norelgestromin and EE were evaluated in 330 healthy women from nine pharmacokinetic studies of single 7-day applications of ORTH0 EVRA®. For both norelgestromin and EE, increasing age, body weight and body surface area each were associated with slight decreases in C₀ and AUC values. However, only a small fraction (10-25%) of the overall variability in the pharmacokinetics of norelgestromin and EE following application of ORTH0 EVRA® may be associated with any or all of the above demographic parameters.

There was no significant effect of race with respect to Caucasians, Hispanics and Blacks.

Renal and Hepatic Impairment
No formal studies were conducted with ORTH0 EVRA® to evaluate the pharmacokinetics, safety, and efficacy in women with renal or hepatic impairment. Steroid hormones may be poorly metabolized in patients with impaired liver function (see PRECAUTIONS).

Drug Interactions
The metabolism of hormonal contraceptives may be influenced by various drugs. Of potential clinical importance are drugs that cause the induction of enzymes that are responsible for the degradation of estrogens and progestins, and drugs that interrupt enter-hepatic recirculation of estrogen (e.g. certain antibiotics).

The proposed mechanism of interaction of antibiotics is different from that of liver enzyme-inducing drugs. Literature suggests possible interactions with the concomitant use of hormonal contraceptives and ampicillin or tetracycline, in a pharmacokinetic drug interaction study, oral administration of tetracycline (400 mg p.o.) for 3 days prior to and 7 days during use of ORTH0 EVRA® did not significantly affect the pharmacokinetics of norelgestromin or EE. The major target for enzyme inducers is the hepatic microporal estrogen-2-hydroxylase (cytochrome P450 3A4); see also PRECAUTIONS. Drug Interactions.

Patch Adhesion
In the clinical trials with ORTH0 EVRA®, approximately 2% of the cumulative number of patches were completely detached. The proportion of subjects with at least 1 patch that completely detached ranged from 5% to 6%, with a reduction from Cycle 1 (6%) to Cycle 13 (2%). For instructions on how to manage detachment of patches, refer to the DOSAGE AND ADMINISTRATION section.

INDICATIONS AND USAGE
ORTH0 EVRA® is indicated for the prevention of pregnancy in women not using other contraceptive methods. This product is effective for up to 21 days (7 units) per cycle, provided the woman applies a new patch at the start of each new 7-day cycle.

Lika once contraceptive, ORTH0 EVRA® is highly effective if used as recommended in this label.

In 3 large clinical trials in North America, Europe and South Africa, 13,300 women (ages 18-45) completed 22,155 cycles of ORTH0 EVRA® use. pregnancy rates were approximately 1 per 100 women-years of ORTH0 EVRA® use. The racial distribution was 91% Caucasian, 4.6% Black, 1.6% Asian, and 2.4% Other.

With respect to weight, 5 of the 15 pregnancies reported with ORTH0 EVRA® use were among women with a baseline body weight 198 lbs. (90 kg), which constituted <3% of the study population. The greater proportion of pregnancies among women at or above 198 lbs. was statistically significant and suggests that ORTH0 EVRA® may be less effective in these women.

Health Care Professionals who consider ORTH0 EVRA® for women at or above 198 lbs. should discuss the patient's individual needs in choosing the most appropriate contraceptive option.

Table 2 lists the accidental pregnancy rates for users of various methods of contraception. The efficacy of these contraceptive methods, except sterilization, IUD, and
values, t-test approach during therapy; treated with levonorgestrel 19 mcg/patch post therapy.

Pharmacokinetics

Absorption

Following application of ORTHO 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 week period. Cmax concentrations for norelgestromin and EE during one week of patch wear are approximately 0.5-0.8 ng/ml and 40-60 pg/ml, respectively, and are generally consistent from all subjects and application sites. These Cmax concentrations are within the reference ranges for norelgestromin (0.6 to 1.2 ng/ml) and EE (55 to 75 pg/ml) establishedagged by the Cmax concentrations observed with subjects taking ORTHO CYCLEN.

Only absorption of norelgestromin and EE from ORTHO EVRA was determined by comparison to an intravenous infusion of norelgestromin and EE. The results indicated that the average dose of norelgestromin and EE absorbed into the systemic circulation is 150 mcg/day and 20 mcg/day, respectively.

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Results from a study of consecutive ORTHO EVRA® wear for 7 days and 10 days indicated that serum concentrations of norelgestromin and EE dropped slightly during the first 6 hours after the patch replacement, still stayed within the reference range and recovered within 12 hours. Target CP of norelgestromin and EE were maintained during 3 days of extended wear of ORTHO EVRA®.

**Figure 3:** Mean (SD) Norelgestromin Serum Concentrations (ng/mL) Following Application of ORTHO 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 4:** Mean (SD) EE Serum Concentrations (ng/mL) Following Application of ORTHO 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.)

Metabolism

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

Distribution

Norgestimate and norelgestromin (a serum metabolite of norelgestromin) are highly bound (80-95%) to serum proteins. Norelgestromin is bound to albumin and to SHBG, while norgestimate is bound primarily to SHBG, which limits its biological activity (Ethnicity)

Cigarette smoking increases the risk of serious cardiovascular side effects from hormonal contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is greater in women over 35 years of age. Women who use hormonal contraceptives, including ORTHO EVRA®, should be strongly advised not to smoke.

ORTHO EVRA® and other contraceptives that contain both an estrogen and a progestin are called combination hormonal contraceptives. There is no epidemiologic data available to determine whether safety and efficacy with the transdermal route of administration would be different than the oral route. Practitioners prescribing ORTHO EVRA® should be familiar with the following information relating to risks.

The use of combination hormonal contraceptives is associated with increased risks of several serious conditions including myocardial infarction, thromboembolic stroke, hepatic neoplasia, and gallbladder disease, although the risk of serious morbidity or mortality is very small in healthy women without underlying risk factors. The risk of morbidity and mortality from these underly-ing risk factors such as hypertension, hyperlipidemia, obesity and diabetes.

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

Throughout this labeling, epidemiologic studies reported are of two types: retrospective or case-control studies and prospective or cohort studies. Case-control studies provide a measure of the relative risk of a disease, namely, a ratio of the incidence of a disease among oral contraceptive users to that among nonusers. The relative risk does not provide information on the actual clinical occurrence of a disease. Cohort studies provide a measure of attributable risk, which is the difference in the incidence of disease between hormonal contraceptive users and nonusers. The attri-butable risk does provide information about the actual occurrence of a disease in the population (adapted from refs. 2 and 3 with the author’s permission). For further information, the reader is referred to a text on epidemiological methods.

1. Thromboembolic Disorders And Other Vascular Problems

a. Thromboembolism

An increased risk of thromboembolic and thrombotic disease associated with the use of hormonal contraceptives is well established. Case-control studies have found the relative risk of use compared to nonusers to be 3 to 5 for the first episode of superficial venous thrombosis, 4 to 11 for deep vein thrombosis or pulmonary embolism, and as high as 13 to 16 for venous thromboembolic disease (VTE)1. Cohort studies have shown the relative risk to be somewhat lower, about 3 for new cases and about 4.5 for new cases requiring hospitalization3. The risk of thromboembolic disease associated with hormonal contraceptives is not related to length of use and disappears after hormonal contraceptive use is stopped4. A rise in risk in the first two years of use is related to length of use and persists after use is stopped. A rise in risk with post-pill use of venous thrombosis in women who had previous risk factors is twice that of women without such medical conditions6. If feasible, hormonal contraceptive therapy should be discontinued at least four weeks prior to elective surgery of a type associated with an increased risk of thromboembolism and during the period of recovery and for at least four weeks following prolonged immobilization. Patients who are unable to stop hormonal contraception use should be informed of the increased risk of thromboembolism and should be advised to seek medical advice prior to surgery.

In the large clinical trials (N=3,330 with 1,704 women-years of exposure), one case of non-fatal pulmonary embolism occurred during ORTHO EVRA® use, and one case of post-operative non-fatal pulmonary embolism was reported following ORTHO EVRA® use, and one case of post-operative non-fatal pulmonary embolism was recorded following ORTHO EVRA® use. It is unknown if the risk of venous thromboembolism with ORTHO EVRA® use is different than with use of combination oral contraceptives. As with other estrogen-progestin combinations, the decision should be left to the earliest manifestations of thrombotic disorders (thrombophlebitis, pulmonary embolism, coronary artery disease, and arterial thrombosis). Should any of these occur or be suspected, ORTHO EVRA® should be discontinued immediately.

b. Myocardial Infarction

An increased risk of myocardial infarction has been attributed to hormonal contraceptive use. This risk is primarily in smokers or women with other underlying risk factors for coronary artery disease such as hypertension, hypercholesterolemia, obesity, and diabetes. Women who use hormonal contraceptives should be advised to stop smoking if at all possible. Smoking in combination with oral contraceptive use has been shown to contribute substantially to the incidence of myocardial infarction in women with mid-risk factors or older with smoking accounting for a majority of excess cases7. Mortality rates associated with cardiac disease have been shown to increase substantially in smokers, especially in those 35 years of age and older among women who use oral contraceptives. (See Figure 5)
Hormonal contraceptives may complicate the effects of well-known risk factors, such as hypertension, diabetes, hyperlipidemias, age and obesity. In particular, some progestins are known to increase LDL cholesterol and cause glucose intolerance, while estrogens may create a state of hypercoagulability. Hormonal contraceptives have been shown to increase blood pressure among some users (see Section 9 in WARNINGS). Similar effects on risk factors have been associated with an increased risk of cardiovascular disease. Hormonal contraceptives, including ORTHO EVRA, must be used with caution in women with cardiovascular disease risk factors.

Nongestational and nocebo estrogen have minimal androgenic activity (see CLINICAL PHARMACOLOGY). There is some evidence that the risk of myocardial infarction associated with hormonal contraceptives is lower when the progestin has minimal androgenic activity than when the activity is greater.

Cerebrovascular diseases

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

In a large study, the relative risk of thrombotic strokes has been shown to range from 2.5 for normotensive users to 5 for users with severe hypertension. The relative risk of hemorrhagic stroke is reported to be 1.2 for nonsmokers who used hormonal contraceptives, 2.8 for smokers who did not use hormonal contraceptives, 7.8 for smokers who used hormonal contraceptives, 1.8 for normotensive users and 25.7 for users with severe hypertension. The attributable risk is also greater in older women.

The relative risk of vascular disease from hormonal contraceptives depends on a balance achieved between doses of estrogen and progestin and the activity of the progestin used in the contraceptives. The activity and amount of both hormones should be considered in the choice of a hormonal contraceptive.

E. Persistence of risk of vascular disease

There are two studies that have shown persistence of risk of vascular disease for ever-users of combination hormonal contraceptives. In a study in the United States, the risk of developing myocardial infarction after the discontinuing combination hormonal contraceptives persists for at least 9 years for women 40-49 years who had used combination hormonal contraceptives for 5 or more years, but the increased risk was not demonstrated in other age groups. In another study in Great Britain, the risk of developing cerebrovascular disease persisted for at least 6 years after discontinuation of any contraceptive, although the risk was greatest for older hormonal contraceptives. However, both studies were performed with combination hormonal contraceptive formulations containing 50 micrograms or higher of estrogen.

It is unknown whether ORTHO EVRA is distinct from other combination hormonal contraceptives with regard to the occurrence of venous and arterial thromboses.

2. Estimates Of Mortality From Combination Hormonal Contraceptive Use

One study gathered data from a variety of sources that have estimated the mortality rate in women with different methods of contraception at different ages (Table 2). These estimates include the combined risk of death associated with contraceptive methods plus the risk attributable to pregnancy in the event of method failure. Each method of contraception has its specific benefits and risks. The study concluded that with regard to the mortality from each contraceptive use, the woman who smoked and who had already given birth showed an increased risk of death, primarily due to heart disease.

The observation of a possible increase of mortality risk of up to 10 for women having combination oral contraceptive use is based on data gathered in the 1970s but not reported until 1980. Currently, the literature suggests that this finding may be due to cholinergic side effects and potential metabolic disturbances in users of low-dose formulations. There is no evidence that this is true for the newer low-dose formulations. There is also no evidence that this is true for the combined hormone use after age 40 in healthy non-smoking women (even with the newer low-dose formulations), there are also greater potential health risks associated with oestrogen in older women and with the alternative surgical and medical procedures.

6. Emotions Disorders

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

7. Contact Lens

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

8. Drug Interactions

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

Contraceptive effectiveness may be reduced when hormonal contraceptives are co-administered with some antibiotics, antifungals, anticoagulants, and other drugs. This may increase metabolism of contraceptive steroids. This could result in unintended pregnancy or breakthrough bleeding. Examples include barbiturates, griseofulvin, efavirenz, phenylbutazone, phenytion, carmustine, febuxostat, oxcarbazepine, tiopurine and possibly with aspirin.

The proposed mechanism of interaction of antibiotics is different from that of liver enzyme-inducing drugs. Literature suggests possible interactions with the coconcurrent use of oral contraceptive and antibiotics, to an uncertain extent. The interaction is a pharmacokinetic drug interaction study, oral administration of hydroxy-1 H1, 500 mg a day for 3 days prior to and 7 days during wash of ORTHO EVRA did not significantly affect the pharmacokinetics of norethisterone or EE.

Several of the anti-HIV protease inhibitors have been studied with co-administration of oral combination hormonal contraceptives: significant changes (increase and decrease) in the mean AUC of the estrogen and progesterin have been noted in some cases. The efficacy and safety of oral contraceptives may be affected. It is unknown whether this applies to ORTHO EVRA. Healthcare professionals should refer to the label of the individual anti-HIV protease inhibitors for further drug-drug interaction information.

Herbal products. St. John's Wort (hypericum perforatum) may induce hepatic enzymes (cytochrome P450 and p-glycoprotein transport) and may reduce the effectiveness of contraceptive steroids. This may also result in breakthrough bleeding.

Increase in Plasma Hormone Levels Associated With Co-Administered Drugs

Co-administration of itraconazole and certain oral contraceptives containing ethinyl estradiol was noted in early literature for patients taking itraconazole. Abdel-Rahman et al. also noted the potential for itraconazole to interfere with the metabolism of contraceptive steroids by inhibiting the metabolism of the progestin component on day 1 of the contraceptive cycle.

Combination hormonal contraceptives containing some synthetic estrogens (e.g., ethinyl estradiol) may inhibit the metabolism of other compounds, including plasmatic concentrations of cyclosporine, prednisolone, and theophylline. This can be considered a risk for patients who take these medications and who use hormonal contraceptives, especially when the progestin is a synthetic progestin.

Some studies have reported that the contraceptive efficacy of certain oral contraceptives may be reduced when these drugs are used with oral contraceptives. Although norethisterone and its metabolites inhibit a variety of P450 enzymes in human liver microsomes, the clinical relevance of such an interaction on the levels of other concomitant medications is likely to be insignificant. Under the recommended dosing regimen, the in vivo concentrations of norethisterone and its metabolites, even at the peak plasma levels, are relatively low compared to the inhibition constant (Ki) based on results of in vitro studies.

Health-care professionals are advised to refer to prescribing information of co-administered drugs for recommendations regarding management of concomitant therapy.

9. Interactions With Laboratory Tests

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

- Increased prothrombin and factors VII, IX, and X; decreased antithrombin III; increased homocysteine-induced platelet aggregability.
- Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormones, as measured by protein-bound Iodine (TBI); T4 by column or free T4 assay may be normal or elevated, reflecting the elevated TBG, free T4 concentration is unaltered.
- Cushing syndrome: plasma cortisol may be increased.
- Sex hormone binding globulin is increased and result in elevated levels of total circulating endogenous sex steroids and corticoids; however, free or bio-logically active levels may decrease or remain unchanged.
- Thyroid function tests may be increased and levels of various other lipids and lipoproteins may be affected.
- Serum folate levels may be depressed by hormonal contraceptive therapy. This may result in mild macrocytosis even if a woman becomes pregnant shortly after discontinuing ORTHO EVRA.

10. Carcinogenesis

No carcinogenicity studies were conducted with noregestromin. However, bridging PK studies were conducted using doses of NUGEE that were used previously in the 2-year rat carcinogenicity study and 10-year mouse bioassay study to support the approval of ORTHO CYCLEN and ORTHO TRI CYCLEN under NDA 19-683 and 19-697, respectively. The PK studies demonstrated that rats and monkeys were exposed to 10 and 9 times the human exposure, respectively, with the proposed ORTHO EVRA transdermal contraceptive system.

Noregesterone was tested in in-vitro mutagenicity assays (bacterial plate incorporation mutation assay, CHO/HPRT mutation assay, chromosomal aberration assay) and in-vivo carcinogenicity tests in mice and hamsters and in Sprague-Dawley rats.
duties that may be necessary if such women do nor have access to effective and acceptable methods of contraception. The Committee recommended that the benefi-

cy of low-dose combination hormonal contraceptive use by healthy non-smoking

women over 40 may outweigh the possible risks.12

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

meets the individual patient needs.

<table>
<thead>
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<th>Month</th>
<th>15-19</th>
<th>20-24</th>
<th>25-29</th>
<th>30-34</th>
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<td>16.2</td>
<td>20.4</td>
<td>31.8</td>
<td>41.6</td>
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</tbody>
</table>

No fertility control methods

Oral contraceptives, non-smoker

Oral contraceptives, smoker

IUD

Contraception

Diaphragm

Intrauterine device

Periodic abstinence

*Deaths are birth-related

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

Carcinoma of the Reproductive Organs and Breast

However, this excess risk appears to decrease over time after COC discon-

It is unknown whether ORTHO EVRA® is distinct from oral contraceptives with regard to the above statements.

Hepatic Neoplasia

Benign hepatic adenomas are associated with hormonal contraceptive use, although the incidence of benign tumors is rare in the United States. Indirect calculations have estimated the attributable risk to be in the range of 3.3 cases/100,000 users for a risk that increases after four or more years of use, especially with hormonal contraceptives containing 50 micrograms or more of estrogen.49. Rupture of benign hepatic adenomas may cause death through intra-abdominal hemorrhage.50. Studies from Italy and the US have shown an increased risk of developing hepatic adenomas in long-term (8 years) oral contraceptive users. However, the absolute risk is extremely rare in the US and the attributable risk (the excess incidence of liver cancers in oral contraceptive users approaches less than one per million users. It is unknown whether ORTHO EVRA® is distinct from oral contraceptives in this regard.

Cataracts

There have been clinical case reports of retinal thrombosis associated with the use of hormonal contraceptives. ORTHO EVRA® should be discontinued if there is un-

explained severe or complete loss of vision, visual field defects do not rule out retinal vascular lesions. Appropriate diagnostic and therapeutic measures should be undertaken immediately.

Hormonal Contraceptive Use Before or During Early Pregnancy

Other adverse events that have been associated with the use of combination hormonal contraceptives include:

- Thrombophlebitis and venous thrombosis
- Hepatic adenomas or benign liver tumors
- Mesenteric thrombosis
- Change in menstrual flow
- Spotting
- Gastrintestinal symptoms (such as abdominal cramps and bloating)
- Temporary infertility after discontinuation of treatment

The following adverse reactions have been reported in users of combination hormonal contraceptives and are believed to be drug-related.

- Nausea
- Vomiting
- Gastrintestinal symptoms (such as abdominal cramps and bloating)
- Breakthrough bleeding
- Metrorrhagia
- Change in menstrual flow
- Breast changes: tenderness, enlargement, secretion
- Change in weight (increase or decrease)
- Change in vaginal and uterine bleeding
10. Headache

The onset or exacerbation of migraine headache or the development of headache with a new pattern that is recurrent, persistent or severe requires discontinuation of hormonal contraceptive use. As discussed earlier (see WARNINGS 1a and 1d), changes in serum triglycerides and lipoprotein levels have been reported in hormonal contraceptive users.

11. Bleeding Irregularities

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

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

In the clinical trials most women started their withdrawal bleeding on the fourth day of the drug-free interval, and the median duration of withdrawal bleeding was 5 to 6 days. Only 10% of women per cycle had 7 or more total days of bleeding and/or spotting (this includes both withdrawal flow and breakthrough bleeding and/or spotting).

12. Ectopic Pregnancy

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

PRECAUTIONS

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

1. Body Weight >198 lbs (90 kg) is recommended for women using ORTHO EVRA®. Women with body weight >198 lbs (90 kg) in women with lower body weights.

2. Physical Examination And Follow-Up

It is good medical practice for women using ORTHO EVRA®, as for all women, to have annual physical examination and physical examination. The physical examination should include careful examination of the breasts, abdomen and pelvic organs, including cervical smears, and relevant laboratory tests. In case of undiagnosed, persistent or recurrent abnormal vaginal bleeding, appropriate measures should be considered, including treatment of any malignancy or other pathology. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

3. Lipid Disorders

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

4. Liver Function

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

5. Fluid Retention

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

6. Carbohydrate And Lipid Metabolic Effects

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

In clinical trials with oral contraceptives containing ethinyl estradiol and norgestimate, there were no clinically significant changes in glucose levels over 24 cycles of use. Moreover, glucose levels were lower in patients with a history of hypertension or hypertension-related disease. In a 6-cycle clinical trial with ORTHO EVRA®, there were no clinically significant changes in fasting blood glucose from baseline to end of treatment.

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

7. Elevated Blood Pressure

Women with significant hypertension should not be started on hormonal contraception. Women with a history of hypertension or hypertension-related diseases, or renal disease should be encouraged to use another method of contraception. If women elect to use ORTHO EVRA®, they should be monitored closely and if a clinically significant elevation of blood pressure occurs, ORTHO EVRA® should be discontinued. For most women, elevated blood pressure will return to normal after stopping hormonal contraceptives, and there is no difference in the incidence of hypertension between former and never users.

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

8. Drug Interactions

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

DOSEAGE AND ADMINISTRATION

To achieve maximum contraceptive effectiveness, ORTHO EVRA® must be used exactly as directed. Complete instructions to facilitate patient counseling on proper system usage may be found in the Patient Package Insert. 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.

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

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

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

If she is menstruating on the first day, she should use back-up contraception for the first week of her menstrual period. If therapy starts after Day 1 of the menstrual cycle, a non-hormonal back-up contraceptive (such as a condom, diaphragm or spermicide) should be used concurrently for the first 7 consecutive days of the first treatment cycle.

Oral Contraceptive Use:

Women should be counseled that ORTHO EVRA® is effective if used continuously. Women who are not using the patch should not use back-up contraception for the first week of her menstrual period.

For women who are not using the patch, the patient should apply her first patch during the first 24 hours of her menstrual period. If therapy starts after Day 1 of the menstrual cycle, a non-hormonal back-up contraceptive (such as a condom, diaphragm or spermicide) should be used concurrently for the first 7 consecutive days of the first treatment cycle.

Oral Contraceptive Use:

Women who are not using the patch should be counseled that ORTHO EVRA® is effective if used continuously. Women who are not using the patch should not use back-up contraception for the first week of her menstrual period.
Where to apply the patch. The patch should be applied to clear, dry, intact healthy skin on the buttock, abdomen, upper outer arm or upper torso, in a space where it won't be rubbed by tight clothing. ORTHO EVRA® should not be placed on skin that is red, irritated or out, nor should it be placed on the breasts.

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

Application of the ORTHO EVRA® patch

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

The foil pouch should be peeled apart and open flat.

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

Half of the clear protective liner is to be peeled away (The sticky surface of the patch is touching the sticky surface of the other protective liner. A corner of the patch is grasped firmly and it is gently removed from the foil pouch.)

The sticky surface of the patch is applied to the skin and the other half of the liner is removed. The woman should pat down firmly 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 stripping.

The patch is worn for seven days (one week). On the "Patch Change Day," Day 8, the used patch is removed and a new one is applied immediately. The used patch still contains some active hormones—it should be carefully folded in half so that it sticks to itself before safely disposing of it in the trash. Used patches should not be flushed down the toilet.

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

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

The next four-week cycle is started by applying a new patch on the usual "Patch Change Day." The day after Day 28 is not a patch-free day; a further patch is applied immediately. If a patch is removed early for any reason, it should be discarded and a new patch applied immediately from the first day of patch removal.
If this ORTHO EVRA® patch becomes partially or completely detached and remains detached, return it to the same package or replace it with a new patch immediately. No back-up contraception is needed. The woman’s “Patch Change Day” will remain the same.

For more than one day (24 hours or more) if the woman is not sure how long the patch has been detached, she MAY NOT BE PROTECTED FROM PREGNANCY. She should stop the current contraceptive cycle and start a new cycle immediately by applying a new patch. There is now a “Day 1” and a new “Patch Change Day.” Back-up contraception, such as condoms, spermicide, or diaphragm, must be used for the first week of the new cycle.

The contraceptive patch ORTHO EVRA® is a thin, beige, plastic patch that sticks to the skin. The sticky part of the patch contains the hormones norelgestromin and ethinyl estradiol in a single patch. ORTHO EVRA® is intended to prevent pregnancy. It does not protect against HIV infection and other sexually transmitted infections.

In Case of Vomiting or Diarrhea
Given the nature of transdermal application, dose delivery should be unaffected by vomiting.

In Case of Skin Irritation
If patch use results in uncomfortable irritation, the patch may be removed and a new patch may solve the problem.

In Case of Skin Irritation
Each beige ORTHO EVRA patch contains 6.0 mg norelgestromin and 0.75 mg EE, Ovral is available in folding cartons containing a single patch (NDC # 0062-1920-15); each patch is packaged in a protective pouch. ORTHO EVRA is available in folding cartons of 1 cycle each (NDC #0062-1920-15); each carton contains 48 single patches. Store patches in their protective pouches. Apply immediately upon removal from the protective pouch. Do not store in the refrigerator or freezer. Used patches should not be flushed down the toilet.

Additional Instructions for Dosing
Each beige ORTHO EVRA patch contains 6.0 mg norelgestromin and 0.75 mg EE, and releases 150 micrograms of norelgestromin and 20 micrograms of EE to the bloodstream per 24 hours. Each patch surface is heat-stamped with ORTHO EVRA 120/20. Each patch is packaged in a protective pouch.

Ortho Evra is available in folding cartons of 1 cycle each (NDC #0062-1920-15); each patch contains 3 patches.

Ortho Evra is also available in folding cartons containing a single patch (NDC #0062-1920-01), intended for use as a replacement in the event that a patch is inadverently lost or destroyed.

Ortho Evra and during your revisits. You should also follow your health-care professional. You should discuss the information provided in this leaflet with him or her, both when you first start using the contraceptive patch ORTHO EVRA and during your revisits. You should also follow your health-care professional’s advice regarding regular check-ups while you are using the contraceptive patch.

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

Clinical trials suggested that ORTHO EVRA may be less effective in women weighing more than 188 lbs. 80 kg. If you weigh more than 188 lbs. 80 kg you should talk to your health-care professional about which method of birth control may be best for you.

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

- Implant: <1%
- Injection: <1%
- Spermicides alone: 20%
- Female sterilization: <1%
- Condom alone (male): 14%
- Condom alone (female): 21%
- Spermicidal jelly (male): 20%
- Periodic abstinence: 25%
- No birth control method: 89%
- Withdrawal: 10%

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

- History of heart attack or stroke
- Blood clots in the legs (thrombophlebitis), lungs (pulmonary embolism), or eyes
- History of blood clots in the deep veins of your legs
- Chest pain (angina pectoris)
- Known or suspected breast cancer or cancer of the lining of the uterus, cervix, or vagina
- Unexplained vaginal bleeding (until your doctor reaches a diagnosis)
- Hypertension or a history of any of these conditions: Your health-care professional can recommend a non-hormonal method of birth control.

Some women should not use ORTHO EVRA because of the risk of serious cardiovascular side effects from hormonal contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 30 years of age. Women who use hormonal contraceptives, including ORTHO EVRA, are strongly advised not to smoke.

- Cigarette smoking increases the risk of serious cardiovascular side effects from hormonal contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 30 years of age. Women who use hormonal contraceptives, including ORTHO EVRA, are strongly advised not to smoke.

Cigarette smoking increases the risk of serious cardiovascular side effects from hormonal contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 30 years of age. Women who use hormonal contraceptives, including ORTHO EVRA, are strongly advised not to smoke.
you are recovering from the birth of a baby.

• you are recovering from a second trimester miscarriage or abortion

• you are breastfeeding

• you weigh 198 pounds or more

• you are taking any other medications

A family history of breast cancer

• Diabetes

• Elevated cholesterol or triglycerides

• Kidney disease

• Liver disease

• Kidney disease

• Scanty or irregular menstrual periods

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

RISKS OF USING HORMONAL CONTRACEPTIVES, INCLUDING ORTHO EVRA®

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

1. Risk of developing blood clots

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

If you use ORTHO EVRA® and need elective surgery, need to stay in bed for a prolonged illness or injury, or have recently delivered a baby, you may be at risk of developing blood clots. You should consult your doctor about stopping ORTHO EVRA® four weeks before surgery and not using it for two weeks after surgery or during bed rest. You should also not use ORTHO EVRA® soon after delivery of a baby.

It is advisable to wait for at least four weeks after delivery if you are breast-feeding. If you are breast-feeding, you should wait until you have weaned your child before using ORTHO EVRA®. (See also the section on Breast Feeding in General Precautions.)

2. Heart attacks and strokes

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

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

3. Gallbladder disease

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

4. Liver tumors

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

5. Cancer of the reproductive organs and breasts

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

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

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

ESTIMATED RISK OF DEATH FROM A BIRTH CONTROL METHOD OR PREGNANCY

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

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

With Control of Fertility Per 100,000 Nonsterile Women by Fertility Control Method According to Age

---|---|---|---|---|---|---
All methods of birth control and pregnancy | 1.5-19 | 20-24 | 25-29 | 30-34 | 35-39 | 40-44

2. You may choose a first day start or Sunday start.

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

OR

• for Sunday start: apply your first patch on the first Sunday after your menstrual period starts. You must use back-up contraception, such as a condom, spermicide, or diaphragm for the first week of your menstrual period.

The day you apply your first patch will be Day 1. Your "Patch Change Day" will be on this day every week.

3. Choose a place on your body to put the patch. Put the patch on your buttocks, abdomen, upper outer arm or upper torso, in a place where it won't be rubbed by tight clothing.

4. Open the foil pouch by tearing it along the top edge and one side edge. Peel the foil pouch apart and open it flat.

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

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

6. Peel away half of the clear plastic and be careful not to accidentally remove the clear liner as you remove the patch.

7. Apply the sticky side of the patch to the skin you've cleaned and dried, then remove the other half of the clear plastic. Press firmly on the patch with the palm of your hand for 10 seconds, making sure the edges stick well. Run your finger around the edge of the patch to make sure it is sticking properly.

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

8. Wear the patch for seven days (one week). On your "Patch Change Day", Day 7, remove the used patch. Apply a new patch immediately. The used patch will contains some medicine—carefully fold it in half so that it sticks to itself before safely disposing of it in the trash. Used patches should not be flushed down the toilet.

9. Apply a new patch for week two (on Day 8) and for weeks three (on Day 15), on your "Patch Change Day". To avoid infection, do not apply the new patch to the same exact place on your skin.
Continue using your contraceptive patches on schedule. If the bleeding occurs earlier and missed amenorrhea is suspected and missed periods are present, continue using your contraceptive patches for the next cycle but be sure to inform your doctor immediately:

1. If you have used ORTHO EVRA® correctly and missed one period, continue using the patch for the first week of your new cycle. 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.

2. 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 previously become loose or fallen off. No tape or wraps should be used to keep the patch in place. If you cannot re-apply a patch, apply a new patch immediately.

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

- Sharp chest pain, coughing of blood, or sudden shortness of breath (indicating a possible clot in the lung)
- Pain in the calf (indicating a possible clot in the leg)
- Crushing chest pain or tightness in the chest (indicating a possible heart attack)
- Swelling, pain, tenderness, redness, or hardness in an arm or leg (indicating a possible stroke)
- Sudden partial or complete loss of vision (indicating a possible clot in the eye)
- Breast lumps (indicating possible breast cancer or fibrocystic disease of the breast)
- Ask your doctor or health care professional to show you how to examine your breasts.

- Severe pain or tenderness in the stomach area (indicating a possible ruptured liver tumor)
- Severe problems with sleeping, weakness, lack of energy, fatigue, or change in mood (possibly indicating severe depression)
- Unusual pain or discomfort when you urinate
- Vomiting
- Bloody diarrhea
- New vision changes
- Dark colored urine or light colored bowel movements

SIDE EFFECTS OF ORTHO EVRA®

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

2. Vaginal bleeding or spotting may occur while you are using ORTHO EVRA®, or irregular vaginal bleeding or spotting may occur while you are using ORTHO EVRA®. Irregular bleeding may vary from slight bleeding between menstrual periods to breakthrough bleeding which is a flow much like a regular period. Irregular bleeding may occur during the first few months of contraceptive patch use but may also occur after you have been using the contraceptive patch for some time. Such bleeding may be temporary and usually does not indicate any serious problems. It is important to continue using your contraceptive patches on schedule. If the bleeding occurs in more than a few cycles or lasts for more than a few days, talk to your health care professional.

3. Problems wearing contact lenses
If you wear contact lenses and notice a change in vision or an inability to wear your lenses, contact your health care professional.

4. Fluid retention or raised blood pressure
Hormonal contraceptives, including the contraceptive patch, can cause edema (fluid retention) with swelling of the fingers or ankles and may raise your blood pressure. If you experience fluid retention, contact your health care professional.

5. Migraines
A worsening of the skin is possible, particularly of the face. This may persist after use of hormonal contraceptives is discontinued.

6. Other side effects
The most common side effects of ORTHO EVRA® include nausea and vomiting, breast symptoms, headaches, menorrhagia, spotting, and abdominal pain. In addition, change in appetite, nervousness, depression, dizziness, loss of scalp hair; rash, edema (fluid retention) in the middle of your patch cycle, at the start of any patch cycle, in the middle of your patch cycle, or near a patch you are wearing. It may cause the patch to become loose.

- Severe problems with sleeping, weakness, lack of energy, fatigue, or change in mood (possibly indicating severe depression)
- Unusual pain or discomfort when you urinate
- Vomiting
- Bloody diarrhea
- New vision changes
- Dark colored urine or light colored bowel movements

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1. Skin Irritation
Skin irritation, redness or rash may occur at the site of application. If this occurs, the patch may be removed and a new patch may be applied to a new location

2. Vaginal bleeding or spotting may occur while you are using ORTHO EVRA®, or irregular vaginal bleeding or spotting may occur while you are using ORTHO EVRA®. Irregular bleeding may vary from slight bleeding between menstrual periods to breakthrough bleeding which is a flow much like a regular period. Irregular bleeding may occur during the first few months of contraceptive patch use but may also occur after you have been using the contraceptive patch for some time. Such bleeding may be temporary and usually does not indicate any serious problems. It is important to continue using your contraceptive patches on schedule. If the bleeding occurs in more than a few cycles or lasts for more than a few days, talk to your health care professional.

3. Problems wearing contact lenses
If you wear contact lenses and notice a change in vision or an inability to wear your lenses, contact your health care professional.

4. Fluid retention or raised blood pressure
Hormonal contraceptives, including the contraceptive patch, can cause edema (fluid retention) with swelling of the fingers or ankles and may raise your blood pressure. If you experience fluid retention, contact your health care professional.

5. Migraines
A worsening of the skin is possible, particularly of the face. This may persist after use of hormonal contraceptives is discontinued.

6. Other side effects
The most common side effects of ORTHO EVRA® include nausea and vomiting, breast symptoms, headaches, menorrhagia, spotting, and abdominal pain. In addition, change in appetite, nervousness, depression, dizziness, loss of scalp hair; rash, edema (fluid retention) in the middle of your patch cycle, at the start of any patch cycle, in the middle of your patch cycle, or near a patch you are wearing. It may cause the patch to become loose.

- Severe problems with sleeping, weakness, lack of energy, fatigue, or change in mood (possibly indicating severe depression)
- Unusual pain or discomfort when you urinate
- Vomiting
- Bloody diarrhea
- New vision changes
- Dark colored urine or light colored bowel movements

SIDE EFFECTS OF ORTHO EVRA®

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

3. While breast-feeding

If you are breast-feeding, consult your health care professional before starting ORTHO EVRA®. Hormonal contraceptives are passed on to the child in the milk. A few medications passed in the breast milk may affect your child's sex hormones.

5. Drug interactions

Certain drugs may interact with hormonal contraceptives, including ORTHO EVRA®, to make them less effective in preventing pregnancy or cause an increase in breakthrough bleeding. Such drugs include rifampin, drugs used for epilepsy such as barbiturates (for example, phenobarbital), anticonvulsants such as topiramate (TOPAMAX), carbamazepine (Tegedepin), phenytoin (Dilantin), and other drugs used in the treatment of HIV/AIDS, and possibly certain antibiotics. Taking these drugs may result in decreased levels of hormones from the ORTHO EVRA® patches, and your contraceptive patch may not work as intended. You should check with your health care professional about how to make patch-changing easier or about using another method of birth control. 

6. Sexually transmitted diseases

ORTH0 EVRA® is intended to prevent pregnancy. It does not protect against HIV (AIDS) or other sexually transmitted diseases. However, if you have HIV (AIDS) or other sexually transmitted diseases such as chlamydia, genital herpes, gonorrhea, hepatitis B, and syphilis. You should take precautions to protect yourself from acquiring other sexually transmitted diseases.

HOW TO USE ORTHO EVRA®

Instructions for Use

ORTH0 EVRA® keeps you from becoming pregnant by transferring hormones to your body through your skin. The patch contains one of the hormones you would get if you were taking an oral contraceptive pill. 

The method uses a 28 day (four week) cycle. You should apply a new patch each week for three weeks (21 total days). You should not apply a patch during the fourth week, week.

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

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

Save these instructions.

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

RISK BESIDES SIDE EFFECTS DURING ORTHO EVRA® USE. Common minor symptoms occur, do not stop using the contraceptive patch. The problem will usually go away. If it doesn't go away, check with your health care professional.

6. MISTAKES IN USING YOUR PATCHES CAN ALSO CAUSE SPOTTING OR LIGHT BLEEDING.

If you miss TWO PERIODS IN A ROW contact your health care professional because you might be pregnant.

5. If you may choose an earlier Patch Change Day by applying a new patch on the day you prefer. You now have a new Day 1 and a new Patch Change Day. You should never have the patch off for more than seven days in a row.

11. BE SURE YOU HAVE READY AT ALL TIMES:

- a NON-HORMONAL BIRTH CONTROL METHOD (patch, condom, spermicide, or diaphragm) if you check with your health care professional.

IF YOU WANT TO MISS ONE PERIOD, your menstrual cycle may be delayed to another time if you request it and your health care professional believes that it is a good medical practice to postpone it. You should be reexamined at least once a year.

PREGNANCY AFTER STOPPING ORTHO EVRA®

There may be some delay in becoming pregnant after you stop using ORTHO EVRA®, especially if you had irregular menstrual cycles before you used hormonal contraceptives. It may be best to postpone conception until you begin menstruation regularly after you have stopped using ORTHO EVRA® and want to become pregnant. There does not appear to be an increase in birth defects in newborn babies when pregnancy occurs soon after stopping hormonal contraceptives.

OVERDOSE

ORTHO EVRA® is unlikely to cause an overdose because the patch releases a steady amount of the hormones. Do not use more than one patch at a time. Serious side effects have not been reported for it to work properly.

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Division of Reproductive and Urologic Drug Products

Regulatory Project Manager Review

Application Number: NDA 21-180
Name of Drug: Ortho Evra® (norelgestromin/ethinyl estradiol transdermal system)
Sponsor: Ortho-McNeil Pharmaceutical
Material Reviewed: SLR-008
Submission Dates: October 7, 2003
Receipt Dates: October 8, 2003

Background and Summary

The original NDA for Ortho Evra® (norelgestromin/ethinyl estradiol transdermal system) was approved November 20, 2001 for the contraceptive indication. Supplement 008, Changes Being Effected, was submitted October 7, 2003 to provide for specific disposal instructions for the patient of the used transdermal contraceptive system.

Review

This labeling revision includes specific disposal instructions, included the trademark symbol which replaced the registered symbol, and a deletion of a repeated footnote reference to #20 in the physician’s insert.

This submission was compared to approval letter of November 20, 2001.

<table>
<thead>
<tr>
<th>Approved Labeling</th>
<th>S-008 Revision 10/7/03</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>DOSAGE AND ADMINISTRATION Application of the ORTHO EVRA patch</td>
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<td>Acceptable.</td>
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<tr>
<td>The patch is worn for seven days (one week). On the “Patch Change Day”, Day 8, the used patch is removed and a</td>
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HOW SUPPLIED
Used patches still contain some active hormones. Each patch should be carefully folded in half so that it sticks to itself before throwing it away.

Acceptable.

Conclusions
The proposed changes are acceptable and the sponsor should be send an approval letter.

Dale Cutright
Regulatory Project Manager

Drafted: DCutright 1-15-04
MKober 1.16.03; Mitra 1.16.03; Davis, Monore

RPM LABELING REVIEW
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
Dale Cutright  
1/29/04 06:35:47 AM  
CSO

Margaret Kober  
1/29/04 01:46:58 PM  
CSO
Dear Ms. Capaccione:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Ortho Evra® (norelgestromin and ethinyl estradiol transdermal system)

NDA Number: NDA 21-180

Supplement number: S-008

Date of supplement: October 7, 2003

Date of receipt: October 8, 2003

This supplemental application, submitted as “Supplement - Changes Being Effected,” proposes a labeling change to clarify the patient instructions for disposal of the used transdermal contraceptive system.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 5, 2003 in accordance with 21 CFR 314.101(a).
All communications concerning this supplement should be addressed as follows:

U.S. Postal Service/ Courier/Overnight Mail:
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, please call Karen Anderson, N.P., Regulatory Project Manager, at 301-827-4260.

Sincerely,

(See appended electronic signature page)

Margaret Kober, R.Ph.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Margaret Kober
12/1/03 03:41:40 PM
Chief, Project Management Staff