

**XULANE- norelgestromin and ethinyl estradiol patch**  
**Mylan Pharmaceuticals Inc.**

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**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use XULANE® safely and effectively. See full prescribing information for XULANE.

XULANE® (norelgestromin and ethinyl estradiol transdermal system)  
Initial U.S. Approval: 2001

**WARNING: CARDIOVASCULAR RISK ASSOCIATED WITH SMOKING, RISK OF VENOUS THROMBOEMBOLISM, AND PHARMACOKINETIC PROFILE OF ETHINYL ESTRADIOL**

*See full prescribing information for complete boxed warning.*

**Women over 35 years old who smoke should not use Xulane. (4)**

**Cigarette smoking increases the risk of serious cardiovascular events from combination hormonal contraceptives (CHC) use. (4)**

**There may be an increased risk of venous thromboembolism (VTE) among women who use the Xulane patch compared to women who use certain oral contraceptives. (5.1)**

**The pharmacokinetic (PK) profile of ethinyl estradiol (EE) for the norelgestromin and ethinyl estradiol transdermal system is different from the PK profile for oral contraceptives in that it has higher area under the time-concentration curve, steady state concentrations and lower peak concentrations. (5.2)**

----- **RECENT MAJOR CHANGES** -----

Contraindications (4) 4/2017

Warnings (5.4) 4/2017

----- **INDICATIONS AND USAGE** -----

Xulane is an estrogen/progestin combination hormonal contraceptive (CHC), indicated for the prevention of pregnancy in women who elect to use a transdermal patch. (1)

Limitation of Use: Xulane may be less effective in preventing pregnancy in women at or above 198 lbs (90 kg). (1)

----- **DOSAGE AND ADMINISTRATION** -----

- Xulane uses a 28-day (4-week) cycle. Apply a new patch to the upper outer arm, abdomen, buttock or back each week for 3 weeks (21 total days). Week 4 is patch-free. (2.1, 2.3)
- Apply each new patch on the same day of the week. Wear only one patch at a time. (2.1)
- Do not cut or alter the patch in any way. (2.1)

----- **DOSAGE FORMS AND STRENGTHS** -----

Transdermal system: 150 mcg/day norelgestromin and 35 mcg/day ethinyl estradiol. (3)

----- **CONTRAINDICATIONS** -----

- A high risk of arterial or venous thrombotic diseases (4)
- Breast cancer or other estrogen- or progestin-sensitive cancer (4)
- Liver tumors or liver disease (4)
- Undiagnosed abnormal uterine bleeding (4)
- Pregnancy (4)
- Co-administration with Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir (4)

----- **WARNINGS AND PRECAUTIONS** -----

- **Vascular risks:** Stop Xulane if a thrombotic event occurs. Stop at least 4 weeks before and through 2 weeks after major surgery. Start no earlier than 4 weeks after delivery, in women who are not breastfeeding. (5.1)
- **Liver disease:** Discontinue Xulane if jaundice occurs. (5.3)
- **High blood pressure:** Do not prescribe Xulane for women with uncontrolled hypertension or hypertension with vascular disease. (5.5)
- **Carbohydrate and lipid metabolic effects:** Monitor prediabetic and diabetic women taking Xulane. Consider an alternate contraceptive method for women with uncontrolled dyslipidemia. (5.7)

- Headache: Evaluate significant change in headaches and discontinue Xulane if indicated. (5.8)
- Uterine bleeding: Evaluate irregular bleeding or amenorrhea. (5.9)

----- **ADVERSE REACTIONS** -----

The most frequent adverse reactions reported during clinical trials ( $\geq 5\%$ ) were breast symptoms, nausea/vomiting, headache, application site disorder, abdominal pain, dysmenorrhea, vaginal bleeding and menstrual disorders, and mood, affect and anxiety disorders. (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact Mylan Pharmaceuticals Inc. at 1-877-446-3679 (1-877-4-INFO-RX) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

----- **DRUG INTERACTIONS** -----

Drugs or herbal products that induce certain enzymes (for example CYP3A4) may decrease the effectiveness of CHCs or increase breakthrough bleeding. Counsel patients to use a back-up or alternative method of contraception when enzyme inducers are used with CHCs. (7.1)

----- **USE IN SPECIFIC POPULATIONS** -----

- Nursing mothers: Not recommended; can decrease milk production. (8.3)

See 17 for **PATIENT COUNSELING INFORMATION** and **FDA-approved patient labeling**.

**Revised: 4/2017**

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## **FULL PRESCRIBING INFORMATION**

## **WARNING: CARDIOVASCULAR RISK ASSOCIATED WITH SMOKING, RISK OF VENOUS THROMBOEMBOLISM, AND PHARMACOKINETIC PROFILE OF ETHINYL ESTRADIOL**

### **Cigarette Smoking and Serious Cardiovascular Risks**

**Cigarette smoking increases the risk of serious cardiovascular events from hormonal contraceptive use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, hormonal contraceptives, including Xulane, should not be used by women who are over 35 years of age and smoke.**

### **Risk of Venous Thromboembolism**

**The risk of venous thromboembolism (VTE) among women aged 15 to 44 who used the norelgestromin and ethinyl estradiol transdermal system compared to women who used several different oral contraceptives was assessed in five U.S. epidemiologic studies using electronic healthcare claims data. The relative risk estimates ranged from 1.2 to 2.2; one of the studies found a statistically significant increased relative risk of VTE for current users of norelgestromin and ethinyl estradiol transdermal system [see *Warnings and Precautions (5.1)*].**

### **Pharmacokinetic (PK) Profile of Ethinyl Estradiol (EE)**

**The PK profile for the norelgestromin and ethinyl estradiol transdermal system is different from the PK profile for oral contraceptives in that it has a higher steady state concentrations and a lower peak concentration. Area under the time-concentration curve (AUC) and average concentration at steady state ( $C_{ss}$ ) for EE are approximately 60% higher in women using norelgestromin and ethinyl estradiol transdermal system compared with women using an oral contraceptive containing 35 mcg of EE. In contrast, the peak concentration ( $C_{max}$ ) for EE is approximately 25% lower in women using norelgestromin and ethinyl estradiol transdermal system. It is not known whether there are changes in the risk of serious adverse events based on the differences in PK profiles of EE in women using norelgestromin and ethinyl estradiol transdermal system compared with women using oral contraceptives containing 30 mcg to 35 mcg of EE. Increased estrogen exposure may increase the risk of adverse events, including VTE [see *Warnings and Precautions (5.2)* and *Clinical Pharmacology (12.3)*].**

## **1 INDICATIONS AND USAGE**

Xulane is indicated for the prevention of pregnancy in women who elect to use a transdermal patch as a method of contraception.

### ***Limitation of Use:***

- Xulane may be less effective in preventing pregnancy in women who weigh 198 lbs (90 kg) or more.

## **2 DOSAGE AND ADMINISTRATION**

To achieve maximum contraceptive effectiveness, Xulane must be used exactly as directed.

Complete instructions to facilitate patient counseling on proper system usage may be found in the FDA-Approved Patient Labeling.

### **2.1 How to Use Xulane**

The Xulane transdermal system uses a 28-day (4-week) cycle. A new patch is applied each week for 3

weeks (21 total days). Week 4 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.

Do not cut, damage or alter the Xulane patch in any way. If the Xulane patch is cut, damaged or altered in size, contraceptive efficacy may be impaired.

On the day after Week 4 ends, a new 4-week cycle is started by applying a new patch. Under no circumstances should there be more than a 7-day patch-free interval between dosing cycles.

## 2.2 How to Start Using Xulane

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

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

### *Use after Childbirth*

Start contraceptive therapy with Xulane in women who elect not to breastfeed no sooner than 4 weeks after childbirth due to increased risk of thromboembolism. If a woman begins using Xulane postpartum, and has not yet had a period, consider the possibility of ovulation and conception occurring prior to use of Xulane, and instruct her to use an additional method of contraception, such as a condom and spermicide or diaphragm and spermicide, for the first 7 days. [See *Warnings and Precautions (5.1) and Pregnancy (8.1).*]

### *Use after Abortion or Miscarriage*

After an abortion or miscarriage that occurs in the first trimester, Xulane may be started immediately. An additional method of contraception is not needed if Xulane is started immediately. If use of Xulane is not started within 5 days following a first trimester abortion, the woman should follow the instructions for a woman starting Xulane for the first time. In the meantime she should be advised to use a non-hormonal contraceptive method. Ovulation may occur within 10 days of an abortion or miscarriage.

Start Xulane no earlier than 4 weeks after a second trimester abortion or miscarriage, due to the increased risk of thromboembolic disease. [See *Contraindications (4) and Warnings and Precautions (5.1).*]

## 2.3 How to Apply Xulane

CHOOSING A PLACE ON THE BODY TO PUT THE PATCH



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

Before applying the patch:

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

#### HOW TO APPLY THE PATCH

	<ul style="list-style-type: none"> <li>• The woman should tear open the pouch at the top edge <b>and</b> one side edge. She should peel open the foil pouch. She should gently remove the contents of the foil pouch and discard the additional pieces of film above and below the patch.</li> </ul>
	<ul style="list-style-type: none"> <li>• The woman should peel away half of the clear plastic. She should avoid touching the sticky surface with her fingers.</li> </ul>
	<ul style="list-style-type: none"> <li>• The woman should apply the sticky side of the patch on the skin she has cleaned and dried. She should then remove the other half of the clear plastic and attach the entire patch to her skin.</li> </ul>
	<ul style="list-style-type: none"> <li>• The woman should press firmly on the patch with the palm of her hand for 10 seconds, making sure that the whole patch adheres to her skin.</li> <li>• She should run her fingers over the entire surface area to smooth out any “wrinkles” around the outer edges of the patch.</li> </ul>

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

#### WHEN TO CHANGE THE XULANE PATCH

- The patch works for 7 days (1 week). The woman should apply a new patch on the same day each week (her Patch Change Day) for 3 weeks in a row. She must make sure she has removed her old patch prior to applying the new patch.
- During Week 4, she **DOES NOT** wear a patch. She must make sure she removes her old patch. (Her period should begin during this week.)
- Following Week 4, she repeats the cycle of three weekly applications followed by a patch-free week.

#### WHAT IF THE PATCH BECOMES LOOSE OR FALLS OFF?

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

##### **If a patch edge lifts up:**

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

##### **If the patch has been off or partially off:**

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

#### IF THE WOMAN FORGETS TO CHANGE HER PATCH

- **at the start of any patch cycle (Week 1/Day 1): SHE MAY NOT BE PROTECTED FROM PREGNANCY.** She should apply the first patch of her new cycle as soon as she remembers. There is now a new “Patch Change Day” and a new “Day 1.” The woman must use back-up contraception, such as a condom and spermicide or diaphragm and spermicide, for the first week of the new cycle.
- **in the middle of the patch cycle (Week 2/Day 8 or Week 3/Day 15),**
  - for **1 or 2 days** (up to 48 hours), she should apply a new patch immediately. The next patch should be applied on the usual “Patch Change Day.” No back-up contraception is needed.
  - for more than 2 days (48 hours or more), SHE MAY NOT BE PROTECTED FROM PREGNANCY. She should stop the current contraceptive cycle and start a new 4-week cycle immediately by putting on a new patch. There is now a new “Patch Change Day” and a

new “Day 1.” The woman must use back-up contraception for 1 week.

- **at the end of the patch cycle (Week 4/Day 22),**
  - If the woman forgets to remove her patch, she should take it off as soon as she remembers. The next cycle should be started on the usual “Patch Change Day,” which is the day after Day 28. No back-up contraception is needed.

**Under no circumstances should there be more than a 7-day patch-free interval between cycles.** If there are more than 7 patch-free days, THE WOMAN MAY NOT BE PROTECTED FROM PREGNANCY and back-up contraception, such as a condom and spermicide or diaphragm and spermicide, must be used for 7 days. As with combined oral contraceptives, the risk of ovulation increases with each day beyond the recommended drug-free period. If she has had intercourse during such an extended patch-free interval, consider the possibility of pregnancy.

### ***Change Day Adjustment***

If the woman wishes to change her Patch Change Day, she should complete her current cycle, removing the third Xulane patch on the correct day. During the patch-free week, she may select an earlier Patch Day Change by applying a new Xulane patch on the desired day. In no case should there be more than 7 consecutive patch-free days.

### ***Breakthrough Bleeding or Spotting***

In the event of unscheduled or breakthrough bleeding or spotting (bleeding that occurs on the days that Xulane is worn), treatment should be continued. If unscheduled bleeding persists longer than a few cycles, consider causes other than Xulane.

If the woman does not have scheduled or withdrawal bleeding (bleeding that should occur during the patch-free week), she should resume treatment on the next scheduled Change Day. If Xulane has been used correctly, the absence of withdrawal bleeding is not necessarily an indication of pregnancy. Nevertheless, consider the possibility of pregnancy, especially if absence of withdrawal bleeding occurs in 2 consecutive cycles. Discontinue Xulane if pregnancy is confirmed.

### ***In Case of Skin Irritation***

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

### ***Additional Instructions for Dosing***

Unscheduled bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing hormonal contraceptives. In case of breakthrough bleeding, as in all cases of irregular bleeding from the vagina, consider nonfunctional causes. In case of undiagnosed persistent or recurrent abnormal bleeding from the vagina, take adequate diagnostic measures to rule out pregnancy or malignancy. If pathology has been excluded, time or a change to another method of contraception may solve the problem.

### ***Use of Hormonal Contraceptives in the Event of a Missed Menstrual Period***

1. If the woman has not adhered to the prescribed schedule, consider the possibility of pregnancy at the time of the first missed period. Discontinue use of Xulane if pregnancy is confirmed.
2. If the woman has adhered to the prescribed regimen and misses one period, she should continue using her contraceptive patches. However, if she has adhered to the prescribed regimen, misses one period and has symptoms associated with pregnancy, rule out pregnancy. Discontinue Xulane use if pregnancy is confirmed.



3. If the woman has adhered to the prescribed regimen and misses two consecutive periods, rule out pregnancy. Discontinue Xulane use if pregnancy is confirmed.

### 3 DOSAGE FORMS AND STRENGTHS

Xulane<sup>®</sup> (norelgestromin and ethinyl estradiol transdermal system) is available in one strength of 150 mcg/day norelgestromin (NGMN) and 35 mcg/day ethinyl estradiol (EE).

Xulane<sup>®</sup> is a 14 cm<sup>2</sup> peach, transdermal system printed with “Xulane<sup>®</sup> (norelgestromin and ethinyl estradiol) 150/35 mcg per day” in brown ink. Each system contains 4.86 mg norelgestromin, USP and 0.53 mg ethinyl estradiol, USP.

### 4 CONTRAINDICATIONS

Do not prescribe Xulane to women who are known to have the following conditions:

- A high risk of arterial or venous thrombotic diseases. Examples include women who are known to:
  - Smoke, if over age 35 [*see Boxed Warning, and Warnings and Precautions (5.1)*]
  - Have deep vein thrombosis or pulmonary embolism, now or in the past [*see Warnings and Precautions (5.1)*]
  - Have inherited or acquired hypercoagulopathies [*see Warnings and Precautions (5.1)*]
  - Have cerebrovascular disease [*see Warnings and Precautions (5.1)*]
  - Have coronary artery disease [*see Warnings and Precautions (5.1)*]
  - Have thrombogenic valvular or thrombogenic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease, or atrial fibrillation) [*see Warnings and Precautions (5.1)*]
  - Have uncontrolled hypertension [*see Warnings and Precautions (5.5)*]
  - Have diabetes mellitus with vascular disease [*see Warnings and Precautions (5.7)*]
  - Have headaches with focal neurological symptoms or have migraine headaches with aura
    - Women over age 35 with any migraine headaches [*see Warnings and Precautions (5.8)*]
- Liver tumors, benign or malignant, or liver disease [*see Warnings and Precautions (5.3), Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)*]
- Undiagnosed abnormal uterine bleeding [*see Warnings and Precautions (5.9)*]
- Pregnancy, because there is no reason to use hormonal contraceptives during pregnancy [*see Warnings and Precautions (5.10) and Use in Specific Populations (8.1)*]
- Breast cancer or other estrogen- or progestin-sensitive cancer, now or in the past [*see Warnings and Precautions (5.12)*]
- Use of Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to the potential for alanine aminotransferase (ALT) elevations [*see Warnings and Precautions (5.4)*]

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Thromboembolic Disorders and Other Vascular Problems

Stop Xulane if an arterial or deep venous thrombotic event (VTE) occurs.

Stop Xulane if there is unexplained loss of vision, proptosis, diplopia, papilledema, or retinal vascular

lesions. Evaluate for retinal vein thrombosis immediately.

If feasible, stop Xulane at least 4 weeks before and through 2 weeks after major surgery or other surgeries known to have an elevated risk of VTE. Discontinue use of Xulane during prolonged immobilization and resume treatment based on clinical judgment.

Start Xulane no earlier than 4 weeks after delivery, in women who are not breastfeeding. The risk of postpartum VTE decreases after the third postpartum week, whereas the risk of ovulation increases after the third postpartum week.

The use of combination hormonal contraceptives (CHCs) increases the risk of VTE. Known risk factors for VTE include smoking, obesity and family history of VTE, in addition to other factors that contraindicate use of CHCs [see *Contraindications (4)*].

Five epidemiologic studies<sup>1-9</sup> that assessed the risk of VTE associated with use of norelgestromin and ethinyl estradiol transdermal system are described below. These are 4 case control studies, that compared VTE rates among women using norelgestromin and ethinyl estradiol transdermal system to rates among women using an OC comparator, and an FDA-funded cohort study that estimated and compared VTE rates among women using various hormonal contraceptives, including norelgestromin and ethinyl estradiol transdermal system. All five studies were retrospective studies from U.S. electronic healthcare databases and included women aged 15 to 44 (10 to 55 in the FDA-funded study) who used norelgestromin and ethinyl estradiol transdermal system or oral contraceptives containing 20 mcg to 35 mcg of ethinyl estradiol (EE) and levonorgestrel (LNG), norethindrone, or norgestimate (NGM). NGM is the prodrug for NGMN, the progestin in Xulane.

Some of the data from the epidemiologic studies suggest an increased risk of VTE with use of norelgestromin and ethinyl estradiol transdermal system compared to use of some combined oral contraceptives (see Table 1). The studies used slightly different designs and reported relative risk estimates ranging from 1.2 to 2.2. None of the studies have adjusted for body mass index, smoking, and family history of VTE, which are potential confounders. The interpretations of these relative risk estimates range from no increase in risk to an approximate doubling of risk. One of the studies found a statistically significant increased risk of VTE for current users of norelgestromin and ethinyl estradiol transdermal system.

The five studies are:

- The i3 Ingenix study with NGM-containing oral contraceptives as the comparator, including a 24-month extension, based on the Ingenix Research Datamart; this study included patient chart review to confirm the VTE occurrence.
- The Boston Collaborative Drug Surveillance Program (BCDSP) with NGM-containing oral contraceptives as the comparator (BCDSP NGM), including two extensions of 17 and 14 months, respectively, based on the Pharmedics database, using only non-fatal idiopathic cases. VTE cases were not confirmed by chart review.
- BCDSP with LNG-containing oral contraceptives as the comparator, based on the Pharmedics database, using only non-fatal idiopathic cases. VTE cases were not confirmed by chart review.
- BCDSP with LNG-containing oral contraceptives as the comparator, based on the MarketScan database, using only non-fatal idiopathic cases. VTE cases were not confirmed by chart review.
- FDA-funded study with two groups of comparators [1) LNG-containing oral contraceptives, and 2) oral contraceptives that contain LNG, norethindrone or norgestimate], based on Kaiser Permanente and Medicaid databases. This study used all cases of VTE (idiopathic and non-idiopathic) and included patient chart review to confirm the VTE occurrence.

The i3 Ingenix and BCDSP NGM studies have provided data on additional cases identified in study extensions; however, each study extension was not powered to provide independent estimates of risk. The pooled estimates provide the most reliable estimates of VTE risk. Risk ratios from the original and various extensions of the i3 Ingenix and BCDSP NGM studies are provided in Table 1. The results of

these studies are presented in Figure 1.

**Table 1: Estimates (Risk Ratios) of Venous Thromboembolism Risk in Current Users of Norelgestromin and Ethinyl Estradiol Transdermal System Compared to Combined Oral Contraceptive Users**

<b>Epidemiologic Study*</b>	<b>Comparator Product</b>	<b>Risk Ratios (95% CI)</b>
i3 Ingenix NGM Study in Ingenix Research Datamart <sup>1,6,7,8</sup>	NGM/35 mcg EE <sup>†</sup>	<b>2.2<sup>‡</sup> (1.2 – 4.0)<sup>§</sup></b>
BCDSP <sup>¶</sup> NGM Study in Pharmetrics database <sup>2,3,5</sup>	NGM/35 mcg EE	<b>1.2 (0.9 – 1.8)<sup>#</sup></b>
BCDSP <sup>¶</sup> LNG Study in Pharmetrics database <sup>4</sup>	LNG <sup>Ⓛ</sup> /30 mcg EE	<b>2.0 (0.9 – 4.1)<sup>β</sup></b>
BCDSP <sup>¶</sup> LNG Study in Marketscan database <sup>4</sup>	LNG/30 mcg EE	<b>1.3 (0.8 – 2.1)<sup>à</sup></b>
FDA-funded Study in Kaiser Permanente and Medicaid databases <sup>è,δ,9</sup>	“All progestins <sup>∅</sup> ”/20 - 35 mcg EE LNG/30 mcg EE	<b>1.4 (0.9 – 2.0)</b> <b>1.2 (0.8 – 1.9)</b>

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

† NGM = norgestimate; EE = ethinyl estradiol

‡ Increase in risk of VTE is statistically significant

§ Pooled risk ratio from references 1 and 6 covering the initial 33-month study plus 24-month extension. [Initial 33 months of data: Risk Ratio (95% CI) = 2.5<sup>C</sup> (1.1-5.5); Separate estimate from the 24 months of data on new cases not included in the previous estimate: Risk Ratio (95% CI) = 1.4 (0.5-3.7)]. These risk ratios are based on idiopathic cases (those in women without other known risk factors for VTE). If all VTE cases are considered, the pooled risk ratio and 95% CI are 2.0 (1.2-3.3)<sup>C</sup>.

¶ BCDSP = Boston Collaborative Drug Surveillance Program; the risk ratios are based on idiopathic cases.

# Pooled risk ratio from references 2, 3 and 5 covering the initial 36-month study, plus 17-month and 14-month extensions. [Initial 36 months of data: Risk Ratio (95% CI) = 0.9 (0.5-1.6); Separate estimate from 17 months of data on new cases not included in the previous estimate: Risk Ratio (95% CI) = 1.1 (0.6-2.1); Separate estimate from 14 months of data on new cases not included in the previous estimates: Risk Ratio (95% CI) = 2.4<sup>C</sup> (1.2-5.0)]

Ⓛ LNG = levonorgestrel

β 48 months of data.

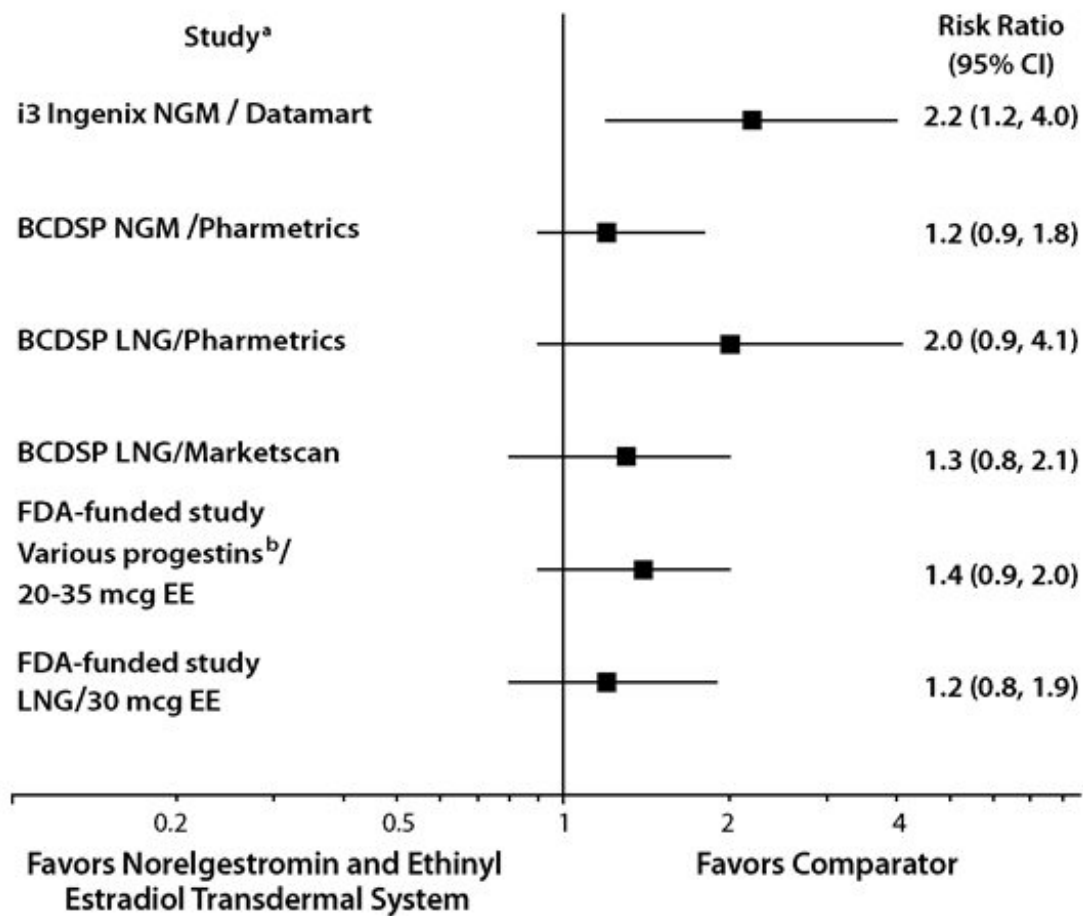
à 69 months of data.

è 84 months of data in FDA-funded study

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

∅ Includes the following progestins: LNG, norethindrone, norgestimate.

**Figure 1: VTE Risk of Norelgestromin and Ethinyl Estradiol Transdermal System Relative to Combined Oral Contraceptives**



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

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

An increased risk of thromboembolic and thrombotic disease associated with the use of combination hormonal contraceptives (CHCs) is well established. Although the absolute VTE rates are increased for users of CHCs compared to non-users, the rates associated with pregnancy are even greater, especially during the postpartum period (see Figure 2).

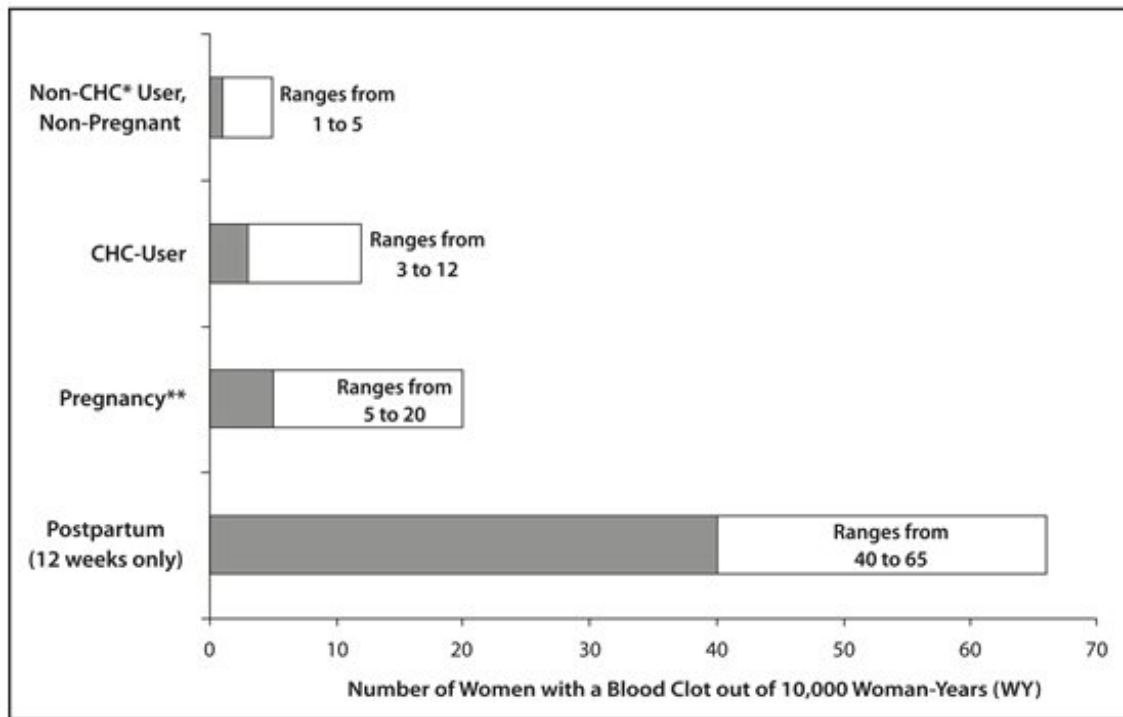
The frequency of VTE in women using CHCs has been estimated to be 3 to 12 cases per 10,000 woman-years.

The risk of VTE is highest during the first year of use of CHCs and when restarting hormonal contraception after a break of 4 weeks or longer. The risk of thromboembolic disease due to CHCs gradually disappears after CHC use is discontinued.

Figure 2 shows the risk of developing a VTE for women who are not pregnant and do not use CHCs, for women who use CHCs, for pregnant women, and for women in the postpartum period.

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

### Figure 2: Likelihood of Developing a VTE



\* CHC = combination hormonal contraception

\*\* Pregnancy data based on actual duration of pregnancy in the reference studies. Based on a model assumption that pregnancy duration is 9 months, the rate is 7 to 27 per 10,000 WY.

Use of CHCs also increases the risk of arterial thromboses such as, cerebrovascular events (thrombotic and hemorrhagic strokes) and myocardial infarctions, especially in women with other risk factors for these events. In general, the risk is greatest among older (> 35 years of age), hypertensive women who also smoke. Use CHCs with caution in women with cardiovascular disease risk factors.

## 5.2 PK Profile of Ethinyl Estradiol

The PK profile for the norelgestromin and ethinyl estradiol transdermal system is different from the PK profile for oral contraceptives in that it has a higher  $C_{SS}$  and a lower  $C_{max}$ . AUC and average  $C_{SS}$  for EE are approximately 60% higher in women using norelgestromin and ethinyl estradiol transdermal system compared with women using an oral contraceptive containing EE 35 mcg. In contrast, the  $C_{max}$  for EE is approximately 25% lower in women using norelgestromin and ethinyl estradiol transdermal system. Inter-subject variability results in increased exposure to EE in some women using either norelgestromin and ethinyl estradiol transdermal system or oral contraceptives. However, inter-subject variability in women using norelgestromin and ethinyl estradiol transdermal system is higher. It is not known whether there are changes in the risk of serious adverse events based on the differences in PK profiles of EE in women using norelgestromin and ethinyl estradiol transdermal system compared with women using oral contraceptives containing 30 mcg to 35 mcg of EE. Increased estrogen exposure may increase the risk of adverse events, including venous thromboembolism. [See Boxed Warning and Clinical Pharmacology (12.3).]

## 5.3 Liver Disease

### *Impaired Liver Function*

Do not use Xulane in women with liver disease, such as acute viral hepatitis or severe (decompensated) cirrhosis of liver [see Contraindications (4)]. Discontinue Xulane if jaundice develops. Acute or chronic disturbances of liver function may necessitate the discontinuation of CHC use until markers of liver function return to normal and CHC causation has been excluded.

## ***Liver Tumors***

Xulane is contraindicated in women with benign and malignant liver tumors [see *Contraindications (4)*]. Hepatic adenomas are associated with CHC use. An estimate of the attributable risk is 3.3 cases/100,000 CHC users. Rupture of hepatic adenomas may cause death through intra-abdominal hemorrhage.

Studies have shown an increased risk of developing hepatocellular carcinoma in long-term (> 8 years) CHC users. However, the risk of liver cancers in CHC users is less than one case per million users.

### **5.4 Risk of Liver Enzyme Elevations with Concomitant Hepatitis C Treatment**

During clinical trials with the Hepatitis C combination drug regimen that contains ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, ALT elevations greater than 5 times the upper limit of normal (ULN), including some cases greater than 20 times the ULN, were significantly more frequent in women using ethinyl estradiol-containing medications, such as CHCs. Discontinue Xulane prior to starting therapy with the combination drug regimen ombitasvir/paritaprevir/ritonavir, with or without dasabuvir [see *Contraindications (4)*]. Xulane can be restarted approximately 2 weeks following completion of treatment with the Hepatitis C combination drug regimen.

### **5.5 High Blood Pressure**

Xulane is contraindicated in women with uncontrolled hypertension or hypertension with vascular disease [see *Contraindications (4)*]. For women with well-controlled hypertension, monitor blood pressure and stop Xulane if blood pressure rises significantly.

An increase in blood pressure has been reported in women taking hormonal contraceptives, and this increase is more likely in older women with extended duration of use. The incidence of hypertension increases with increasing concentrations of progestin.

### **5.6 Gallbladder Disease**

Studies suggest a small increased relative risk of developing gallbladder disease among CHC users. Use of CHCs may also worsen existing gallbladder disease. A past history of CHC-related cholestasis predicts an increased risk with subsequent CHC use. Women with a history of pregnancy-related cholestasis may be at an increased risk for CHC-related cholestasis.

### **5.7 Carbohydrate and Lipid Metabolic Effects**

Carefully monitor prediabetic and diabetic women who take Xulane. CHCs may decrease glucose tolerance in a dose-related fashion. In a 6-cycle clinical trial with norelgestromin and ethinyl estradiol transdermal system there were no clinically significant changes in fasting blood glucose from baseline to end of treatment.

Consider alternative contraception for women with uncontrolled dyslipidemia. A small proportion of women will have adverse lipid changes while on hormonal contraceptives.

Women with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis when using hormonal contraceptives.

### **5.8 Headache**

If a woman taking Xulane develops new headaches that are recurrent, persistent or severe, evaluate the cause and discontinue Xulane if indicated.

Consider discontinuation of Xulane in the case of increased frequency or severity of migraine during hormonal contraceptive use (which may be prodromal of a cerebrovascular event).

### **5.9 Bleeding Irregularities**

### ***Unscheduled Bleeding and Spotting***

Unscheduled (breakthrough) bleeding and spotting sometimes occur in women using norelgestromin and ethinyl estradiol transdermal system. Consider non-hormonal causes and take adequate diagnostic measures to rule out malignancy, other pathology, or pregnancy in the event of unscheduled bleeding, as in the case of any abnormal vaginal bleeding. If pathology and pregnancy have been excluded, time or a change to another contraceptive product may resolve the bleeding.

In the clinical trials, most women started their scheduled (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 scheduled and unscheduled bleeding and/or spotting). Three clinical studies of the efficacy of norelgestromin and ethinyl estradiol transdermal system in preventing pregnancy assessed scheduled and unscheduled bleeding [see *Clinical Studies (14)*] in 3,330 women who completed 22,155 cycles of exposure. A total of 36 (1.1%) of the women discontinued norelgestromin and ethinyl estradiol transdermal system at least in part, due to bleeding or spotting.

Table 2 summarizes the proportion of subjects who experienced unscheduled (breakthrough) bleeding/spotting by treatment cycle.

**Table 2: Unscheduled (Breakthrough) Bleeding/Spotting (Subjects Evaluable for Efficacy)**

Treatment Cycle	Pooled data from 3 studies N = 3319	
	n	%*
Cycle 1	2994	18.2
Cycle 2	2743	11.9
Cycle 3	2699	11.6
Cycle 4	2541	10.1
Cycle 5	2532	9.2
Cycle 6	2494	8.3
Cycle 7	698	8.3
Cycle 8	692	8.7
Cycle 9	654	8.6
Cycle 10	621	8.7
Cycle 11	631	8.9
Cycle 12	617	6.3
Cycle 13	611	8.0

\* Percentage of subjects with breakthrough bleeding/spotting events.

### ***Amenorrhea and Oligomenorrhea***

In the event of amenorrhea, consider the possibility of pregnancy. If the patient has not adhered to the prescribed dosing schedule (missed one patch or started the patch on a day later than she should have), consider the possibility of pregnancy at the time of the first missed period and take appropriate diagnostic measures. If the patient has adhered to the prescribed regimen and misses two consecutive periods, rule out pregnancy.

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

### **5.10 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 do not suggest 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. Discontinue Xulane use if pregnancy is confirmed.

Administration of CHCs should not be used as a test for pregnancy [*see Use in Specific Populations (8.1)*].

### **5.11 Depression**

Carefully observe women with a history of depression and discontinue Xulane if depression recurs to a serious degree.

### **5.12 Carcinoma of Breasts and Cervix**

Xulane is contraindicated in women who currently have or have had breast cancer because breast cancer may be hormonally sensitive [*see Contraindications (4)*].

There is substantial evidence that CHCs do not increase the incidence of breast cancer. Although some past studies have suggested that CHCs might increase the incidence of breast cancer, more recent studies have not confirmed such findings.

Some studies suggest that combination oral contraceptive use has been associated with an increase in the risk of cervical cancer or intraepithelial neoplasia. However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors.

### **5.13 Effect on Binding Globulins**

The estrogen component of CHCs may raise the serum concentrations of thyroxine-binding globulin, sex hormone-binding globulin and cortisol-binding globulin. The dose of replacement thyroid hormone or cortisol therapy may need to be increased.

### **5.14 Monitoring**

A woman who is taking hormonal contraceptive should have a yearly visit with her healthcare provider for a blood pressure check and for other indicated healthcare.

### **5.15 Hereditary Angioedema**

In women with hereditary angioedema, exogenous estrogens may induce or exacerbate symptoms of angioedema.

### **5.16 Chloasma**

Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation while using Xulane.

## **6 ADVERSE REACTIONS**

The following serious adverse reactions with the use of combination hormonal contraceptives, including Xulane, are discussed elsewhere in the labeling:

- Serious cardiovascular events and stroke [*see Boxed Warning and Warnings and Precautions (5.1)*]
- Vascular events, including venous and arterial thromboembolic events [*see Warnings and Precautions (5.1)*]
- Liver disease [*see Warnings and Precautions (5.3)*]

Adverse reactions commonly reported by users of combination hormonal contraceptives are:



- Irregular uterine bleeding
- Nausea
- Breast tenderness
- Headache

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The data described below reflect exposure to norelgestromin and ethinyl estradiol transdermal system in 3330 sexually active women (3322 of whom had safety data) who participated in three Phase 3 clinical trials designed to evaluate contraceptive efficacy and safety. These subjects received six or 13 cycles of contraception (norelgestromin and ethinyl estradiol transdermal system or an oral contraceptive comparator in 2 of the trials). The women ranged in age from 18 to 45 years and were predominantly white (91%).

The most common adverse reactions ( $\geq 5\%$ ) reported during clinical trials were breast symptoms, nausea/vomiting, headache, application site disorder, abdominal pain, dysmenorrhea, vaginal bleeding and menstrual disorders, and mood, affect and anxiety disorders. The most common events leading to discontinuation were application site reaction, breast symptoms (including breast discomfort, engorgement and pain), nausea and/or vomiting, headache and emotional lability.

Adverse drug reactions reported by  $\geq 2.5\%$  of norelgestromin and ethinyl estradiol transdermal system-treated subjects in these trials are shown in Table 3.

**Table 3: Adverse Drug Reactions Reported by  $\geq 2.5\%$  of Norelgestromin and Ethinyl Estradiol Transdermal System-treated Subjects in Three Phase 3 Clinical Trials**

<b>System/Organ Class*</b> <b>Adverse reaction</b>	<b>Norelgestromin and Ethinyl Estradiol Transdermal System (n = 3322)</b>
<b>Reproductive system and breast disorders</b>	
Breast symptoms <sup>†</sup>	22.4%
Dysmenorrhea	7.8%
Vaginal bleeding and menstrual disorders <sup>†</sup>	6.4%
<b>Gastrointestinal disorders</b>	
Nausea	16.6%
Abdominal pain <sup>†</sup>	8.1%
Vomiting	5.1%
Diarrhea	4.2%
<b>Nervous system disorders</b>	
Headache	21.0%
Dizziness	3.3%
Migraine	2.7%
<b>General disorders and administration site conditions</b>	
Application site disorder <sup>†</sup>	17.1%
Fatigue	2.6%
<b>Psychiatric disorders</b>	
Mood, affect and anxiety disorders <sup>†</sup>	6.3%

<b>Skin and subcutaneous tissue disorders</b>	
Acne	2.9%
Pruritus	2.5%
<b>Infections and infestations</b>	
Vaginal yeast infection <sup>†</sup>	3.9%
<b>Investigations</b>	
Weight increased	2.7%

\* MedDRA version 10.0

<sup>†</sup> Represents a bundle of similar terms

Additional adverse drug reactions that occurred in < 2.5% of norelgestromin and ethinyl estradiol transdermal system-treated subjects in the above clinical trials datasets are:

- **Gastrointestinal disorders:** Abdominal distension
- **General disorders and administration site conditions:** Fluid retention<sup>1</sup>, malaise
- **Hepatobiliary disorders:** Cholecystitis
- **Investigations:** Blood pressure increased, lipid disorders<sup>1</sup>
- **Musculoskeletal and connective tissue disorders:** Muscle spasms
- **Psychiatric disorders:** Insomnia, libido decreased, libido increased
- **Reproductive system and breast disorders:** Galactorrhea, genital discharge, premenstrual syndrome, uterine spasm, vaginal discharge, vulvovaginal dryness
- **Respiratory, thoracic and mediastinal disorders:** Pulmonary embolism
- **Skin and subcutaneous tissue disorders:** Chloasma, dermatitis contact, erythema, skin irritation

<sup>1</sup>Represents a bundle of similar terms

## 6.2 Postmarketing Experience

The following adverse reactions (Table 4) have been identified during postapproval use of norelgestromin and ethinyl estradiol transdermal system. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

**Table 4: Alphabetical List of Adverse Drug Reactions Identified During Postmarketing Experience with Norelgestromin and Ethinyl Estradiol Transdermal System by System Organ Class\***

<b>System Organ Class</b>	<b>Adverse Drug Reactions</b>
<b>Cardiac disorders</b>	Myocardial infarction <sup>†</sup>
<b>Endocrine disorders</b>	Hyperglycemia, insulin resistance
<b>Eye disorders</b>	Contact lens intolerance or complication
<b>Gastrointestinal disorders</b>	Colitis
<b>General disorders and administration site conditions</b>	Application site reaction <sup>†</sup> , edema <sup>†</sup>
<b>Hepatobiliary disorders</b>	Blood cholesterol abnormal, cholelithiasis, cholestasis, hepatic lesion, jaundice cholestatic, low density lipoprotein increased
<b>Immune system disorders</b>	Allergic reaction <sup>†</sup> , urticaria
<b>Investigations</b>	Blood glucose abnormal, blood glucose decreased
<b>Metabolism and nutrition disorders</b>	Increased appetite

<b>Neoplasms benign, malignant and unspecified (Incl. cysts and polyps)</b>	Breast cancer <sup>†</sup> , cervix carcinoma, hepatic adenoma, hepatic neoplasm
<b>Nervous system disorders</b>	Dysgeusia, migraine with aura
<b>Psychiatric disorders</b>	Anger, emotional disorder, frustration, irritability
<b>Reproductive system and breast disorders</b>	Breast mass, cervical dysplasia, fibroadenoma of breast, menstrual disorder <sup>†</sup> , suppressed lactation, uterine leiomyoma
<b>Skin and subcutaneous tissues disorders</b>	Alopecia, eczema, erythema multiforme, erythema nodosum, photosensitivity reaction, pruritus generalized, rash <sup>†</sup> , seborrheic dermatitis, skin reaction
<b>Vascular disorders</b>	Arterial thrombosis <sup>†</sup> , cerebrovascular accident <sup>†</sup> , deep vein thrombosis <sup>†</sup> , hemorrhage intracranial <sup>†</sup> , hypertension, hypertensive crisis, pulmonary embolism <sup>†</sup> , thrombosis <sup>†</sup>

\* MedDRA version 10.0

† Represents a bundle of similar terms

## 7 DRUG INTERACTIONS

Consult the labeling of concurrently-used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.

### 7.1 Effects of Other Drugs on Combined Hormonal Contraceptives

#### ***Substances Decreasing the Plasma Concentrations of CHCs and Potentially Diminishing the Efficacy of CHCs***

Drugs or herbal products that induce certain enzymes, including cytochrome P450 3A4 (CYP3A4), may decrease the plasma concentrations of CHCs and potentially diminish the effectiveness of CHCs or increase breakthrough bleeding. Some drugs or herbal products that may decrease the effectiveness of hormonal contraceptives include phenytoin, barbiturates, carbamazepine, bosentan, felbamate, griseofulvin, oxcarbazepine, rifampicin, topiramate, rifabutin, rufinamide, aprepitant, and products containing St. John's wort. Interactions between hormonal contraceptives and other drugs may lead to breakthrough bleeding and/or contraceptive failure. Counsel women to use an alternative method of contraception or a back-up method when enzyme inducers are used with CHCs, and to continue back-up contraception for 28 days after discontinuing the enzyme inducer to ensure contraceptive reliability.

#### ***Substances Increasing the Plasma Concentrations of CHCs***

Co-administration of atorvastatin or rosuvastatin and certain CHCs containing EE increase AUC values for EE by approximately 20% to 25%. Ascorbic acid and acetaminophen may increase plasma EE concentrations, possibly by inhibition of conjugation. CYP3A4 inhibitors such as itraconazole, voriconazole, fluconazole, grapefruit juice, or ketoconazole may increase plasma hormone concentrations.

#### ***Human Immunodeficiency Virus (HIV)/Hepatitis C Virus (HCV) Protease Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors***

Significant changes (increase or decrease) in the plasma concentrations of estrogen and/or progestin have been noted in some cases of co-administration with HIV protease inhibitors (decrease [e.g., nelfinavir, ritonavir, darunavir/ritonavir, (fos)amprenavir/ritonavir, lopinavir/ritonavir, and tipranavir/ritonavir] or increase [e.g., indinavir and atazanavir/ritonavir])/HCV protease inhibitors or with non-nucleoside reverse transcriptase inhibitors (decrease [e.g., nevirapine] or increase [e.g.,

etravirine]).

## **7.2 Effects of Combined Hormonal Contraceptives on Other Drugs**

CHCs containing EE may inhibit the metabolism of other compounds (e.g., cyclosporine, prednisolone, theophylline, tizanidine, and voriconazole) and increase their plasma concentrations. CHCs have been shown to decrease plasma concentrations of acetaminophen, clofibrac acid, morphine, salicylic acid, and temazepam. Significant decrease in plasma concentration of lamotrigine has been shown, likely due to induction of lamotrigine glucuronidation. This may reduce seizure control; therefore, dosage adjustments of lamotrigine may be necessary.

Women on thyroid hormone replacement therapy may need increased doses of thyroid hormone because serum concentration of thyroid-binding globulin increases with use of CHCs [*see Warnings and Precautions (5.13)*].

## **7.3 Concomitant Use with HCV Combination Therapy – Liver Enzyme Elevation**

Do not co-administer Xulane with HCV drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to potential for ALT elevations [*see Warnings and Precautions (5.4)*].

## **7.4 Interference with Laboratory Tests**

The use of contraceptive steroids may influence the results of certain laboratory tests, such as coagulation factors, lipids, glucose tolerance, and binding proteins.

# **8 USE IN SPECIFIC POPULATIONS**

## **8.1 Pregnancy**

There is little or no increased risk of birth defects in women who inadvertently use hormonal contraceptives during early pregnancy. Epidemiologic studies and meta-analyses have not found an increased risk of genital or non-genital birth defects (including cardiac anomalies and limb reduction defects) following exposure to low dose hormonal contraceptives prior to conception or during early pregnancy.

The administration of hormonal contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy. Hormonal contraceptives should not be used during pregnancy to treat threatened or habitual abortion.

## **8.3 Nursing Mothers**

The effects of Xulane in nursing mothers have not been evaluated and are unknown. When possible, advise the nursing mother to use other forms of contraception until she has completely weaned her child. Estrogen-containing CHCs can reduce milk production in breastfeeding mothers. This is less likely to occur once breastfeeding is well-established; however, it can occur at any time in some women. Small amounts of contraceptive steroids and/or metabolites are present in breast milk.

## **8.4 Pediatric Use**

Safety and efficacy of norelgestromin and ethinyl estradiol transdermal system have been established in women of reproductive age. Efficacy is expected to be the same for post-pubertal adolescents under the age of 18 and for users 18 years and older. Use of this product before menarche is not indicated.

## **8.5 Geriatric Use**

Xulane has not been studied in postmenopausal women and is not indicated in this population.

## **8.6 Hepatic Impairment**

No studies with Xulane have been conducted in women with hepatic impairment. However, steroid hormones may be poorly metabolized in patients with impaired liver function. Acute or chronic disturbances of liver function may necessitate the discontinuation of combined hormonal contraceptive use until markers of liver function return to normal and combined hormonal contraceptive causation has been excluded. [See *Contraindications (4) and Warnings and Precautions (5.3).*]

### **8.7 Renal Impairment**

No studies with Xulane have been conducted in women with renal impairment.

### **8.8 Women with Weight $\geq$ 198 lbs (90 kg)**

Xulane may be less effective in preventing pregnancy in women who weigh 198 lbs (90 kg) or more.

## **10 OVERDOSAGE**

Overdosage may cause nausea and vomiting, and withdrawal bleeding may occur in females. In case of suspected overdose, all Xulane patches should be removed and symptomatic treatment given.

## **11 DESCRIPTION**

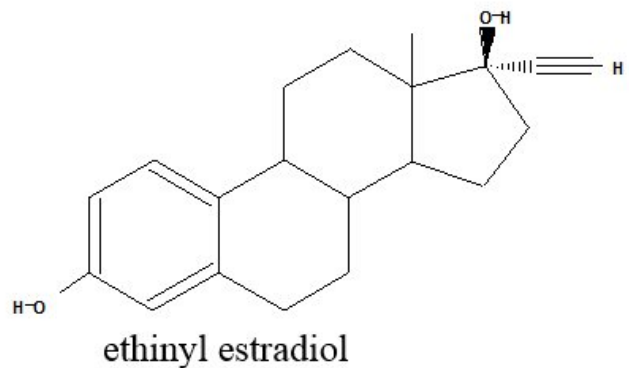
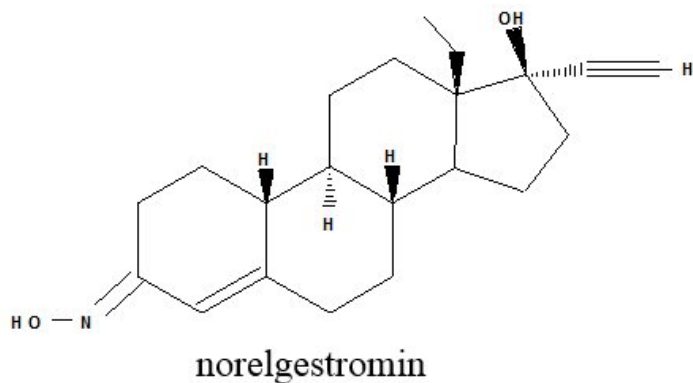
Xulane is a transdermal system with a contact surface area of 14 cm<sup>2</sup>. It contains 4.86 mg norelgestromin, USP (NGMN) and 0.53 mg ethinyl estradiol, USP (EE), and its delivery rate is approximately 150 mcg of NGMN and 35 mcg of EE per day. Systemic exposures (as measured by area under the curve [AUC] and steady state concentration [ $C_{ss}$ ]) of NGMN and EE during use of norelgestromin and ethinyl estradiol transdermal system are higher and the  $C_{max}$  is lower than those produced by an oral contraceptive containing NGM 250 mcg / EE 35 mcg. [See *Boxed Warning and Clinical Pharmacology (12.3).*]

Xulane is a thin, matrix-type transdermal system consisting of three layers. The backing layer is composed of a peach flexible film consisting of a 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 polyisobutene adhesive, crospovidone, mineral oil, non-woven polyester fabric, oleyl alcohol and dipropylene glycol as inactive components. The active components in this layer are the hormones, NGMN and EE. The third layer is the release liner, which protects the adhesive layer during storage and is removed just prior to application. It is a transparent polyester film with a fluoropolymer coating on the side that is in contact with the middle adhesive layer.

The outside of the backing layer is printed with “Xulane<sup>®</sup> (norelgestromin and ethinyl estradiol) 150/35 mcg per day” in brown ink.

Xulane transdermal systems are packaged with additional pieces of protective film above and below the system within each pouch. These pieces of protective film are removed and discarded at the time of use.

The structural formulas of the components are:



**Molecular weight, NGMN: 327.47**

**Molecular weight, EE: 296.41**

**Chemical name for NGMN: 18, 19-dinorpregn-4-en-20-yn-3-one, 13-ethyl-, 17-hydroxy, 3-oxime, (17 $\alpha$ )-**

**Chemical name for EE: 19-Norpregna-1,3,5(10)-trien-20-yne-3, 17 $\beta$ -diol, (17 $\alpha$ )-**

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

NGMN is the active progestin largely responsible for the progestational activity that occurs in women following application of norelgestromin and ethinyl estradiol transdermal system. NGMN is also the primary active metabolite produced following oral administration of NGM, the progestin component of some oral contraceptive products.

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

### 12.2 Pharmacodynamics

One clinical trial assessed the return of hypothalamic-pituitary-ovarian axis function post-therapy and found that follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estradiol mean values, though suppressed during therapy, returned to near baseline values during the 6 weeks post-therapy.

### 12.3 Pharmacokinetics

#### **Absorption**

The systemic delivery rate of NGMN and EE from norelgestromin and ethinyl estradiol transdermal system is approximately 150 mcg of NGMN and 35 mcg of EE per day based on a comparative analysis with intravenous (IV) data. Following a single application of norelgestromin and ethinyl estradiol transdermal system, both NGMN and EE reach a plateau by approximately 48 hours. Pooled data from the 3 clinical studies have demonstrated that steady state is reached within 2 weeks of application. In one of the clinical studies,  $C_{ss}$  concentrations across all subjects ranged from 0.305 to 1.53 ng/mL for NGMN and from 23 to 137 pg/mL for EE.

Absorption of NGMN and EE following application of norelgestromin and ethinyl estradiol transdermal system to the buttock, upper outer arm, abdomen and upper torso (excluding breast) was examined. While absorption from the abdomen was slightly lower than from other sites, absorption from these anatomic sites was considered to be therapeutically equivalent.

The mean (%CV) PK parameters  $C_{ss}$  and  $AUC_{0-168}$  for NGMN and EE following a single buttock application of norelgestromin and ethinyl estradiol transdermal system are summarized in Table 5.

In multiple dose studies,  $AUC_{0-168}$  for NGMN and EE was found to increase over time (Table 5). In a three-cycle study, these PK parameters reached steady state conditions during Cycle 3 (Figures 3 and 4). Upon removal of the patch, serum levels of EE and NGMN reach very low or non-measurable levels within 3 days.

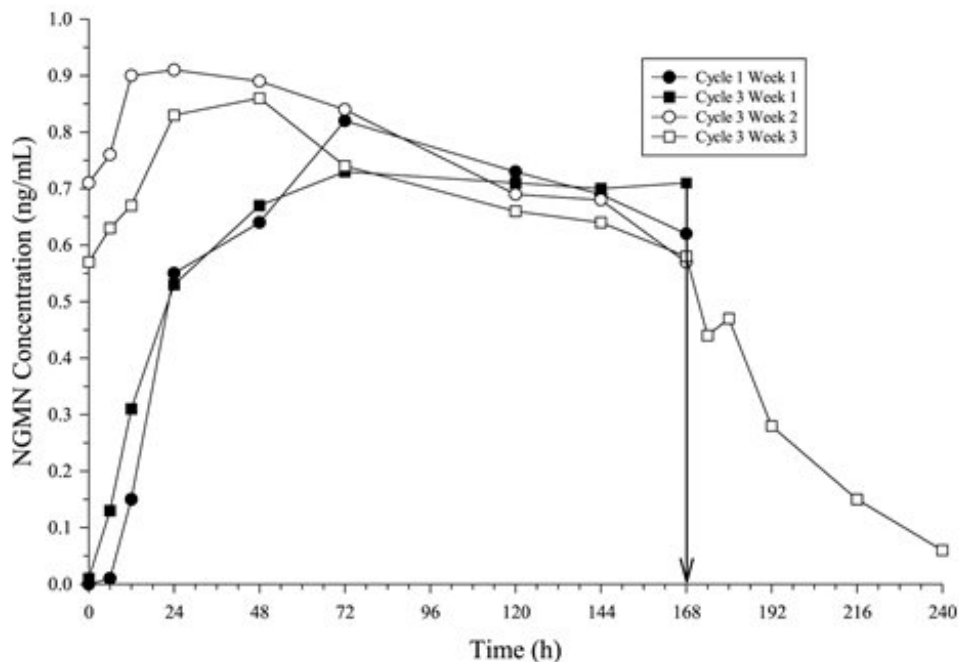
**Table 5: Mean (%CV\*) PK Parameters of NGMN and EE Following Three Consecutive Cycles of Norelgestromin and Ethinyl Estradiol Transdermal System Wear on the Buttock**

Analyte	Parameter	Cycle 1 Week 1	Cycle 3 Week 1	Cycle 3 Week 2	Cycle 3 Week 3
NGMN	$C_{ss}$ (ng/mL)	0.70 (39.4)	0.70 (41.8)	0.80 (28.7)	0.70 (45.3)
	$AUC_{0-168}$ (ng·h/mL)	107 (44.2)	105 (43.2)	132 (43.4)	120 (43.9)
	$t_{1/2}$ (h)	nc	nc	nc	32.1 (40.3)
EE	$C_{ss}$ (pg/mL)	46.4 (38.5)	47.6 (36.4)	59.0 (42.5)	49.6 (54.4)
	$AUC_{0-168}$ (pg·h/mL)	6796 (39.3)	7160 (40.4)	10054 (41.8)	8840 (58.6)
	$t_{1/2}$ (h)	nc	nc	nc	21.0 (43.2)

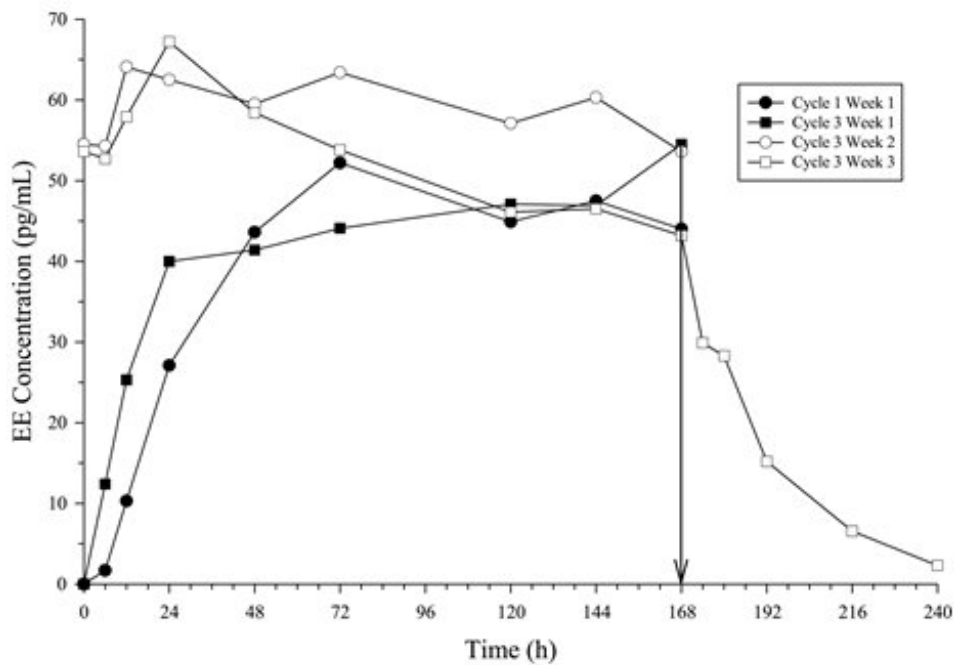
nc = not calculated

\* %CV is % of Coefficient of variation = 100 (standard deviation/mean)

**Figure 3: Mean Serum NGMN Concentrations (ng/mL) in Healthy Female Volunteers Following Application of Norelgestromin and Ethinyl Estradiol Transdermal System on the Buttock for Three Consecutive Cycles (Vertical arrow indicates time of patch removal)**



**Figure 4: Mean Serum EE Concentrations (pg/mL) in Healthy Female Volunteers Following Application of Norelgestromin and Ethinyl Estradiol Transdermal System on the Buttock for Three Consecutive Cycles (Vertical arrow indicates time of patch removal.)**



The absorption of NGMN and EE following application of norelgestromin and ethinyl estradiol transdermal system was studied under conditions encountered in a health club (sauna, whirlpool and treadmill) and in a cold water bath. The results indicated that for NGMN, there were no significant treatment effects on  $C_{ss}$  or AUC when compared to normal wear. For EE, increased exposures were observed due to sauna, whirlpool and treadmill. There was no significant effect of cold water on these parameters.

Results from a study of consecutive norelgestromin and ethinyl estradiol transdermal system wear for 7 days and 10 days indicated that serum concentrations of NGMN and EE dropped slightly during the first 6 hours after the patch replacement, and recovered within 12 hours. By Day 10 of patch administration, both NGMN and EE concentrations had decreased by approximately 25% when compared to Day 7 concentrations.

### **Metabolism**

Since norelgestromin and ethinyl estradiol transdermal system is applied transdermally, first-pass metabolism (via the gastrointestinal tract and/or liver) of NGMN and EE that would be expected with oral administration does not occur. Hepatic metabolism of NGMN occurs and metabolites include norgestrel, which is highly bound to SHBG, and various hydroxylated and conjugated metabolites. EE is also metabolized to various hydroxylated products and their glucuronide and sulfate conjugates.

### **Distribution**

NGMN and norgestrel (a serum metabolite of NGMN) are highly bound (> 97%) to serum proteins. NGMN is bound to albumin and not to SHBG, while norgestrel is bound primarily to SHBG, which limits its biological activity. EE is extensively bound to serum albumin and induces an increase in the serum concentrations of SHBG (see Table 5).

### **Elimination**

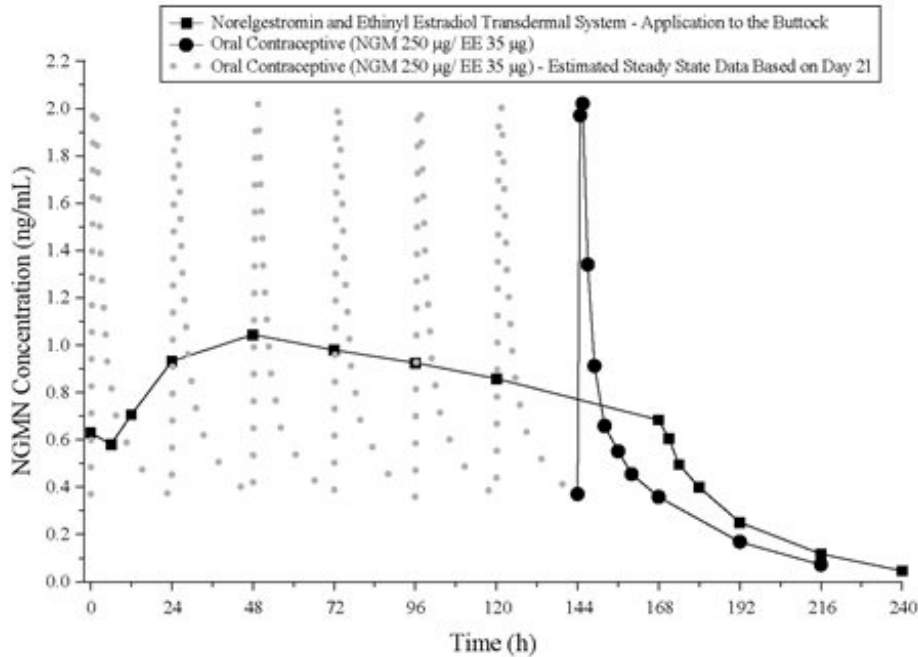
Following removal of patches, the elimination kinetics of NGMN and EE were consistent for all studies with half-life values of approximately 28 hours and 17 hours, respectively. The metabolites of NGMN and EE are eliminated by renal and fecal pathways.

### **Transdermal versus Oral Contraceptives**



The norelgestromin and ethinyl estradiol transdermal system delivers EE and NGMN over a 7-day period while oral contraceptives (containing NGM 250 mcg / EE 35 mcg) are administered on a daily basis. Figures 5 and 6 present mean PK profiles for EE and NGMN following administration of an oral contraceptive (containing NGM 250 mcg / EE 35 mcg) compared to the 7-day norelgestromin and ethinyl estradiol transdermal system (containing NGMN 4.86 mg / EE 0.53 mg) during Cycle 2 in 32 healthy female volunteers.

**Figure 5: Mean Serum Concentration-Time Profiles of NGMN Following Once-Daily Administration of an Oral Contraceptive for Two Cycles or Application of Norelgestromin and Ethinyl Estradiol Transdermal System for Two Cycles to the Buttock in Healthy Female Volunteers. [Oral contraceptive: Cycle 2, Days 15 to 21, Norelgestromin and Ethinyl Estradiol Transdermal System: Cycle 2, Week 3]**



**Figure 6: Mean Serum Concentration-Time Profiles of EE Following Once-Daily Administration of an Oral Contraceptive for Two Cycles or Application of Norelgestromin and Ethinyl Estradiol Transdermal System for Two Cycles to the Buttock in Healthy Female Volunteers. [Oral contraceptive: Cycle 2, Days 15 to 21, Norelgestromin and Ethinyl Estradiol Transdermal System: Cycle 2, Week 3]**

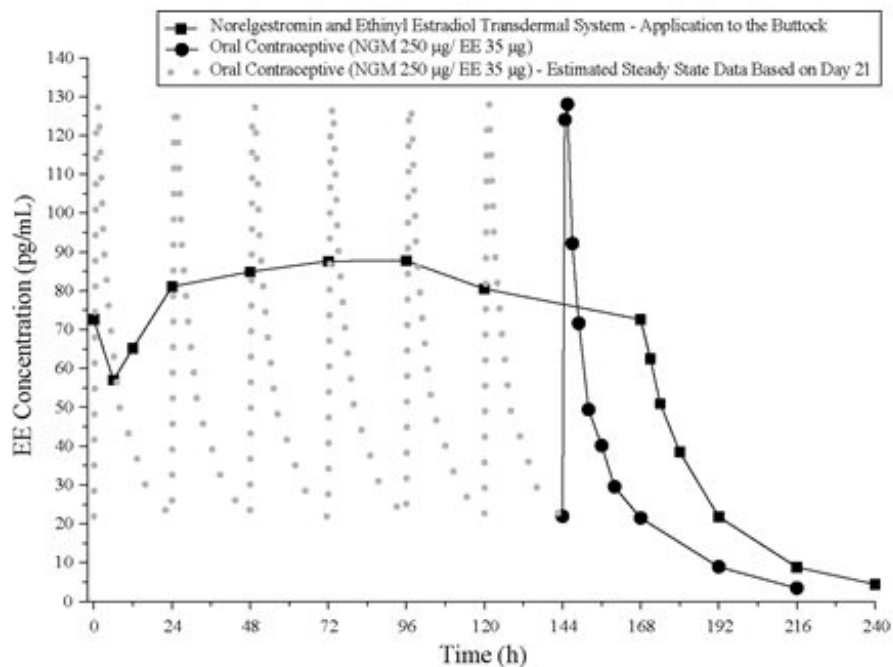


Table 6 provides the mean (%CV) for NGMN and EE pharmacokinetic (PK) parameters.

**Table 6: Mean (% CV) NGMN and EE Steady State Pharmacokinetic Parameters Following Application of Norelgestromin and Ethinyl Estradiol Transdermal System and Once-Daily Administration of an Oral Contraceptive (containing NGM 250 mcg / EE 35 mcg) in Healthy Female Volunteers**

Parameter	Norelgestromin and Ethinyl Estradiol Transdermal System*	ORAL CONTRACEPTIVE†
NGMN‡		
C <sub>max</sub> (ng/mL)	1.12 (33.6)	2.16 (25.2)
AUC <sub>0-168</sub> (ng·h/mL)	145 (36.8)	123 (30.2)§
C <sub>ss</sub> (ng/mL)	0.888 (36.6)	0.732 (30.2)¶
EE		
C <sub>max</sub> (pg/mL)	97.4 (31.6)	133 (27.7)
AUC <sub>0-168</sub> (pg·h/mL)	12,971 (33.1)	8,281(26.9)§
C <sub>ss</sub> (pg/mL)	80.0 (33.5)	49.3 (26.9)¶

\* Cycle 2, Week 3

† Cycle 2, Day 21

‡ NGM is rapidly metabolized to NGMN following oral administration

§ Average weekly exposure, calculated as AUC<sub>24</sub> x 7

¶ C<sub>avg</sub>

In general, overall exposure for NGMN and EE (AUC and C<sub>ss</sub>) was higher in subjects treated with norelgestromin and ethinyl estradiol transdermal system for both Cycle 1 and Cycle 2, compared to that for the oral contraceptive, while C<sub>max</sub> values were higher in subjects administered the oral contraceptive. Under steady state conditions, AUC<sub>0-168</sub> and C<sub>ss</sub> for EE were approximately 55% and 60% higher, respectively, for the transdermal patch, and the C<sub>max</sub> was about 35% higher for the oral contraceptive, respectively. Inter-subject variability (%CV) for the PK parameters following delivery

from norelgestromin and ethinyl estradiol transdermal system was higher relative to the variability determined from the oral contraceptive. The mean PK profiles are different between the two products and caution should be exercised when making a direct comparison of these PK parameters.

In Table 7, percent change in concentrations (%CV) of markers of systemic estrogenic activity (Sex Hormone Binding Globulin [SHBG] and Corticosteroid Binding Globulin [CBG]) from Cycle 1 Day 1 to Cycle 1 Day 22 is presented. Percent change in SHBG concentrations was higher for norelgestromin and ethinyl estradiol transdermal system users compared to women taking the oral contraceptive; percent change in CBG concentrations was similar for norelgestromin and ethinyl estradiol transdermal system and oral contraceptive users. Within each group, the absolute values for SHBG were similar for Cycle 1, Day 22 and Cycle 2, Day 22.

**Table 7: Mean Percent Change (%CV) in SHBG and CBG Concentrations Following Once-Daily Administration of an Oral Contraceptive (containing NGM 250 mcg / EE 35 mcg) for One Cycle and Application of Norelgestromin and Ethinyl Estradiol Transdermal System for One Cycle in Healthy Female Volunteers**

Parameter	Norelgestromin and Ethinyl Estradiol Transdermal System	ORAL CONTRACEPTIVE
	(% change from Day 1 to Day 22)	(% change from Day 1 to Day 22)
SHBG	334 (39.3)	200 (43.2)
CBG	153 (40.2)	157 (33.4)

### ***Drug Interactions***

In a PK drug interaction study, oral administration of tetracycline HCl, 500 mg four times daily for 3 days prior to and 7 days during wear of norelgestromin and ethinyl estradiol transdermal system did not significantly affect the PK of NGMN or EE.

### ***Use in Specific Populations***

#### *Effects of Age, Body Weight, Body Surface Area and Race*

The effects of age, body weight, body surface area and race on the PK of NGMN and EE were evaluated in 230 healthy women from nine pharmacokinetic studies of single 7-day applications of norelgestromin and ethinyl estradiol transdermal system. For both NGMN and EE, increasing age, body weight and body surface area each were associated with slight decreases in  $C_{SS}$  and AUC values. However, only a small fraction (10% to 25%) of the overall variability in the PK of NGMN and EE following application of norelgestromin and ethinyl estradiol transdermal system 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.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

See *Warnings and Precautions* (5.3, 5.12) and *Use in Specific Populations* (8.1).

Norelgestromin was tested in *in vitro* mutagenicity assays (bacterial plate incorporation mutation assay, CHO/HGPRT mutation assay, chromosomal aberration assay using cultured human peripheral lymphocytes) and in one *in vivo* test (rat micronucleus assay) and found to have no genotoxic potential.

## **14 CLINICAL STUDIES**

In 3 large clinical trials lasting 12 months, in North America, Europe and South Africa, 3,330 women

(ages 18 to 45) completed 22,155 cycles of norelgestromin and ethinyl estradiol transdermal system use, the pregnancy rate in women aged 18 to 35 years was 1.07 (95% confidence interval 0.60, 1.76) per 100 woman-years of norelgestromin and ethinyl estradiol transdermal system use. The racial distribution was 91% Caucasian, 4.9% Black, 1.6% Asian, and 2.4% Other.

With respect to weight, 5 of the 15 pregnancies reported with norelgestromin and ethinyl estradiol transdermal system use were among women with a baseline body weight  $\geq$  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 norelgestromin and ethinyl estradiol transdermal system may be less effective in these women.

### ***Patch Adhesion***

In the clinical trials with norelgestromin and ethinyl estradiol transdermal system, approximately 2% of the cumulative number of patches completely detached and 3% partially detached. The proportion of subjects with at least one patch that completely detached ranged from 2% to 6%, with a reduction from Cycle 1 (6%) to Cycle 13 (2%). For instructions on how to manage detachment of patches, refer to *Dosage and Administration* (2).

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## **16 HOW SUPPLIED/STORAGE AND HANDLING**

## 16.1 How Supplied

Xulane<sup>®</sup> (norelgestromin and ethinyl estradiol transdermal system) is available in one strength of 150 mcg/day NGMN and 35 mcg/day EE.

Xulane<sup>®</sup> is a 14 cm<sup>2</sup> peach, transdermal system printed with “Xulane<sup>®</sup> (norelgestromin and ethinyl estradiol) 150/35 mcg per day” in brown ink. Each system contains 4.86 mg norelgestromin, USP and 0.53 mg ethinyl estradiol, USP.

Each transdermal system is packaged in a protective pouch.

Xulane<sup>®</sup> (norelgestromin and ethinyl estradiol transdermal system) is available in folding cartons of one cycle each (NDC 0378-3340-53); each cycle contains 3 systems.

## 16.2 Special Precautions for Storage and Disposal

**Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]**

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

Do not store in the refrigerator or freezer.

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

## 17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information and Instructions for Use)

### 17.1 General

Counsel patients about the following information:

- Cigarette smoking increases the risk of serious cardiovascular events from combined hormonal contraceptive use, and that women who are over 35 years old and smoke should not use combined hormonal contraceptives.
- The use of CHCs increases the risk of VTE. However, pregnancy increases the risk of VTE as much or more than the use of CHCs. The risk of VTE in women using CHCs is 3 to 12 cases per 10,000 woman-years. The risk of VTE is highest during the first year of use of CHCs and when restarting hormonal contraception after a break of 4 weeks or longer. The risk of thromboembolic disease due to CHCs gradually disappears after use is discontinued.
- Xulane does not protect against HIV infection (AIDS) and other sexually transmitted infections.
- The Warnings and Precautions associated with combined hormonal contraceptives.
- Xulane is not to be used during pregnancy; if pregnancy occurs during use of Xulane, instruct the patient to stop further use.
- Apply a single patch the same day every week (Weeks 1 through 3). Instruct patients what to do in the event a patch is missed. See “WHAT IF I FORGET TO CHANGE MY PATCH?” section in FDA-Approved Patient Labeling.
- Use a back-up or alternative method of contraception when enzyme inducers are used with Xulane.
- Combined hormonal contraceptives may reduce breast milk production; this is less likely to occur if breastfeeding is well established.
- Women who start combined hormonal contraceptives postpartum, and who have not yet had a period, should use an additional method of contraception until they have used a patch for 7 consecutive days.
- Amenorrhea may occur. Consider pregnancy in the event of amenorrhea. Rule out pregnancy in the

event of amenorrhea in two or more consecutive cycles, amenorrhea in one cycle if the woman has not adhered to the dosing schedule, or if associated with symptoms of pregnancy, such as morning sickness or unusual breast tenderness.

- If the Xulane 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, becomes stuck to itself or another surface, has other material stuck to it, or 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.
  - A woman may not be protected from pregnancy if a patch is partially or completely detached for  $\geq 24$  hours (or if the woman is not sure how long the patch has been detached). She should start a new cycle immediately by applying a new patch. Back-up contraception, such as a condom and spermicide or diaphragm and spermicide, must be used for the first week of the new cycle.

The brands listed are trademarks of their respective owners.

## Patient Information

**Xulane® [zhoo' lane]**

**(norelgestromin and ethinyl estradiol transdermal system)**

**150 mcg/day norelgestromin and 35 mcg/day ethinyl estradiol**

### **What is the most important information I should know about Xulane?**

**Do not use Xulane if you smoke cigarettes and are over 35 years old. Smoking increases your risk of serious cardiovascular side effects from hormonal birth control methods, including death from heart attack, blood clots or stroke. This risk increases with age and the number of cigarettes you smoke.**

**Women 15 to 44 years of age who use Xulane may have an increased risk of blood clots compared to women who use certain birth control pills.**

**You will be exposed to about 60% more estrogen if you use Xulane than if you use a typical birth control pill containing 35 micrograms of estrogen. In general, increased estrogen may increase the risk of side effects, including blood clots.**

Hormonal birth control methods help to lower the chances of becoming pregnant. They do not protect against HIV infection (AIDS) and other sexually transmitted infections.

### **What is Xulane?**

Xulane is a birth control patch. It contains two female hormones, an estrogen called ethinyl estradiol, and a progestin called norelgestromin.

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

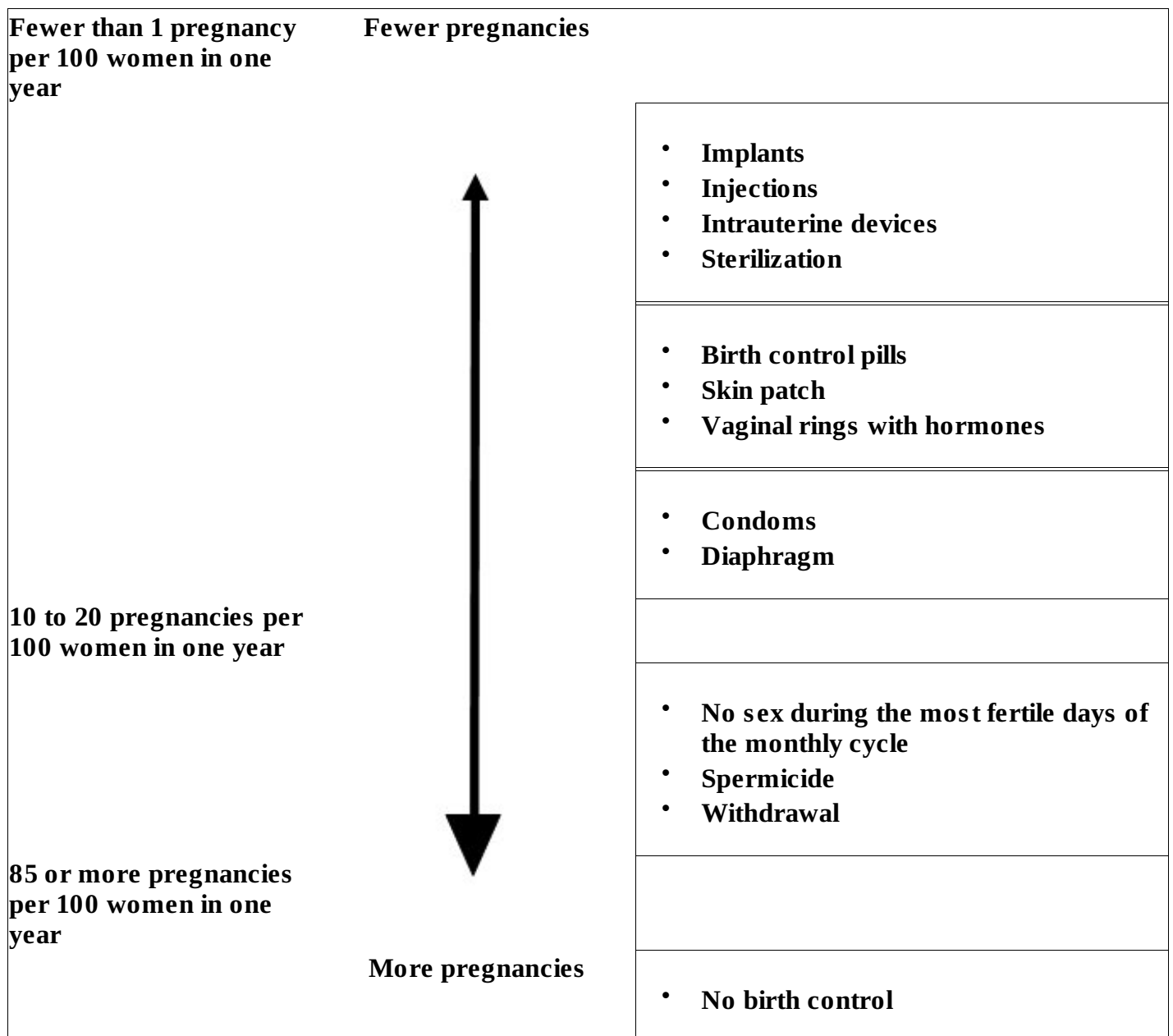
### **How well does Xulane work?**

Your chance of getting pregnant depends on how well you follow the directions for using Xulane. The better you follow the directions, the less chance you have of getting pregnant.

In clinical studies, 1 to 2 out of 100 women got pregnant during the first year that they used norelgestromin and ethinyl estradiol transdermal system.

Xulane may not be as effective in women weighing more than 198 lbs. (90 kg). If you weigh more than 198 lbs. (90 kg), talk to your healthcare provider about which method of birth control is right for you.

The following chart shows the chance of getting pregnant for women who use different methods of birth control. Each box on the chart contains a list of birth control methods that are similar in effectiveness. The most effective methods are at the top of the chart. The box on the bottom of the chart shows the chance of getting pregnant for women who do not use birth control and are trying to get pregnant.



### Who Should Not Use Xulane?

Do not use Xulane if you:

- smoke and are over 35 years old
- have or have had blood clots in your arms, legs, eyes or lungs

- have an inherited problem that makes your blood clot more than normal
- have had a stroke
- have had a heart attack
- have certain heart valve problems or heart rhythm problems that can cause blood clots to form in the heart
- have high blood pressure that medicine cannot control
- have diabetes with kidney, eye, nerve, or blood vessel damage
- have had certain kinds of severe migraine headaches with aura, numbness, weakness or changes in vision, or have any migraine headaches if you are over age 35
- have liver disease, including liver tumors, take any Hepatitis C drug combination containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir. This may increase levels of the liver enzyme “alanine aminotransferase” (ALT) in the blood.
- have unexplained vaginal bleeding
- are pregnant or think you may be pregnant. However, Xulane is not known to cause birth defects when used by accident during pregnancy.
- have had breast cancer or any cancer that is sensitive to female hormones

Hormonal birth control methods may not be a good choice for you if you have ever had jaundice (yellowing of the skin or eyes) caused by pregnancy or related to previous use of hormonal birth control.

Tell your healthcare provider if you have ever had any of the above conditions. Your healthcare provider may recommend another method of birth control.

### **What should I tell my healthcare provider before using Xulane?**

#### **Before you use Xulane tell your healthcare provider:**

- about all your medical conditions
- if you are pregnant or think you are pregnant
- if you are scheduled for surgery. Xulane may increase your risk of blood clots after surgery. You should stop using your Xulane patch at least 4 weeks before you have surgery and not restart it until at least 2 weeks after your surgery.
- if you are scheduled for any laboratory tests. Certain blood tests may be affected by hormonal birth control methods.
- are breastfeeding or plan to breastfeed. Hormonal birth control methods that contain estrogen, like Xulane, may decrease the amount of milk you make. A small amount of hormones from the Xulane patch may pass into your breast milk. Consider another method of birth control until you are ready to stop breastfeeding.

Tell your healthcare provider about all medicines and herbal products that you take.

Some medicines and herbal products may make hormonal birth control less effective, including, but not limited to:

- certain seizure medicines (carbamazepine, felbamate, oxcarbazepine, phenytoin, rufinamide, and topiramate)
- aprepitant
- barbiturates
- bosentan
- griseofulvin
- certain combinations of HIV medicines (nelfinavir, ritonavir, ritonavir-boosted protease



inhibitors)

- certain non-nucleoside reverse transcriptase inhibitors (nevirapine)
- rifampin and rifabutin
- St. John's wort

Use another birth control method (such as a condom and spermicide or diaphragm and spermicide) when you take medicines that may make the Xulane patch less effective.

Some medicines and grapefruit juice may increase your level of the hormone ethinyl estradiol if used together, including:

- acetaminophen
- ascorbic acid
- medicines that affect how your liver breaks down other medicines (itraconazole, ketoconazole, voriconazole, and fluconazole)
- certain HIV medicines (atazanavir, indinavir)
- atorvastatin
- rosuvastatin
- etravirine

Hormonal birth control methods may interact with lamotrigine, an anti-seizure medicine used for epilepsy. This may increase the risk of seizures, so your healthcare provider may need to adjust the dose of lamotrigine.

Women on thyroid replacement therapy may need increased doses of thyroid hormone.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

### **How should I use Xulane?**

- **For detailed instructions, see the step-by-step instructions for using Xulane at the end of this Patient Information.**
- Use Xulane exactly as your healthcare provider tells you to use it.
- Wear one Xulane patch at a time. Make sure you remove your old Xulane patch before applying your new Xulane patch.
- **Do not** skip using any Xulane patches, even if you do not have sex often.
- Xulane is applied in a 4-week cycle.
  - Apply your Xulane patch 1 time each week for 3 weeks (21 total days).
  - Apply each new Xulane patch on the same day of the week. This day will be your "Patch Change Day." For example, if you apply your first Xulane patch on a Monday, all of your Xulane patches should be applied on a Monday.
  - **Do not** apply your Xulane patch during Week 4. Make sure you remove your old Xulane patch. This is your patch-free week. Your menstrual period should start during your patch-free week.
  - Begin a new 4 week cycle by applying a new Xulane patch on the day after Week 4 ends. Repeat the cycle of 3 weekly applications followed by a patch-free week.

<i>Calendar</i>						
<i>Sunday</i>	<i>Monday</i>	<i>Tuesday</i>	<i>Wednesday</i>	<i>Thursday</i>	<i>Friday</i>	<i>Saturday</i>
<b>Day 1</b>	Week 1 →					
<b>Day 8</b>	Week 2 →					
<b>Day 15</b>	Week 3 →					
<b>X</b>	Week 4 <b>NO PATCH</b> →					

- Your Xulane patch should never be off for more than 7 days in a row. If your Xulane patch is off for more than 7 days in a row and you have sex during this time, you could become pregnant.
- If you miss a period you might be pregnant. Some women miss their periods or have light periods on hormonal birth control methods even when they are not pregnant. Call your healthcare provider if you miss one period and have not used your Xulane patch every day or you miss two periods in a row.

### What are the possible side effects of Xulane?

See "What is the most important information I should know about Xulane?"

### Xulane may cause serious side effects, including:

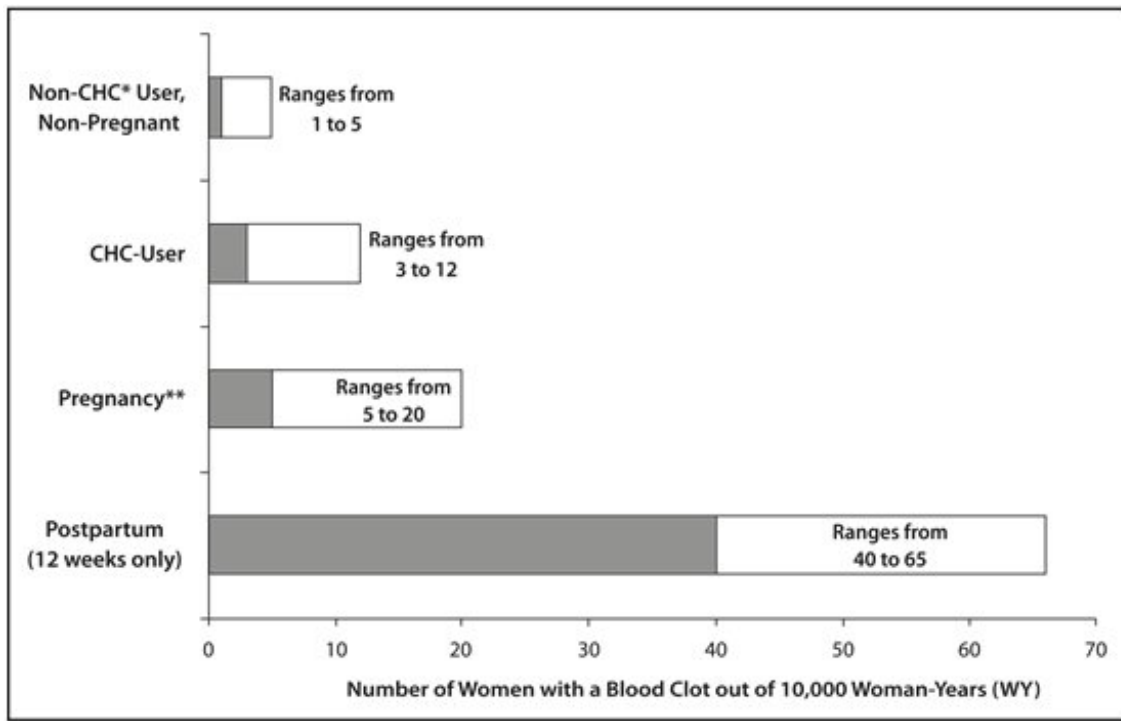
- **blood clots.** Like pregnancy, hormonal birth control methods increase the risk of serious blood clots (see following graph), especially in women who have other risk factors, such as smoking, obesity, or age greater than 35. This increased risk is highest when you first start using hormonal birth control and when you restart the same or different hormonal birth control after not using it for a month or more. Some studies have reported that women who use norelgestromin and ethinyl estradiol transdermal system have a higher risk of getting a blood clot. Talk with your healthcare provider about your risk of getting a blood clot before using Xulane or deciding which type of birth control is right for you.

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

- legs (deep vein thrombosis)
- lungs (pulmonary embolus)
- eyes (loss of eyesight)
- heart (heart attack)
- brain (stroke)

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

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



\*CHC = combination hormonal contraception

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

**Call your healthcare provider right away if you have:**

- leg pain that will not go away
- sudden shortness of breath
- sudden blindness, partial or complete
- severe pain or pressure in your chest
- sudden, severe headache unlike your usual headaches
- weakness or numbness in an arm or leg, or trouble speaking
- yellowing of the skin or eyeballs

**Other serious risks include**

- liver problems including liver tumors
- gallbladder disease
- high blood pressure

The most common side effects of Xulane are:

- breast symptoms (discomfort, swelling, or pain)
- nausea
- headache
- skin irritation, redness, pain, swelling, itching or rash at the patch application site
- stomach pain
- pain during menstruation
- vaginal bleeding and menstrual disorders, such as spotting or bleeding between periods

- mood, affect and anxiety disorders

Some women have spotting or light bleeding, breast tenderness, or feel sick to their stomach during norelgestromin and ethinyl estradiol transdermal system use. If these symptoms occur, do not stop using the Xulane patch. The problem will usually go away. If it doesn't go away, check with your healthcare provider.

Less common side effects are:

- acne
- less sexual desire
- bloating or fluid retention
- blotchy darkening of your skin, especially your face
- high blood sugar, especially in women with diabetes
- high fat (cholesterol, triglycerides) levels in the blood
- depression, especially if you have had depression in the past. Call your healthcare provider immediately if you have any thoughts of harming yourself.
- problems tolerating contact lenses
- weight gain

Tell your healthcare provider about any side effect that bothers you or that does not go away.

These are not all the possible side effects of Xulane. For more information, ask your healthcare provider or pharmacist.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

### **How should I store and throw away used Xulane patches?**

- Store at room temperature between 20° to 25°C (68° to 77°F).
- Do not store Xulane patches outside of their pouches. Apply immediately upon removal from the protective pouch.
- Do not store in the refrigerator or freezer.
- Used Xulane patches still contain some active hormones. To throw away the Xulane patch, fold the sticky side of the patch together, place it in a sturdy child-proof container, and place this container in the trash. Do not flush used Xulane patches down the toilet.
- Return unused, unneeded, or expired patches to your pharmacist.

### **Keep Xulane and all medicines out of the reach of children.**

### **General information about the safe and effective use of Xulane**

Medicines are sometimes prescribed for purposes other than those listed in Patient Information. Do not use Xulane for a condition for which it was not prescribed. Do not give Xulane to other people, even if they have the same symptoms that you have. It may harm them.

This leaflet summarizes the most important information about Xulane. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about Xulane that is written for health professionals.

For more information, contact Mylan Pharmaceuticals Inc. at 1-877-446-3679 (1-877-4-INFO-RX).

### **What are the ingredients in Xulane?**

**Active ingredient:** norelgestromin and ethinyl estradiol

**Inactive ingredient:** polyethylene, polyester, polyisobutene adhesive, crospovidone, mineral oil, non-woven polyester fabric, oleyl alcohol, dipropylene glycol, and a polyester film with a fluoropolymer coating.

### **Do hormonal birth control methods cause cancer?**

Hormonal birth control methods do not seem to cause breast cancer. However, if you have breast cancer now, or have had it in the past, do not use hormonal birth control methods because some breast cancers are sensitive to hormones.

Women who use hormonal birth control methods may have a slightly higher chance of getting cervical cancer. However, this may be due to other reasons such as having more sexual partners.

### **What should I know about my period when using Xulane?**

When you use Xulane you may have bleeding and spotting between periods, called unplanned bleeding. Unplanned bleeding may vary from slight staining between menstrual periods to breakthrough bleeding which is a flow much like a regular period. Unplanned bleeding occurs most often during the first few months of Xulane use, but may also occur after you have been using the patch for some time. Such bleeding may be temporary and usually does not indicate any serious problems. It is important to continue using the patch on schedule. If the unplanned bleeding or spotting is heavy or lasts for more than a few days, you should discuss this with your healthcare provider.

### **What if I miss my scheduled period when using Xulane?**

Some women miss periods on hormonal birth control, even when they are not pregnant. However, if you go 2 or more months in a row without a period, or you miss your period after a month where you did not use all of your patches correctly, or you have symptoms associated with pregnancy, such as morning sickness or unusual breast tenderness, call your healthcare provider because you may be pregnant. Stop taking Xulane if you are pregnant.

### **What if I want to become pregnant?**

You may stop using Xulane whenever you wish. Consider a visit with your healthcare provider for a pre-pregnancy checkup before you stop using the patch.

## **Instructions for Use**

**Xulane is for skin use only.**

**Do not cut, damage, or alter the Xulane patch in any way.**

**How to start using your Xulane patch:**

**Figure A**



- **If you are not currently using hormonal birth control,** you have 2 ways to begin using your Xulane patch. Choose the way that is best for you:
  - **First day start:** Apply your first Xulane patch during the first 24 hours of your menstrual

period.

- **Sunday start:** Apply your first Xulane patch on the first Sunday after your menstrual period begins. Use a non-hormonal contraceptive method of birth control, such as a condom and spermicide or diaphragm and spermicide, for the first 7 days of your first cycle only. If your period starts on Sunday, apply your first Xulane patch that day, and no back-up birth control is needed.

- **If you are changing from the pill or vaginal contraceptive ring to the Xulane patch:**

- Complete your current pill cycle or vaginal ring cycle. Apply your first Xulane patch on the day you would normally start your next pill or insert your next vaginal ring.
- If you do not get your period within 1 week after taking your last active pill or removing your last vaginal ring, check with your healthcare provider to make sure you are not pregnant. You may still go ahead and start Xulane for contraception.
- If you apply your Xulane patch more than 1 week after taking your last active pill or removing your last vaginal ring, use a non-hormonal contraceptive method with the Xulane patch for the first 7 days of patch use.

- **If you are starting Xulane after childbirth:**

- If you are not breastfeeding, wait 4 weeks before using Xulane and use a non-hormonal contraceptive method of birth control, such as a condom and spermicide or diaphragm and spermicide, for the first 7 days of your first cycle only. If you have had sex since your baby was born, wait for your first period, or see your healthcare provider to make sure you are not pregnant before starting Xulane.

- **If you are starting Xulane after a miscarriage or abortion:**

- You may start Xulane immediately after a miscarriage or abortion that occurs in the first 12 weeks (first trimester) of pregnancy. You do not need to use another contraceptive method.
- If you do not start Xulane within 5 days after a first trimester miscarriage or abortion, use a non-hormonal contraceptive method of birth control, such as a condom and spermicide or diaphragm and spermicide, while you wait for your period to start. You have 2 ways to begin using your Xulane patch. Choose the way that is best for you:
  - **First day start:** Apply your first Xulane patch during the first 24 hours of your menstrual period.
  - **Sunday start:** Apply your first Xulane patch on the first Sunday after your menstrual period begins. Use a non-hormonal contraceptive method of birth control, such as a condom and spermicide or diaphragm and spermicide, for the first 7 days of your first cycle only. If your period starts on Sunday, apply your first Xulane patch that day, and no back-up birth control is needed.
- If you are starting Xulane after a miscarriage or abortion that occurs **after** the first 12 weeks of pregnancy (second trimester), wait 4 weeks before using Xulane and use a non-hormonal contraceptive method of birth control, such as a condom and spermicide or diaphragm and spermicide, for the first 7 days of your first cycle only. If you have had sex since your miscarriage or abortion, wait for your first period, or see your healthcare provider to make sure you are not pregnant before starting Xulane.

Figure B is a picture of the Xulane patch.

**Figure B**





**Step 1. Choose a place on your body for your Xulane patch**



- The Xulane patch may be placed on your upper outer arm, abdomen, buttock or back in a place where it will not be rubbed by tight clothing. Avoid the waistline because clothing and belts may cause your patch to be rubbed off.
- **Do not** apply the patch to your breasts.
- Apply the Xulane patch only to skin that is clean, dry, and free of any powder, make-up, cream, oil, or lotion.
- Do not apply the Xulane patch to cut or irritated skin, or in the same location as the previous Xulane patch.

**Step 2: Apply your Xulane patch**

A photograph showing hands tearing open the foil pouch of the Xulane patch.	<ul style="list-style-type: none"><li>• Tear open the pouch at the top edge <b>and</b> one side edge. Peel open the foil pouch. Gently remove the contents of the foil pouch and discard the additional pieces of film above and below the Xulane patch.</li></ul>
A photograph showing hands peeling away half of the clear plastic from the Xulane patch.	<ul style="list-style-type: none"><li>• Peel away half of the clear plastic. Avoid touching the sticky surface with your fingers.</li></ul>

	<ul style="list-style-type: none"> <li>• Apply the sticky side of the Xulane patch to clean, dry skin. Remove the other half of the clear plastic and apply the entire patch to your skin.</li> </ul>
	<ul style="list-style-type: none"> <li>• Press firmly on the Xulane patch with the palm of your hand for 10 seconds, making sure that the whole patch sticks to your skin.</li> <li>• Run your fingers over the entire surface area to smooth out any “wrinkles” around the outer edges of the Xulane patch.</li> <li>• Check your Xulane patch every day to make sure all edges are sticking correctly.</li> </ul>

### Step 3: Throwing away your Xulane patch

- To throw away the Xulane patch, fold the sticky side of the patch together, place it in a sturdy child-proof container, and place the container in the trash.
- Used Xulane patches should not be flushed in the toilet.

### Important notes :

- **Your Xulane patch must stick securely to your skin to work properly.**
- **Do not** try to reapply a Xulane patch if it is no longer sticky, if it has become stuck to itself or another surface, or if it has other material stuck to it. **Do not** tape or wrap the patch to your skin or reapply a patch that is partially adhered to clothing.
- **If your Xulane patch edge lifts up:**
  - Press down firmly on the patch with the palm of your hand for 10 seconds, making sure that the whole patch sticks to your skin. Run your fingers over the entire surface area to smooth out any “wrinkles” around the edges of the Xulane patch.
  - If your Xulane patch does not stick completely, remove it and apply a new Xulane patch.
  - **Do not** tape or wrap the Xulane patch to your skin or reapply a Xulane patch that is partially stuck to clothing.
- **If your Xulane patch has been off or partially off:**
  - **For less than 1 Day**, try to reapply it. If the Xulane patch does not stick completely, apply a new Xulane patch immediately. No back-up contraception is needed and your "Patch Change Day" will stay the same.
  - **For more than 1 Day or if you are not sure for how long**, you could become pregnant. To reduce this chance, apply a new Xulane patch and start a new 4 week cycle. You will now have a new "Patch Change Day." Use a non-hormonal back-up contraception method such as a condom and spermicide or diaphragm and spermicide for the first week of your new 4 week Xulane cycle.
- **If you want to move your "Patch Change Day" to a different day of the week**, finish your current cycle. Remove your third Xulane patch on the correct day.



- **During week 4**, the "Patch Free Week" (Day 22 through Day 28), you may choose an **earlier** "Patch Change Day" by applying a new patch on the day you prefer. You now have a new Day 1 and a new "Patch Change Day."
- **If your Xulane patch becomes uncomfortable** or your application site is red, painful or swollen, change your Xulane patch. Remove your Xulane patch and apply a new patch to a new location until your next "Patch Change Day."
- **If you forget to change or remove your Xulane patch:**
  - **At the start of any patch cycle (Week 1, Day 1):**
    - **You could become pregnant. You must use a back-up contraception method for 7 days.** Apply the first Xulane patch of your new cycle as soon as you remember. You now have a new "Patch Change Day" and a new Day 1.
  - **In the middle of your patch cycle (Week 2 or Week 3):**
    - **If you forget to change your Xulane patch for 1 or 2 days**, apply a new Xulane patch as soon as you remember. Apply your next patch on your normal "Patch Change Day." No back-up contraception method is needed.
    - **If you forget to change your Xulane patch for more than 2 days**, you could become pregnant. Start a new 4 week cycle as soon as you remember by putting on a new Xulane patch. You now have a different "Patch Change Day" and a new Day 1. You must use a back-up contraception method for the first 7 days of your new cycle.
  - **At the end of your patch cycle (Week 4):**
    - **If you forget to remove your Xulane patch**, take it off as soon as you remember. Start your next cycle on your normal "Patch Change Day," the day after Day 28. No back-up contraception method is needed.
- **If you forget to apply your Xulane patch at the start of your next patch cycle**, you could become pregnant. Apply the first Xulane patch of your new cycle as soon as you remember. You now have a new "Patch Change Day" and a new Day 1. Use a non-hormonal back-up contraception method such as a condom and spermicide or diaphragm and spermicide for the first 7 days of your new 4 week Xulane cycle.
- **If you have trouble remembering to change your Xulane patch**, talk to your healthcare provider about how to make patch changing easier or about using another method of contraception.
- **If you are not sure how to use your Xulane patch:**
  - Use a back-up contraception method such as a condom and spermicide or diaphragm and spermicide anytime you have sex. Make sure to have one of these non-hormonal contraception methods ready at all times.
  - Talk to your healthcare provider for instructions on using your Xulane patch.

This Patient Information and Instructions for Use have been approved by the U.S. Food and Drug Administration.

Manufactured for:

**Mylan Pharmaceuticals Inc.**

Morgantown, WV 26505 U.S.A.

Revised: 4/2017  
NEETS:R14

**PRINCIPAL DISPLAY PANEL – 150/35 mcg per day**

**NDC 0378-3340-53**

**Contents: 3 Transdermal Systems | Rx only**

**Xulane®**

**(norelgestromin and ethinyl  
estradiol transdermal system)**

**150/35 mcg per day**

Each 14 cm<sup>2</sup> system contains 4.86 mg norelgestromin, USP and 0.53 mg ethinyl estradiol, USP. The inactive components are polyisobutene adhesive, crospovidone, mineral oil, non-woven polyester fabric, oleyl alcohol, dipropylene glycol, polyester backing film laminate and polyester release liner.

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

**For Transdermal Use Only**

See patient instructions. Apply immediately upon removal from pouch. Each transdermal system is intended to be worn 7 days as prescribed.

**Package not child-resistant. Keep out of reach of children.**

**Do not store unpouched. Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]**

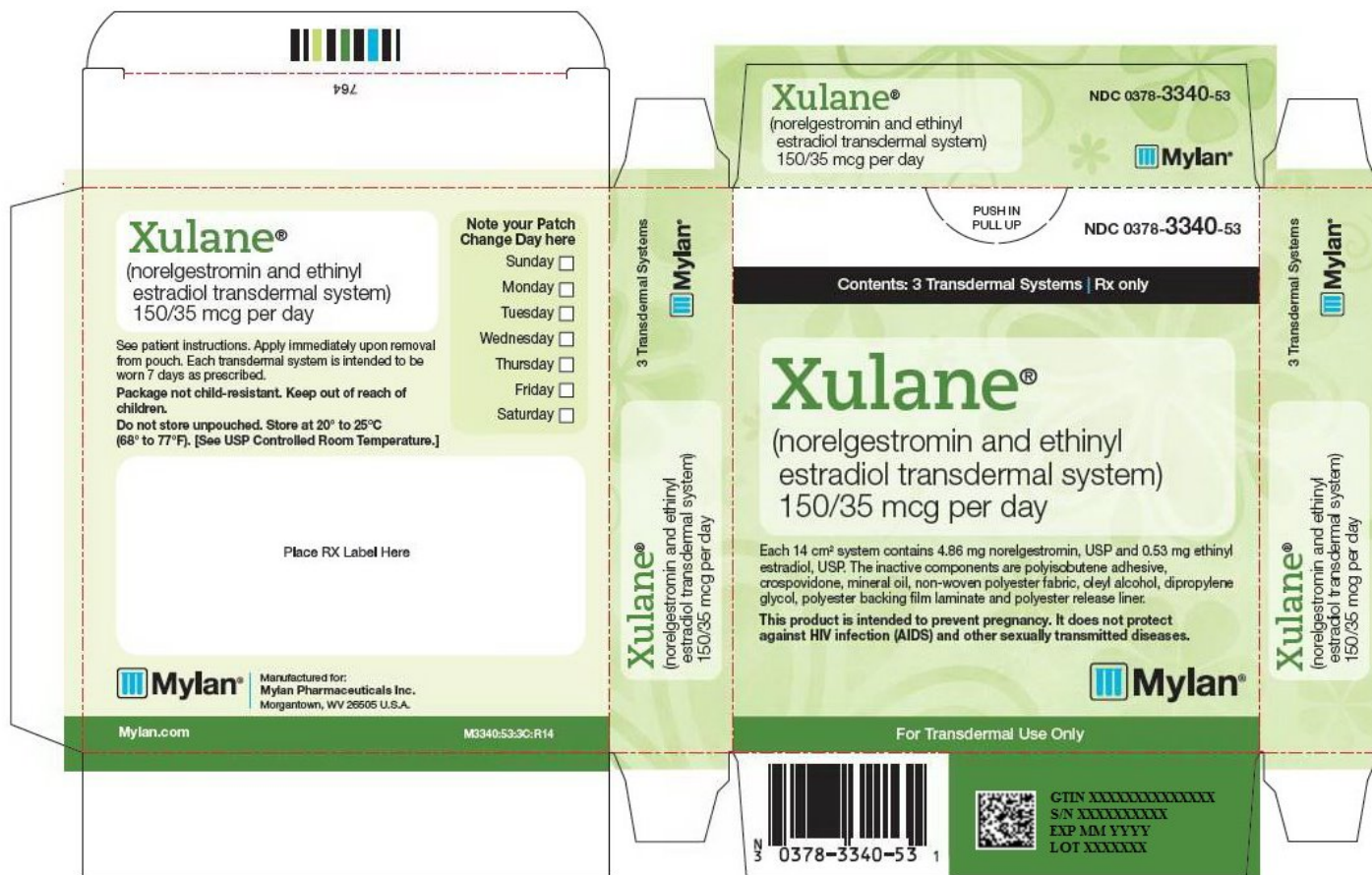
Manufactured for:

**Mylan Pharmaceuticals Inc.**

Morgantown, WV 26505 U.S.A.

**Mylan.com**

**M3340:53:3C:R14**



<b>XULANE</b>			
norelgestromin and ethinyl estradiol patch			
<b>Product Information</b>			
<b>Product Type</b>	HUMAN PRESCRIPTION DRUG	<b>Item Code (Source)</b>	NDC:0378-3340
<b>Route of Administration</b>	TRANSDERMAL		
<b>Active Ingredient/Active Moiety</b>			
	<b>Ingredient Name</b>	<b>Basis of Strength</b>	<b>Strength</b>
	NORELGESTROMIN (UNII: R0TAY3X631) (NORELGESTROMIN - UNII:R0TAY3X631)	NORELGESTROMIN	150 ug in 1 d
	ETHINYL ESTRADIOL (UNII: 423D2T571U) (ETHINYL ESTRADIOL - UNII:423D2T571U)	ETHINYL ESTRADIOL	35 ug in 1 d
<b>Inactive Ingredients</b>			
	<b>Ingredient Name</b>		<b>Strength</b>
	CROSPVIDONE (15 MPAS AT 5%) (UNII: 68401960MK)		
	MINERAL OIL (UNII: T5L8T28FGP)		
	OLEYL ALCOHOL (UNII: 172F2WN8DV)		
	DIPROPYLENE GLYCOL (UNII: E107L85C40)		
<b>Packaging</b>			

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0378-3340-53	3 in 1 CARTON	04/16/2014	
1	NDC:0378-3340-16	1 in 1 POUCH		
1		7 d in 1 PATCH; Type 0: Not a Combination Product		
2	NDC:0378-3340-32	1 in 1 CARTON	06/13/2016	
2	NDC:0378-3340-17	1 in 1 POUCH		
2		7 d in 1 PATCH; Type 0: Not a Combination Product		

### Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA200910	04/16/2014	

**Labeler** - Mylan Pharmaceuticals Inc. (059295980)

Revised: 4/2017

Mylan Pharmaceuticals Inc.