

PRODUCTS

Generic Allegra-D Approved

A combination of fexofenadine HCl and pseudoephedrine HCl in an extended-release tablet (60 mg/120 mg) is indicated for the relief of symptoms associated with seasonal allergic rhinitis in adults and children 12 years and older. For more information, contact Barr Pharmaceuticals Inc. by calling 800-222-0190 or 201-930-3302.

Rapid Fecal Occult Blood Test

The Clearview ULTRA fecal occult blood test, a rapid two-step immunoassay, is now available. Results are available in less than 5 minutes and only one sample is required from the patient. The test does not require the patient to follow a restricted diet. For more information, contact Wampole Laboratories by calling 800-257-9525 or 609-627-8000.

Dictionary of Drug Names

The 2005 U.S. Pharmacopeia Dictionary of Adopted Names and International Drug Names is available. This 41st edition contains nationally and internationally recognized names for all drugs. The dictionary is available in book form for \$299 or in a

combination book-online package for \$345. For more information, contact U.S. Pharmacopeia by visiting <http://store.usp.org> or by calling 800-227-8772.

Fertility Treatment Launched

Menopur (menotropins for injection) is indicated for the development of multiple follicles and pregnancy in patients undergoing assisted reproductive technology procedures, such as in vitro fertilization. This purified human menopausal gonadotropin contains equal amounts of follicle-stimulating hormone and luteinizing hormone.

ORTHO EVRA® (NORELGESTROMIN / ETHINYL ESTRADIOL TRANSDERMAL SYSTEM)

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

Rx only

ORTHO EVRA® is a combination transdermal contraceptive patch with a contact surface area of 20 cm². It contains 6.00 mg norelgestromin and 0.75 mg ethinyl estradiol (EE), and releases 150 micrograms of norelgestromin and 20 micrograms of EE to the bloodstream per 24 hours.

IMPORTANT NOTE—This information is a BRIEF SUMMARY of the complete prescribing information provided with the product and therefore should not be used as the basis for prescribing the product. This summary was prepared by deleting from the complete prescribing information certain text, tables and references. The physician should be thoroughly familiar with the complete prescribing information before prescribing the product.

INDICATIONS AND USAGE: ORTHO EVRA® is indicated for the prevention of pregnancy. Like oral contraceptives, ORTHO EVRA® is highly effective if used as recommended in this label.

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

CONTRAINDICATIONS: ORTHO EVRA® should not be used in women who currently have the following conditions: 1. Thrombophlebitis, thromboembolic disorders 2. A past history of deep vein thrombophlebitis or thromboembolic disorders 3. Cerebrovascular or coronary artery disease (current or past history) 4. Valvular heart disease with complications 5. Severe hypertension 6. Diabetes with vascular involvement 7. Headaches with focal neurological symptoms 8. Major surgery with prolonged immobilization 9. Known or suspected carcinoma of the breast or personal history of breast cancer 10. Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia 11. Undiagnosed abnormal genital bleeding 12. Cholestatic jaundice of pregnancy or jaundice with prior hormonal contraceptive use 13. Acute or chronic hepatocellular disease with abnormal liver function 14. Hepatic adenomas or carcinomas 15. Known or suspected pregnancy 16. Hypersensitivity to any component of this product.

WARNINGS

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 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, thromboembolism, stroke, hepatic neoplasia, and gallbladder disease. The risks of these conditions are increased in women who have predisposing conditions. The risk of myocardial infarction and mortality increases significantly in the presence of other underlying risk factors such as hypertension, hyperlipidemias, obesity and diabetes.

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

Throughout this labeling, epidemiological studies reported are of two types: retrospective or case control studies and 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. These studies provide information on the relative risk of occurrence of a disease in the population (adapted from refs. 2 and 3 with the author's permission). For further information, the reader is referred to a text on epidemiological methods.

1. Thromboembolic Disorders And Other Vascular Problems: a. Thromboembolism: An increased risk of thromboembolic and thrombotic disease associated with the use of hormonal contraceptives is well established. Case control studies have found the relative risk of users compared to nonusers to be 3 for the first episode of superficial venous thrombosis, 4 to 11 for deep vein thrombosis or pulmonary embolism, and 1.5 to 6 for women with predisposing conditions for venous thromboembolic disease. Cohort studies have shown the relative risk to be somewhat lower, about 3 for new cases and about 4.5 for new cases requiring hospitalization. The risk of thromboembolic disease associated with hormonal contraceptives is not related to length of use and disappears after hormonal contraceptive use is stopped. A two- to four-fold increase in relative risk of post-operative thromboembolic complications has been reported with the use of hormonal contraceptives. The relative risk of venous thrombosis in women who have predisposing conditions is twice that of women without such medical conditions. If feasible, hormonal contraceptives should be discontinued at least four weeks prior to and for two weeks after elective surgery of a type associated with an increase in risk of thromboembolism and during and following prolonged immobilization. Since the immediate postpartum period is also associated with an increased risk of thromboembolism, hormonal contraceptive use should be started no earlier than four weeks after delivery in women who elect not to breast-feed. 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. It is unknown if the risk of venous thromboembolism with ORTHO EVRA® use is different than with use of combination oral contraceptives. As with any combination hormonal contraceptive, the clinician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, pulmonary embolism, cerebrovascular disorders, and retinal 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, morbid obesity, and diabetes. The relative risk of heart attack for current hormonal contraceptive users has been estimated to be 1.2 for non-smokers who used hormonal contraceptives, 2.6 for smokers who did not use hormonal contraceptives, 7.6 for smokers who used hormonal contraceptives, 1.8 for nonusers of users and 25.7 for users with severe hypertension. The attributable risk is also greater in older women. **d. Dose-related risk of vascular disease from hormonal contraceptives:** A positive association has been observed between the amount of estrogen and progestin in hormonal contraceptives and the risk of vascular disease. A decline in serum high-density lipoprotein (HDL) has been reported with many progestational agents, and a decline in serum high-density lipoproteins has been associated with an increased incidence of coronary heart disease. Because estrogens increase HDL cholesterol, the net effect of a hormonal contraceptive depends on a balance achieved between doses of estrogen and progestin and the activity of the progestin used in the contraceptives. The activity and amount of both hormones should be considered in the choice of a hormonal contraceptive. **e. Persistence of risk of vascular disease:** There are two conditions that have shown persistence of risk of vascular disease for ever-users of combination hormonal contraceptives. In a study in the United States, the risk of developing myocardial infarction after discontinuing combination hormonal contraceptives persists for at least 9 years for women 40-49 years who had used combination hormonal contraceptives for five or more years, but this increased risk was not demonstrated in other age groups. In another study in Great Britain, the risk of developing cerebrovascular disease persisted for at least 6 years after discontinuation of combination hormonal contraceptives, although excess risk was very small. However, both studies were performed with combination hormonal contraceptive formulations containing 50 micrograms or higher of estrogens. It is unknown whether ORTHO EVRA® is distinct from other combination hormonal contraceptives with regard to the occurrence of venous and arterial thrombosis. **2. Estimates Of Mortality From Combination Hormonal Contraceptive Use:** One study gathered data from a variety of sources that have estimated the mortality rate associated with different methods of

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

Pigmentation Treatment

Aclaro (4% hydroquinone) emulsion treats ultraviolet-induced dyschromia and discoloration due to oral contraceptive use, pregnancy, hormone therapy, or skin trauma. For more information, contact JJSJ Pharmaceuticals by visiting www.aclaro4.com or calling 800-499-4468.

Soft, Inflatable Speculum

The FemSpec is a soft, rolled, tamponlike speculum that the physician can inflate

for a better fit during gynecologic exams. This disposable product is patient friendly. The speculum comes in small, medium, and large sizes. Contact FemSpec LLC by visiting the Web site www.femspec.com or by calling 415-561-2565.

Alendronate/Vitamin D in One Tablet

Fosamax Plus D (alendronate sodium/cholecalciferol) is approved for treatment of osteoporosis in postmenopausal women. The once-weekly tablet combines 70-mg alendronate sodium with 2,800-IU vitamin D₃. For more information, contact Merck & Co. by calling 800-344-7833.

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

The observation of a possible increase in risk of mortality with age for combination oral contraceptive users is based on data gathered in the 1970s but not reported until 1983. Current clinical practice involves the use of a variety of formulations and a careful consideration of risk factors. In 1989, the Fertility and Maternal Health Drugs Advisory Committee was asked to review the use of combination hormonal contraceptives in women 40 years of age and over. The Committee concluded that although cardiovascular disease risks may be increased with combination hormonal contraceptive use after age 40 in healthy non-smoking women (even with the newer low-dose formulations), there are also greater potential health risks associated with pregnancy in older women and with the attendant surgical and medical procedures that may be necessary if such women do not have access to effective and acceptable means of contraception. The Committee recommended that the benefits of low-dose combination hormonal contraceptive use by healthy non-smoking women over 40 may outweigh the possible risks. Although the data are mainly obtained with oral contraceptives, this is likely to apply to ORTHO EVRA® as well. Women of all ages who use combination hormonal contraceptives should use the lowest possible dose formulation that is effective and meets the individual patient needs. **3. Carcinoma Of The Reproductive Organs And Breasts:** Numerous epidemiological studies give conflicting reports on the relationship between breast cancer and COC use. The risk of having breast cancer diagnosed may be slightly increased among current and recent users of combination oral contraceptives. However, this excess risk appears to decrease over time after COC discontinuation and by 10 years after cessation the increased risk disappears. Some studies report an increased risk with duration of use while other studies do not and no consistent relationships have been found with dose or type of steroid. Some studies have found a small increase in risk for women who first use COCs before age 20. Most studies show a similar pattern of risk with COC use regardless of a woman's reproductive history or her family breast cancer history. In addition, breast cancers diagnosed in current or ever oral contraceptive users may be less clinically advanced than in never-users. Women who currently breast-feed or have breast-fed should not use oral contraceptives because breast cancer is usually a hormonally sensitive tumor. Some studies suggest that combination oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia in some populations of women. However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors. In spite of many studies of the relationship between oral contraceptive use and breast and cervical cancer, a causal relationship has not been established. It is not known whether ORTHO EVRA® is distinct from oral contraceptives with regard to the above statements. **4. Hepatic Neoplasia:** Benign hepatic adenomas are associated with hormonal contraceptive use, although the incidence of benign tumors is rare in the United States. Indirect calculations have estimated the attributable risk to be in the range of 3.3 cases/100,000 for users, a risk that increases after four or more years of use, especially with hormonal contraceptives containing 50 micrograms or more of estrogen. Rupture of benign, hepatic adenomas may cause death through intra-abdominal hemorrhage. Studies from Britain and the US have shown an increased risk of developing hepatocellular carcinoma in long term (>8 years) oral contraceptive users. However, these cancers are extremely rare in the U.S. and the attributable risk (the excess incidence) of liver cancers in oral contraceptive users approaches less than one per million women per year. ORTHO EVRA® is distinct from oral contraceptives in this regard. **5. Ocular Lesions:** There have been clinical case reports of retinal thromboses associated with the use of hormonal contraceptives. ORTHO EVRA® should be discontinued if there is unexplained partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions. Appropriate diagnostic and therapeutic measures should be undertaken immediately. **6. Hormonal Contraceptive Use Before Or During Early Pregnancy:** Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. Studies also did not indicate a teratogenic effect, particularly in so far as cardiac anomalies and limb reduction defects are concerned, when oral contraceptives are taken inadvertently during early pregnancy. Combination hormonal contraceptives such as ORTHO EVRA® should not be used to induce withdrawal bleeding as a test for pregnancy. ORTHO EVRA® should not be used during pregnancy to treat threatened or habitual abortion. It is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out. If the patient has not adhered to the prescribed schedule for the use of ORTHO EVRA®, the possibility of pregnancy should be considered at the time of the first missed period. Hormonal contraceptive use should be discontinued if pregnancy is confirmed. **7. Gallbladder Disease:** Earlier studies have reported an increased lifetime relative risk of gallbladder surgery in users of hormonal contraceptives and estrogens. More recent clinical trials have shown that the relative risk of developing gallbladder disease among hormonal contraceptive users may be minimal. The recent findings of minimal risk may be related to the use of hormonal contraceptive formulations containing lower hormonal doses of estrogens and progestins. Combination hormonal contraceptives such as ORTHO EVRA® may worsen existing gallbladder disease and may accelerate the development of this disease in previously asymptomatic women. Women with a history of combination hormonal contraceptive-related gallbladder disease should be advised to discontinue use of ORTHO EVRA®. In clinical trials, women while taking hormonal contraceptives should be monitored earlier (see WARNINGS 1 and 1d), changes in serum triglycerides and lipoprotein levels have been reported in hormonal contraceptive users. **8. Elevated Blood Pressure:** Women with significant hypertension should not be started on hormonal contraceptive. 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 occurrence 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. **10. Headache:** The onset or exacerbation of migraine headache or the development of headache with a new pattern that is recurrent, persistent or severe requires discontinuation of ORTHO EVRA® and evaluation of the cause. **11. Bleeding Irregularities:** Breakthrough bleeding and spotting are sometimes encountered in women using ORTHO EVRA®. Non-hormonal causes should be considered and adequate diagnostic measures taken to rule out malignancy, other pathology or pregnancy. In the event of breakthrough bleeding, as in the case of any abnormal vaginal bleeding, if pathology has been excluded, time or a change to another contraceptive product may resolve the bleeding. In the event of amenorrhea, pregnancy should be ruled out before initiating use of ORTHO EVRA®. Some women may encounter amenorrhea or oligomenorrhea after discontinuation of hormonal contraceptive use, especially when such a condition was pre-existent. Bleeding Patterns: In the clinical trials most women started their withdrawal bleeding on the fourth day of the drug-free interval, and the median duration of withdrawal bleeding was 5 to 6 days. On average 26% of women per cycle had 7 or more total days of bleeding and/or spotting (this includes both withdrawal flow and breakthrough bleeding and/or spotting). **12. Ectopic Pregnancy:** Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

PRECAUTIONS: Women should be counseled that ORTHO EVRA® does not protect against HIV infection (AIDS) and other sexually transmitted infections. 1. Body Weight ≥198 lbs. (90 kg): Results of clinical trials suggest that ORTHO EVRA® may be less effective in women with body weight ≥198 lbs. (90 kg) than in women with lower body weights. **2. Physical Examination:** It is good medical practice for women using ORTHO EVRA® to be examined by a physician for all women, to have annual medical evaluation and physical examinations. The physical examination, however, may be deferred until after initiation of hormonal contraceptives if requested by the woman and judged appropriate by the clinician. The physical examination should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology, and relevant laboratory tests. In case of undiagnosed, persistent or recurrent abnormal vaginal bleeding, there should be a change of contraceptive method or discontinuation. Persistent or recurrent abnormal vaginal bleeding may be due to benign or malignant conditions such as endometrial hyperplasia, uterine leiomyomas, or other pathology. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care. **3. Lipid Disorders:** Women who are being treated for hyperlipidemias should be followed closely if they elect to use ORTHO EVRA®. Some progestins may elevate LDL levels and may render the control of hyperlipidemias more difficult. **4. Liver Function:** If jaundice develops in any woman using ORTHO EVRA®, she should discontinue the use of ORTHO EVRA®. ORTHO EVRA® should be poorly metabolized in patients with impaired liver function. **5. Fluid Retention:** Steroid hormones like those in ORTHO EVRA® may cause some degree of fluid retention. ORTHO EVRA® should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention. **6. Emotional Disorders:** Women who become significantly depressed while using combination hormonal contraceptives such as ORTHO EVRA® should stop the medication and use another method of contraception in an attempt to determine whether the symptom is drug related. Women with a history of depression should be carefully observed and ORTHO EVRA® discontinued if significant depression occurs. **7. Contact Lenses:** Contact lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist. **8. Drug Interactions: Changes in Contraceptive Effectiveness Associated with Co-Administration of Other Drugs:** Contraceptive effectiveness may be reduced when hormonal contraceptives are co-administered with some antibiotics,

antifungals, anticonvulsants, and other drugs that increase metabolism of contraceptive steroids. This could result in unintended pregnancy or breakthrough bleeding. Examples include barbiturates, griseofulvin, rifampin, phenylbutazone, phenytoin, carbamazepine, felbamate, oxcarbazepine, topiramate and possibly with ampicillin. 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 500 mg q.d. for 3 days prior to and 7 days during wear of ORTHO EVRA® did not significantly affect the pharmacokinetics of norelgestromin 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 progestin have been noted in some cases. The efficacy and safety of oral contraceptive products 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 containing St. John's Wort (hypericum perforatum) may induce hepatic enzymes (cytochrome P450) and p-glycoprotein transporter 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 barbiturate and certain oral contraceptives containing ethinyl estradiol increase AUC values for ethinyl estradiol by approximately 20%. Ascorbic acid and acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. CYP 3A4 inhibitors such as itraconazole or ketoconazole may increase plasma hormone levels. **Changes in Plasma Levels of Co-Administered Drugs:** Combination hormonal contraceptives containing some synthetic estrogens (e.g., ethinyl estradiol) may inhibit the metabolism of other compounds. Increased plasma concentrations of cyclosporine, prednisone, and theophylline have been reported with concomitant administration of oral contraceptives. In addition, oral contraceptives may induce the conjugation of other compounds. Decreased plasma concentrations of acetaminophen and increased clearance of temazepam, salicylic acid, morphine and diazepam have been noted when these drugs were administered with oral contraceptives. Although norelgestromin and its metabolites inhibit a variety of P450 enzymes in human liver microsomes, the clinical consequences of such an interaction at the levels of other concomitant medications is likely to be insignificant. Under the recommended dosing regimen, the in vivo concentrations of norelgestromin and its metabolites, even at the peak serum levels, are relatively low compared to the inhibitory constant (K_i) based on results of *in vitro* studies. Healthcare professionals are advised to also refer to prescribing information of co-administered drugs for recommendations regarding management of concomitant therapy. **Interactions With Laboratory Tests:** Certain enzyme and liver function tests and blood components may be affected by hormonal contraceptives: a. Increased prothrombin and fibrinogen levels; VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability. b. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T₄ by column or by radioimmunoassay. Free T₃ resin uptake is decreased, reflecting the elevated TBG, free T₄ concentration is unaltered. c. Other binding proteins may be elevated and alter the binding of various hormones. d. Free and total testosterone and dihydroxy and levels of total circulating endogenous sex steroids and corticoids; however, free or biologically active levels either decrease or remain unchanged. e. Triglycerides may be increased and levels of various other lipids and lipoproteins may be affected. f. Glucose tolerance may be decreased. g. Serum folate levels may be depressed by hormonal contraceptive therapy. This may be of clinical significance if a woman becomes pregnant shortly after discontinuing ORTHO EVRA®. **10. Carcinogenesis:** In carcinogenicity studies were conducted with norelgestromin. However, bridging PK studies were conducted using doses of NMG/EE which were used previously in the 2-year rat carcinogenicity study and 10-year monkey toxicity study to support the approval of ORTHO-CYCLEN and ORTHO TRI-CYCLEN under NDAs 19-653 and 19-697, respectively. The PK studies demonstrated that rats and monkeys were exposed to 16 and 8 times the human exposure, respectively, with the proposed ORTHO EVRA® transdermal contraceptive system. Norelgestromin was tested in *in vitro* mutagenicity assays (bacterial plate incorporation mutation assay, CHO/HGPRT mutation assay, chromosomal aberration assay using cultured human peripheral lymphocytes) and in one-in-vivo test (micronucleus assay) and found to have no genotoxic potential. See WARNINGS Section. **11. Pregnancy:** Pregnancy Category X. See CONTRAINDICATIONS and WARNINGS Section. Norelgestromin was tested for its reproductive toxicity in a rabbit developmental toxicity study by the SC route of administration. Doses of 0, 1, 2, 4 and 6 mg/kg body weight, which gave systemic exposure approximately 25 to 125 times the human exposure with ORTHO EVRA®, were administered daily on gestation days 7-19. Malformations reported were paw hyperflexion at 4 and 6 mg/kg and paw hyperextension and cleft palate at 6 mg/kg. **12. Nursing Mothers:** The effects of ORTHO EVRA® in nursing mothers have not been evaluated and are unknown. Small amounts of combination hormonal contraceptive steroids have been identified in the milk of nursing mothers and a few adverse effects on the child have been reported, including jaundice and breast enlargement. In addition, combination hormonal contraceptives given in the postpartum period may interfere with lactation by decreasing the quantity and quality of breast milk. Long-term follow-up of infants whose mothers used combination hormonal contraceptives while breast feeding has shown no deleterious effects. However, the nursing mother should be advised not to use ORTHO EVRA® but to use other forms of contraception until she has completely weaned her child. **13. Pediatric Use:** Safety and efficacy of ORTHO EVRA® have not been established in users of reproductive age. Safety and efficacy are expected to be the same for post-pubertal adolescents under the age of 16 and for users 16 years and older. Use of this product before menarche is not indicated. **14. Geriatric Use:** This product has not been studied in women over 65 years of age and is not indicated in this population. **15. Sexually Transmitted Diseases:** Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases. **16. Patch Adhesion:** Experience with more than 70,000 ORTHO EVRA® patches worn for contraception for 6-13 cycles showed that 4.7% of patches were replaced because they either fell off (1.8%) or were partly detached (2.9%). Similarly, in a small study of patch wear under conditions of physical exertion and variable temperature and humidity, less than 2% of patches were replaced for complete or partial detachment. If the ORTHO EVRA® patch becomes partially or completely detached and remains detached, insufficient drug delivery occurs. A patch should not be re-applied if it is no longer sticky, if it has become stuck to itself or another surface, if it has other material stuck to it, or if it has become loose or fallen off before. If a patch cannot be re-applied, a new patch should be applied immediately. Supplemental adhesives or wraps should not be used to hold the ORTHO EVRA® patch in place. If a patch is partially or completely detached for more than one day (24 hours or more) OR if the woman is not sure how long the patch has been detached, she may not be protected from pregnancy. She should stop the current contraceptive cycle and start a new cycle immediately by applying a new patch. Back-up contraception, such as condoms, spermicide, or diaphragm, must be used for the first week of the new cycle.

INFORMATION FOR THE PATIENT: See Patient Package Insert. **ADVERSE REACTIONS:** The most common adverse events reported by 9 to 22% of women using ORTHO EVRA® in clinical trials (N=3,330) were the following, in order of decreasing incidence: breast symptoms, headache, application site reaction, nausea, upper respiratory infection, menstrual cramps, and abdominal pain. The most frequent adverse events leading to discontinuation in 1 to 2.4% of women using ORTHO EVRA® in the trials included the following: nausea and/or vomiting, application site reaction, breast symptoms, headache, and emotional lability. 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 ORTHO EVRA®. An increased risk of the following serious adverse reactions has been associated with the use of combination hormonal contraceptives (see WARNINGS Section): 1. Thrombophlebitis and venous thrombosis with or without embolism 2. Arterial thromboembolism 3. Pulmonary embolism 4. Myocardial infarction 5. Cerebral hemorrhage 6. Cerebral thrombosis 7. Hypertension 8. Gallbladder disease 9. Hepatic adenomas or benign liver tumors. There is evidence of an association between the following conditions and the use of combination hormonal contraceptives: 1. Mesenteric thrombosis 2. Retinal thrombosis. The following adverse reactions have been reported in users of combination hormonal contraceptives and are believed to be drug-related: 1. Nausea 2. Vomiting 3. Gastrointestinal symptoms (such as abdominal cramps and bloating) 4. Breakthrough bleeding 5. Spotting 6. Change in menstrual flow 7. Amenorrhea 8. Temporary infertility after discontinuation of treatment 9. Edema 10. Melasma which may persist 11. Breast changes: tenderness, enlargement, secretion 12. Change in weight (increase or decrease) 13. Change in cervical erosion and secretions 14. Diminution in lactation when given immediately postpartum 15. Cholestatic jaundice 16. Migraine 17. Rash (allergic) 18. Mental depression 19. Reduced tolerance to carbohydrates 20. Vaginal candidiasis 21. Change in corneal curvature (steepening) 22. Intolerance to contact lenses. The following adverse reactions have been reported in users of combination hormonal contraceptives and a cause and effect association has been neither confirmed nor refuted: 1. Pre-menstrual syndrome 2. Contact lens 3. Changes in appetite 4. Cystitis-like syndrome 5. Headache 6. Nervousness 7. Dizziness 8. Hirsutism 9. Loss of scalp hair 10. Erythema multiforme 11. Erythema nodosum 12. Hemorrhagic eruption 13. Vaginitis 14. Porphyria 15. Impaired renal function 16. Hemolytic uremic syndrome 17. Acne 18. Changes in libido 19. Colitis 20. Budd-Chiari Syndrome. **OVERDOSE:** Serious ill effects have not been reported following accidental ingestion of large doses of hormonal contraceptives. Overdose may cause nausea and vomiting, and withdrawal bleeding may occur in females. Given the nature and dosing of ORTHO EVRA® patch, it is unlikely that overdose will occur. Serious ill effects have not been reported following acute ingestion of large doses of oral contraceptives by young children. In case of suspected overdose, all ORTHO EVRA® patches should be removed and symptomatic treatment given.