

Norelgestromin/Ethinyl Estradiol Transdermal System (Ortho Evra™, Ortho-McNeil Pharmaceuticals, Inc.)

Estrogen exposure and the risk of thromboembolism

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The norelgestromin/ethinyl estradiol transdermal patch was approved by the Food and Drug Administration (FDA) in 2001. It was the first, and is still the only, contraceptive available in a transdermal dosage form. Each 20-cm² patch contains 0.75 mg ethinyl estradiol and 6 mg norelgestromin and is designed to release 20 mcg of ethinyl estradiol and 150 mcg of norelgestromin over 24 hours. Improved compliance with the patch over oral contraceptives has been seen in clinical trials, especially in the adolescent population.¹⁻³ The patch has proven to be as effective as oral contraceptives in preventing pregnancy, and had a similar safety profile in clinical trials.^{1-2, 4-8}

On November 10, 2005 the FDA approved updated labeling for the norelgestromin/ethinyl estradiol transdermal patch. The new labeling warns health care providers and patients that the product exposes women to higher levels of estrogen than most oral contraceptives. The new warning states that women who use the norelgestromin/ethinyl estradiol transdermal patch are exposed to about 60% more estrogen, as measured by area-under-the-curve (AUC) and steady state concentration (C_{ss}), than if they were to take a typical oral contraceptive containing 35 micrograms of estrogen.⁹ This warning is based on an unpublished study comparing the two contraceptive methods. The AUC (pg·h/mL) values are reported to be 8281 and 12971 for the 35 mcg oral contraceptive at day 21 and the transdermal patch at week 3, respectively. Also, the C_{ss} (pg/mL) for the same time are 49.3 and 80, oral and transdermal.¹⁰ Despite the increased overall exposure to estrogen, the peak concentration of estrogen is 25% lower with the norelgestromin/ethinyl estradiol transdermal patch than with typical oral contraceptives.⁹ This effect would be expected, as the transdermal system is designed to minimize peak and trough concentrations seen with orally administered medications.

In general, increased estrogen exposure may increase the risk of venous thromboembolism (VT). It is not known, however, whether women using the norelgestromin/ethinyl estradiol transdermal patch are at greater risk for experiencing these adverse events.⁹ Public media has published information stating an increased risk of stroke and thromboembolic events in patients using the contraceptive patch, however, these cases were based on spontaneous reporting to the FDA. Since no comparison to traditional oral contraceptives was performed, it cannot be determined if the number of events differs among the two groups. Additional studies are currently being conducted to determine if patients are at an increased risk of serious side effects when using the contraceptive patch in comparison to the 35 mcg oral tablet.⁹

Summary

Indication. The norelgestromin/ethinyl estradiol transdermal patch is indicated for the prevention of pregnancy.

Monitoring Parameters. Efficacy should be monitored by confirming regular menstrual cycles. Safety can be evaluated by monitoring for signs of thromboembolism, including painful, inflamed extremities; severe headache; and difficulty breathing. Liver function tests, cholesterol screening, visual exams, and signs of depression should also be monitored periodically.

Dose. The patch must be used exactly as directed for maximum contraceptive effectiveness. Each patch should be applied to the buttocks, abdomen, upper torso (excluding the breast), or the upper arm, and should be worn for 7 days for three consecutive weeks per month and no patch worn on the fourth week. Poor adhesion has been reported and up to 4.7% of patches require replacement. If detached more than one day, a new patch should be applied and the cycle restarted.

Pregnancy. Category X

Breast Feeding. The effects of the norelgestromin/ethinyl estradiol transdermal patch in nursing mothers have not been evaluated and are unknown. Small amounts of combination hormonal contraceptives have been identified in the milk of nursing mothers and adverse effects, including jaundice and breast enlargement, have been reported in nursing children. Combination hormonal contraceptives given in the postpartum period may also interfere with lactation by decreasing the quantity and quality of breast milk. Long-term follow-up of infants whose mothers used combination hormonal contraceptives while breastfeeding has shown no deleterious effects. However, advise the nursing mother not to use the transdermal patch, but to use other forms of contraception until she has completely weaned her child.

Special Populations. May be less effective in women with body weight \geq 90 kg.

Children. Safety and efficacy are expected to be the same for post pubertal adolescents <16 years of age and for users \geq 16 years of age. Use of the norelgestromin/ethinyl estradiol transdermal patch before menarche is not indicated.

Renal Insufficiency. No adjustment necessary.

Hepatic Insufficiency. The hormones are poorly metabolized in patients with impaired liver function.

Cost. Average wholesale price (AWP) for a carton that contains 3 patches (1 cycle) is \$41.22. A carton containing a single patch used for replacement is \$13.74.

TABLE 1. PHARMACOKINETIC SUMMARY

STUDY	DESIGN	OUTCOMES	COMMENTS
Skee D et al ¹¹	Single center, randomized, open label, 4-way crossover N = 37 Subjects applied a 20-cm ² patch for 7 days at each site (abdomen, buttock, upper outer arm, upper torso)	Pharmacokinetic Parameters Absorption at all sites was within the reference mean C _{ss} for both 17d-NGM and EE. AUC (EE) (pg•h/mL) mean (±SD) Abdomen 7163 (2211), Arm 8751 (2272), Buttock 8397 (2622), Torso 8599 (3161)	Mean C _{ss} range based on studies of the mean C _{avg} for Ortho-Cyclen All patches remained attached Most frequent AE: nausea, headache, vomiting, rhinitis, pharyngitis, abdominal pain, menstrual disorder, itching at application sight
Abrams LS et al ¹²	Randomized, open label, 3-period, crossover N = 30 Subjects wore a 10-cm ² , 15-cm ² , and 20-cm ² on abdomen for 7 days each with 1 month washout between patches	Pharmacokinetic parameters (N=29) 17d-NGM C _{ss} below reference range more frequently with smaller patches For 20-cm ² patch, C _{ss} below reference range in 3 patients, within range in 25 patients, above range in 1 patient EE C _{ss} below reference range more frequently with smaller patches For 20-cm ² patch, C _{ss} below range in 1 patient, within range in 22 patients, above range in 6 patients	All patches remained attached No serious AEs reported Most common AEs: headache (only in the 20-cm ² patch) and nausea
Abrams LS et al ¹³	Single center, open label N = 12 20-cm ² patch applied to abdomen for 7 days, followed by 2nd patch for 10 days	Pharmacokinetic Parameters Both NGMN and EE remained in reference range for first 7 days, and for 9 days of second cycle AUC (EE) (pg•h/mL) mean (±SD) • 0-168 h = 6769 (3083) • 168-336 h = 8353 (3098) • 168-408 h = 10816 (3695)	Remained therapeutic for 2 days past recommended changing day, allowing for flexibility in changing doses Only AE reported were application site reactions and nausea
Abrams LS et al ¹⁴	Open label, parallel, 2-way crossover, single center N = 26 Patch on buttocks or abdomen for 7 days or single IV infusion of 252 mcg NGMN and 25 mcg of EE	Pharmacokinetic Parameters Patch shown to administer 20 mcg EE and 150 mcg NGMN based on the clearance of the IV preparation and the steady state concentration of the patch administration AUC were similar to previous study numbers	Most frequent AE were headache, pain, pharyngitis

EE = ethinyl estradiol; 17d-NGM (NGMN) 17-deacetylnorgestimate (norelgestromin); AUC = area-under-the-curve; C_{ss} = steady state concentration; AE = adverse event

TABLE 2. PHARMACOKINETIC RESULTS¹⁵

Pharmacokinetic parameter	Geometric mean			Ratio of points estimates (95% confidence interval)		
	Ring (n=8)	Patch (n=6)	COC (n=8)	COC/Ring	Patch/Ring	Patch/COC
C _{max} (pg/mL)	36.8	104.0	165	4.5 (3.9-5.3)*	2.8 (2.4-2.4)*	0.63 (0.53-0.75)*
AUC ₀₋₂₁ (ng•h/mL)	10.4	35.4	21.7	2.1 (1.7-2.6)*	3.4 (2.8-4.2)*	1.6 (1.3-2.0)*
AUC _{0-last} (ng•h/mL)	10.8	37.2	22.3	2.1 (1.7-2.5)*	3.4 (2.8-3.4)*	1.7 (1.3-2.1)*
AUC _{0-∞} (ng•h/mL)	10.9	37.4	22.5	2.1 (1.7-2.5)*	3.4 (2.8-4.3)*	1.7 (1.3-2.1)*

*p<0.05

CLINICAL PHARMACOLOGY

Combination oral contraceptives act by suppression of gonadotropins. Although the primary mechanism of action is inhibition of ovulation, other alterations include changes in the cervical mucus, which increase the difficulty of sperm entry into the uterus, and changes in the endometrium, which reduce the likelihood of implantation.¹⁰

PHARMACOKINETICS

Pharmacokinetic parameters were evaluated by the manufacturer prior to the norelgestromin/ethinyl estradiol transdermal patch being approved to market. Most of the data were published in abstract form and/or in a poster presentation. While the C_{ss} were compared to average concentrations (C_{avg}) of oral ethinyl estradiol 35 mcg/norethindrone 1 mg that had been determined in previous trials, there were never any direct comparisons of pharmacokinetic parameters, including AUC, between oral and transdermal contraceptive products. Each of the evaluations of the transdermal patch reported similar AUC values for ethinyl estradiol (EE). These trials are summarized in table 1.

Wilhelmus van den Heuvel et al completed an open-label, randomized study comparing the pharmacokinetics of EE from the contraceptive vaginal ring (15 mcg EE), the transdermal patch (20 mcg EE), and a combined oral contraceptive (COC) containing 30 mcg EE.¹⁵ Twenty-four healthy women were randomized to receive 21 days of one of the estrogen treatments. Baseline characteristics were well balanced. Results are summarized in table 2. The transdermal patch exhibited the highest AUC values out of each of the therapies. The overall exposure of EE in patients using the patch compared to COC was about 60% higher in the patch group, which correlates with the FDA reports.

Adverse events were also evaluated as part of the study design. No major adverse events were reported in any of the groups, but the patch group reported the most treatment-related adverse events ($n = 57$). The most common were headache ($n = 9$), breast tenderness ($n = 7$) and nausea ($n = 6$).

DRUG INTERACTIONS

Contraceptive effectiveness may be reduced when hormonal contraceptives are administered with some antibiotics, antifungals, anticonvulsants, or other drugs that may increase metabolism of contraceptive steroids. Significant changes in AUC have been seen with oral contraceptives when administered with protease inhibitor medications, possibly affecting their safety and efficacy. It is not known if these interactions occur with the use of the transdermal patch. Herbal products containing St. Johns Wort may induce hepatic enzymes and p-glycoprotein transporter and may reduce the effectiveness of steroid contraceptives. Atorvastatin has been shown to increase AUC levels for ethinyl estradiol by 20% when co-administered. Cytochrome P450 3A4 inhibitors (such as itraconazole or ketoconazole) may increase plasma hormone levels. Increased plasma concentrations of cyclosporine, prednisolone, and theophylline have been reported when administered with oral contraceptives. Decreased plasma levels of acetaminophen and increased clearance of temazepam, salicylic acid, morphine and clofibrac acid have been noted when taken with oral contraceptives.¹⁰

CLINICAL TRIALS

The norelgestromin/ethinyl estradiol transdermal patch has been determined to be as efficacious as traditional COCs when evaluated in head-to-head studies, as well as demonstrating improved compliance due to the once weekly application.¹⁻⁸

Safety

The risk of VT is well established with regard to the use of hormone contraception. There is a 10-fold increase in the rate of VT among women using oral contraceptives (OCs) containing more than 50 mcg of estrogen, compared to a 7-fold increase in those using formulations containing 50 mcg of estrogen and a 4-fold increase among users of OCs containing less than 50 mcg of estrogen. However, it is still unclear whether the overall exposure to estrogen or the maximum concentration of estrogen, or both, is the cause of the increased events. The initial reporting of VT was seen in the 1960s and since that time, the estrogen content has decreased steadily in the OCs.¹⁶

In Phase III clinical trials ($n = 3,330$), one case of non-fatal pulmonary embolism (PE) occurred during appropriate norelgestromin/ethinyl estradiol transdermal patch use, and one case of postoperative, nonfatal PE occurred. In the case of the postoperative PE, the patient wore the patch up to the day of surgery, which is not currently recommended in the dosing protocol.¹⁷ The effect of the norelgestromin/ethinyl estradiol transdermal patch on coagulation parameters was also evaluated in an open-label, randomized trial ($n = 103$). The study found that the transdermal patch increased the conversion of prothrombin to thrombin, resulting in an increase in fibrin degradation products. This finding, however, was no different than the OC group, which exhibited similar changes in the coagulation parameters.¹⁸

ADVERSE EFFECTS

The adverse effect profile is similar to that of traditional OCs.¹⁰ The most commonly reported AEs in clinical trials were headache, nausea, application site reactions, and breast tenderness.^{1-8,11-15} Contraindications, warnings and precautions are summarized in Table 3.

PRODUCT AVAILABILITY/COST/DOSE

The norelgestromin/ethinyl estradiol transdermal patch is available in cartons containing one cycle (three patches) and cartons containing a single patch, which would be intended for use as a replacement patch in the event a patch is lost or destroyed.¹⁰ The AWP is \$41.22 for the one-cycle cartons and \$13.47 for the single patch cartons. The patch must be used exactly as directed for maximum contraceptive effectiveness. Each patch should be applied to the buttocks, abdomen, upper torso (excluding the breast), or the upper arm, and should be worn for seven days for three consecutive weeks per month and no patch worn on the fourth week.⁸ Poor adhesion has been reported and up to 4.7% of patches require replacement.⁷ If detached more than one day, a new patch should be applied and the cycle restarted.¹⁰

CONCLUSION

Based on current data, there is no indication that patients utiliz-

**TABLE 3. CONTRAINDICATIONS/
WARNINGS/PRECAUTIONS¹⁰**

Contraindications

- Thrombophlebitis, thromboembolic disorders (current or past history)
- Cerebrovascular or coronary artery disease (current or past history)
- Valvular heart disease with complications
- Severe hypertension
- Diabetes with vascular involvement
- Headaches with focal neurological symptoms
- Major surgery with prolonged immobilization
- Known or suspected carcinoma of the breast or personal history of breast cancer
- Undiagnosed abnormal genital bleeding
- Cholestatic jaundice of pregnancy or jaundice with prior hormonal contraceptive use
- Acute or chronic hepatocellular disease with abnormal liver function
- Hepatic adenomas or carcinomas
- Known or suspected pregnancy
- Hypersensitivity to any component of the product

Warnings

- Cigarette smoking increases the risk of serious cardiovascular side effects from hormonal contraceptive use. The risk increases with age and heavy smoking.
- Patients may be at an increased risk of the following:
 - Thromboembolism
 - Myocardial infarction
 - Cerebrovascular disease
 - Carcinoma of reproductive organs and breast
 - Hepatic neoplasia
 - Ocular lesions
 - Gallbladder disease
 - Carbohydrate and lipid metabolic effects
 - Elevated blood pressure
 - Headache
 - Bleeding irregularities
 - Ectopic pregnancy

Precautions

- Women should be counseled that the patch does not protect against human immunodeficiency virus (HIV) or sexually transmitted diseases (STDs).
- May be less effective in women with body weight \geq 90 kg.
- Some progestins may elevate low density lipoprotein (LDL).
- If jaundice develops, the patch should be discontinued. The hormones are poorly metabolized in patients with impaired liver function.
- May cause some degree of fluid retention
- May cause some emotional disturbances. Women with a history of depression should be carefully observed. If signs of depression are seen, the patch should be stopped immediately.
- Contact lens wearers who develop visual changes or changes in lens tolerance should see an ophthalmologist.
- Pregnancy category X
- The effects of the patch in nursing mothers have not been evaluated and are unknown.
- Use of this product before menarche is not indicated.

ing the norelgestromin/ethinyl estradiol transdermal patch have an increased frequency of VT or any other serious adverse event. Historically, higher doses of estrogen have been linked to greater adverse events, which would indicate that there is a potential for these events to occur in transdermal patch users. Doses greater than 50 mcg have shown the highest increase in risk, but no comparison trials have been completed to identify if the estrogen exposure of the norelgestromin/ethinyl estradiol transdermal patch is equivalent to that of a 50 mcg or higher oral contraceptive.

The patch may still be beneficial in populations who have poor compliance, such as adolescents and young women, and this group is typically at a lower risk of VT overall. In contrast, the patch should not be recommended in women over the age of 35 and/or smokers, as these groups are at an increased risk of VT. Until clinical trials are published which may answer the questions that remain regarding risk of VT and other serious adverse events, each individual practitioner needs to make a clinical decision based on patient risk factors and contraceptive needs when choosing a contraceptive method. In addition, women need to be made aware of the increased estrogen exposure and potential safety concerns in order to enable them to make an informed decision regarding their own care. ●

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