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

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**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)

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**RECENT MAJOR CHANGES**

- Thromboembolic Disorders and Other Vascular Problems (5.1) 10/2015

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**INDICATIONS AND USAGE**

Xulane is an estrogen/progestin combination hormonal contraceptive (CHC), indicated for contraception 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)

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**DOSAGE AND ADMINISTRATION**

- Xulane uses a 28-day (4-week) cycle. Apply a new patch to the upper outer arm above 198 lbs (90 kg). (2.1)
- Apply new each 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)

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**DOSAGE FORMS AND STRENGTHS**

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

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**ADVERSE REACTIONS**

The most frequent adverse reactions reported during clinical trials (≥ 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.

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**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)

---

**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. (5.4)
- Carbohydrate and lipid metabolic effects: Monitor prediabetic and diabetic women taking Xulane. Consider an alternate contraceptive method for women with uncontrolled dyslipidemia. (5.6)
- Headache: Evaluate significant change in headaches and discontinue Xulane if indicated. (5.7)
- Uterine bleeding: Evaluate irregular bleeding or amenorrhea. (5.8)

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**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: MARCH 2016

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**FULL PRESCRIBING INFORMATION: CONTENTS**

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

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2.2 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 may want to make sure the skin is clean and dry.
- The woman should not use lotions, creams, oils, powders, or make-up at the patch site.

HOW TO APPLY THE PATCH

- The woman should peel open the pouch at the top edge and 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.
- The woman should peel away half of the clear plastic. She should avoid touching the sticky surface with her fingers.
- 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.
- 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.
- She should run her fingers over the entire surface area to smooth out any “wrinkles” around the outer edges of the patch.

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

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- She should run her fingers over the entire surface area to smooth out any “wrinkles” around the outer edges of the patch.

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 system, she should use a non-hormonal contraceptive concurrently for the first 7 days of patch use.

Use after Childbirth

Start contraceptive therapy 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)].

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.

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Use after Childbirth

Start contraceptive therapy 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)].
• 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 apply the 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 back-up 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 diazepam 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 diazepam 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 one 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 diazepam 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 Change Day 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
Transdermal system: 150 mcg/day norelgestromin and 35 mcg/day ethinyl estradiol.

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 (5.5))
  - 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 (5.1))
  - Have diabetes mellitus with vascular disease (see Warnings and Precautions (5.6))
  - Have headaches with focal neurological symptoms or have migraine headaches with aura
  - Women over age 35 with any migraine headaches (see Warnings and Precautions (5.7))

- Liver tumors, benign or malignant, or liver disease [see Warnings and Precautions (5.3), Adverse Reactions in Specific Populations (8.6) and Clinical Pharmacology (12.3)]

- Undiagnosed abnormal uterine bleeding (see Warnings and Precautions (5.8))

- Pregnancy, because there is no reason to use hormonal contraceptives during pregnancy (see Warnings and Precautions (5.9) 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 (5.11))

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 for 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 contribute to the use of CHCs [see Contraindications (4)].

Five epidemiologic studies1-9 that assessed the risk of VTE associated with use of norelgestromin and ethinyl estradiol transdermal system are described below. These are four 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 (NMG). LNG 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 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 13 Ingenix study with NMG-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 NMG-containing oral contraceptives as the comparator (BCDSP NMG), including two extensions of 17 and 14 months, respectively, based on the Pharmetrics 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 Pharmetrics 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 Marktecs database, using only non-fatal idiopathic cases. VTE cases were not confirmed by chart review.

The following study included patient chart review to confirm the VTE occurrence.
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 in 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.

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

<table>
<thead>
<tr>
<th>Epidemiologic Study</th>
<th>Comparator Product</th>
<th>Risk Ratios (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>i3 Ingenix NGM Study in Ingenix Research Dafmart</td>
<td>LNG/35 mcg EE</td>
<td>2.2 (1.2 – 4.0)</td>
</tr>
<tr>
<td>BCDSPI NGM Study in Pharimetrics database</td>
<td>LNG/35 mcg EE</td>
<td>1.9 (0.9 – 3.9)</td>
</tr>
<tr>
<td>BCDSPI LNG Study in Pharimetrics database</td>
<td>LNG/30 mcg EE</td>
<td>2.0 (0.9 – 4.1)</td>
</tr>
<tr>
<td>BCDSPI LNG Study in MarketScan database</td>
<td>LNG/30 mcg EE</td>
<td>1.2 (0.8 – 1.9)</td>
</tr>
<tr>
<td>FDA-funded study in Davis/Permanente and Medicaid databases</td>
<td>LNG/30 mcg EE</td>
<td>1.0 (0.2 – 5.1)</td>
</tr>
</tbody>
</table>

* 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.

1. NGM = norgestimate; EE = ethinyl estradiol
2. Increase in risk of VTE is statistically significant
3. Pooled risk ratio from references 1 and 5 covering the initial 33-month study plus 24-month extension. (Initial 33 months of data: Risk Ratio (95% CI) = 2.5 (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). Risk ratios are based on idiopathic cases (those in women with 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). (Figure 1 shows the risk of developing a VTE for women not pregnant and not using CHCs are followed for one year, between 1 and 5 of these women will develop a VTE. Gradually disappears after CHC use is discontinued.)

5. BCDSPI = Boston Collaborative Drug Surveillance Program, the risk ratios are based on idiopathic cases.
6. Pooled risk ratio from references 2, 3, and 5 covering the initial 36-month study, plus 17-month and 24-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) = 2.0 (1.2-3.3).)

7. LNG = levonorgestrel
8. 46 months of data.
9. 69 months of data.
10. Results for “All users,” i.e., initiation and continuing use of several combination hormonal contraceptives. "All prog- estins" 20-35 mcg EE, Risk Ratio (95% CI) = 1.6 (1.2-2.1) and LNG/30 mcg EE, Risk Ratio (95% CI) = 1.3 (1.0-1.6).

*Includes the following progesterins: LNG, norethindrone, norgestimate.

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>i3 Ingenix NGM / Dafmart</td>
<td>2.2 (1.2-4.0)</td>
</tr>
<tr>
<td>BCDSPI NGM / Pharimetrics</td>
<td>1.2 (0.9-1.8)</td>
</tr>
<tr>
<td>BCDSPI LNG / Pharimetrics</td>
<td>2.0 (0.9-4.1)</td>
</tr>
<tr>
<td>BCDSPI LNG / MarketScan</td>
<td>1.3 (0.8-2.1)</td>
</tr>
<tr>
<td>FDA-funded study</td>
<td>1.4 (0.9-2.0)</td>
</tr>
<tr>
<td>LNG/30 mcg EE</td>
<td>1.2 (0.8-1.9)</td>
</tr>
</tbody>
</table>

5.4 High Blood Pressure

Xulane is contraindicated in women with uncontrolled hypertension or hypertension with vascular disease. 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. Women may experience an increase in blood pressure with subsequent CHC use and stop Xulane if blood pressure rises significantly.

5.5 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 gallbladder disease may be at an increased risk for developing gallbladder disease among CHC users.

5.6 Carbohydrate and Lipid Metabolic Effects

Carefully monitor prediabetic and diabetic women who take Xulane. CHCs may decrease glucose tolerance in a dose-related fashion. Women with well-controlled diabetes have been reported in women taking hormonal contraceptives. Women with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis when using hormonal contraceptives.

5.7 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).

5.8 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 with spotting by treatment cycle.

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

<table>
<thead>
<tr>
<th>Treatment Cycle</th>
<th>n</th>
<th>%a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle 1</td>
<td>2994</td>
<td>18.2</td>
</tr>
<tr>
<td>Cycle 2</td>
<td>2743</td>
<td>11.9</td>
</tr>
<tr>
<td>Cycle 3</td>
<td>2699</td>
<td>11.6</td>
</tr>
<tr>
<td>Cycle 4</td>
<td>2541</td>
<td>10.1</td>
</tr>
<tr>
<td>Cycle 5</td>
<td>2532</td>
<td>9.2</td>
</tr>
<tr>
<td>Cycle 6</td>
<td>2494</td>
<td>8.3</td>
</tr>
<tr>
<td>Cycle 7</td>
<td>698</td>
<td>8.3</td>
</tr>
<tr>
<td>Cycle 8</td>
<td>692</td>
<td>8.7</td>
</tr>
<tr>
<td>Cycle 9</td>
<td>654</td>
<td>8.6</td>
</tr>
<tr>
<td>Cycle 10</td>
<td>621</td>
<td>8.7</td>
</tr>
<tr>
<td>Cycle 11</td>
<td>631</td>
<td>8.9</td>
</tr>
<tr>
<td>Cycle 12</td>
<td>617</td>
<td>8.3</td>
</tr>
<tr>
<td>Cycle 13</td>
<td>611</td>
<td>8.0</td>
</tr>
</tbody>
</table>

aPercentage 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.

5.9 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)).

5.10 Depression

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

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

Xulane is contraindicated 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 if pregnancy is confirmed.

5.12 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.

5.13 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.

5.14 Hereditary Angioedema

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

5.15 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 (5.1))

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 two of the trials). The women ranged in age from 18 to 45 years and were predominantly white (91%).

The most common adverse reactions (≥ 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 ≥ 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 ≥ 2.5% of Norelgestromin and Ethinyl Estradiol Transdermal System-Treated Subjects in Three Phase 3 Clinical Trials

<table>
<thead>
<tr>
<th>System/Organ Class</th>
<th>Norelgestromin and Ethinyl Estradiol Transdermal System (n = 3322)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reproductive system and breast disorders</td>
<td>Breast symptoms† 22.4%</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea 16.6%</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Abdominal pain† 8.1%</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache 21.0%</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Application site disorder† 17.1%</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Mood, affect and anxiety disorders† 6.3%</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Acne 2.9%</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Vaginal yeast infection† 3.9%</td>
</tr>
<tr>
<td>Investigations</td>
<td>Weight increased 2.7%</td>
</tr>
</tbody>
</table>

* MedDRA version 10.0
† 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†, malaise
- Hepatobiliary disorders: Cholelithiasis
- Investigations: Blood pressure increased, lipid disorders†
7.2 Effects of Combined Hormonal Contraceptives on Other Drugs

Substances Decreasing the Plasma Concentrations of CHCs

7.3 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

Xulane has not been studied in premenopausal 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 (5.12)].

8.7 Renal Impairment

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

8.8 Women with Weight ≥ 198 lbs (90 kg)

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

10 OVERDOSAGE

Overdose 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 cm². It contains 4.86 mg norgestimate (NGMN) and 0.043 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 [Css]) of NGMN and EE during use of norgestimate and ethinyl estradiol transdermal system are higher and the Cmax is lower than those produced by an oral contraceptive containing Norgestimate 200 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, crosspovidone, mineral oil, non-woven polyester fabric, ethyl 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® (norgestimate 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: 269.41

Chemical name for NGMN: 18, 19-Dinorgestren-4-ene-20-3-one, 13-ethyl-17-hydroxy-3-oxime, (17α)

Chemical name for EE: 19-Norpregna-1,3,5 (10)-trien-20-yne-3,17-diol, (17α)
12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

NGMN is the active progestin largely responsible for the progестational 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 three clinical studies have demonstrated that steady state is reached within 2 weeks of application. In one of the clinical studies, 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 for NGMN and EE following a single application of norelgestromin and ethinyl estradiol transdermal system to the buttock, upper outer arm, abdomen and upper torso (excluding breast) were examined. While absorption from the abdomen was slightly lower than from other sites, absorption from these anatomic sites was considered to be therapeutically equivalent.

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<table>
<thead>
<tr>
<th>Analyte</th>
<th>Parameter</th>
<th>Cycle 1</th>
<th>Cycle 2</th>
<th>Cycle 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Week 1</td>
<td>Week 2</td>
<td>Week 3</td>
</tr>
<tr>
<td>NGMN</td>
<td>C_{ss} (ng/mL)</td>
<td>0.70 (39.4)</td>
<td>0.70 (41.8)</td>
<td>0.80 (28.7)</td>
</tr>
<tr>
<td></td>
<td>AUC_{0-24} (ng·h/mL)</td>
<td>107 (44.2)</td>
<td>105 (43.2)</td>
<td>123 (43.4)</td>
</tr>
<tr>
<td></td>
<td>t_{1/2} (h)</td>
<td>nc</td>
<td>nc</td>
<td>nc</td>
</tr>
<tr>
<td>EE</td>
<td>C_{ss} (pg/mL)</td>
<td>46.4 (38.5)</td>
<td>47.1 (36.4)</td>
<td>50.1 (42.5)</td>
</tr>
<tr>
<td></td>
<td>AUC_{0-24} (pg·h/mL)</td>
<td>6796 (39.1)</td>
<td>7160 (40.4)</td>
<td>10054 (41.8)</td>
</tr>
<tr>
<td></td>
<td>t_{1/2} (h)</td>
<td>nc</td>
<td>nc</td>
<td>nc</td>
</tr>
</tbody>
</table>

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.

The results from a study of consecutive norelgestromin and ethinyl estradiol transdermal system weared 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 NGMN 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 NGMN 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.

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.

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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.)

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 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)
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\textsubscript{avg} 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, and Impairment of Fertility

See Warnings and Precautions (5.3, 5.11) and Use in Specific Populations (8.1).

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Norelgestromin and Ethinyl Estradiol Transdermal System</th>
<th>ORAL CONTRACEPTIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>( C_{\text{avg}} ) (ng/mL)</td>
<td>11.2 (33.6)</td>
<td>2.16 (25.2)</td>
</tr>
<tr>
<td>( AUC_{0-168} ) (ng·h/mL)</td>
<td>145 (36.8)</td>
<td>123 (30.2)</td>
</tr>
<tr>
<td>( C_{\text{max}} ) (ng/mL)</td>
<td>0.888 (36.6)</td>
<td>0.732 (30.2)</td>
</tr>
<tr>
<td>EE</td>
<td>97.4 (31.6)</td>
<td>133 (27.7)</td>
</tr>
<tr>
<td>( AUC_{0-168} ) (pg·h/mL)</td>
<td>12,971 (33.1)</td>
<td>8,281 (26.9)</td>
</tr>
<tr>
<td>( C_{\text{avg}} ) (pg/mL)</td>
<td>80.0 (33.5)</td>
<td>49.3 (26.9)</td>
</tr>
</tbody>
</table>

\* Cycle 2, Week 3
\( C_{\text{avg}} \) is rapidly metabolized to NGMN following oral administration
\( AUC_{0-168} \)

In general, overall exposure for NGMN and EE (AUC and \( C_{\text{avg}} \)) 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 \( C_{\text{max}} \) values were higher in subjects administered the oral contraceptive. Under steady state conditions, \( AUC_{0-168} \) and \( C_{\text{avg}} \) for EE were approximately to that for the oral contraceptive, while \( C_{\text{max}} \) values were higher in subjects administered 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 NDM 250 mcg / EE 35 mcg) for One Cycle and Application of Norelgestromin and Ethinyl Estradiol Transdermal System for One Cycle in Healthy Female Volunteers

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Norelgestromin and Ethinyl Estradiol Transdermal System</th>
<th>ORAL CONTRACEPTIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>( % \text{ change from Day 1 to Day 22} )</td>
<td>SHBG 334 (39.3)</td>
<td>200 (43.2)</td>
</tr>
<tr>
<td>CBG</td>
<td>153 (40.2)</td>
<td>157 (33.4)</td>
</tr>
</tbody>
</table>

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

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 was higher for the transdermal patch, and the \( C_{\text{max}} \) values were higher for the oral contraceptive.

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 NDM 250 mcg / EE 35 mcg) in Healthy Female Volunteers

In Table 6, 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>
<thead>
<tr>
<th>Parameter</th>
<th>Norelgestromin and Ethinyl Estradiol Transdermal System</th>
<th>ORAL CONTRACEPTIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>( % \text{ change from Day 1 to Day 22} )</td>
<td>SHBG 334 (39.3)</td>
<td>200 (43.2)</td>
</tr>
<tr>
<td>CBG</td>
<td>153 (40.2)</td>
<td>157 (33.4)</td>
</tr>
</tbody>
</table>

In general, overall exposure for NGMN and EE (AUC and \( C_{\text{avg}} \)) 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 \( C_{\text{max}} \) values were higher in subjects administered the oral contraceptive. Under steady state conditions, \( AUC_{0-168} \) and \( C_{\text{avg}} \) for EE were approximately 55% and 60% higher, respectively, for the transdermal patch, and the \( C_{\text{max}} \) 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.

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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.
Combined hormonal contraceptives may reduce breast milk production; this is less likely to occur if breastfeeding is well established.

Xulane does not protect against HIV infection (AIDS) and other sexually transmitted infections.

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 heart attack
- 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
- 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.

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.
• 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 re-
lated 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)
• aripiprazole
• 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 (itra-
conazole, 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 one 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 ap-
plied 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.

What is the risk of developing a blood clot? (See the following graph)
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.

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)

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)
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 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, 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:

• 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 one 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 one 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 two 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 apply your Xulane patch more than one week after taking your last active pill or removing your last vaginal ring, use a non-hormonal contraceptive method while you wait for your period to start. You have two 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.

Figure B is a picture of the Xulane patch.
Step 2: Apply your Xulane patch

- Tear open the pouch at the top edge and 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.

- Peel away half of the clear plastic. Avoid touching the sticky surface with your fingers.

- 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.

- 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.

- Run your fingers over the entire surface area to smooth out any “wrinkles” around the outer edges of the Xulane patch.

- Check your Xulane patch every day to make sure all edges are sticking correctly.

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.

Mylan®

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Morgantown, WV 26505 U.S.A.

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