

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Etonogestrel/Ethinyl Estradiol Vaginal Ring safely and effectively. See full prescribing information for Etonogestrel/Ethinyl Estradiol Vaginal Ring.

Etonogestrel/Ethinyl Estradiol Vaginal Ring
Initial U.S. Approval: 2001

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

See full prescribing information for complete boxed warning.

- Women over 35 years old who smoke should not use Etonogestrel/Ethinyl Estradiol Vaginal Ring. (4)
- Cigarette smoking increases the risk of serious cardiovascular events from combination hormonal contraceptive (CHC) use. (4)

RECENT MAJOR CHANGES

Dosage and Administration	
Deviations from the Recommended Regimen (2.3)	12/2018
Warnings and Precautions	
Hypersensitivity Reactions (5.6)	12/2018

INDICATIONS AND USAGE

Etonogestrel/Ethinyl Estradiol Vaginal Ring is an estrogen/progestin combination hormonal contraceptive (CHC) indicated for use by women to prevent pregnancy. (1)

DOSAGE AND ADMINISTRATION

One Etonogestrel/Ethinyl Estradiol Vaginal Ring is inserted in the vagina. The ring must remain in place continuously for three weeks, followed by a one-week ring-free interval. (2)

DOSAGE FORMS AND STRENGTHS

Etonogestrel/Ethinyl Estradiol Vaginal Ring is a polymeric vaginal ring containing 11.7 mg etonogestrel and 2.7 mg ethinyl estradiol, which releases on average 0.12 mg/day of etonogestrel and 0.015 mg/day of 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)
- Hypersensitivity, including anaphylaxis and angioedema, to any of the components of Etonogestrel/Ethinyl Estradiol Vaginal Ring (4)
- Co-administration with Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir (4)

WARNINGS AND PRECAUTIONS

- Vascular risks: Stop Etonogestrel/Ethinyl Estradiol Vaginal Ring use if a thrombotic event occurs. Stop Etonogestrel/Ethinyl Estradiol Vaginal Ring use 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)
- Toxic Shock Syndrome (TSS): If patient exhibits signs or symptoms of TSS, consider the possibility of this diagnosis and initiate appropriate medical evaluation and treatment. (5.2)
- Liver disease: Discontinue Etonogestrel/Ethinyl Estradiol Vaginal Ring use if jaundice develops. (5.3)
- High blood pressure: If used in women with well-controlled hypertension, monitor blood pressure and stop Etonogestrel/Ethinyl Estradiol Vaginal Ring use if blood pressure rises significantly. (5.5)
- Carbohydrate and lipid metabolic effects: Monitor prediabetic and diabetic women. Consider an alternate contraceptive method for women with uncontrolled dyslipidemia. (5.9)
- Headache: Evaluate significant change in headaches and discontinue Etonogestrel/Ethinyl Estradiol Vaginal Ring use if indicated. (5.10)
- Uterine bleeding: Evaluate irregular bleeding or amenorrhea. (5.11)

ADVERSE REACTIONS

The most common adverse reactions ($\geq 2\%$) in clinical trials were: vaginitis, headache (including migraine), mood changes (e.g., depression, mood swings, mood altered, depressed mood, affect lability), device-related events (e.g., expulsion/discomfort/foreign body sensation), nausea/vomiting, vaginal discharge, increased weight, vaginal discomfort, breast pain/discomfort/tenderness, dysmenorrhea, abdominal pain, acne, and decreased libido. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Merck, Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Drugs or herbal products that induce certain enzymes, such as 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)

USE IN SPECIFIC POPULATIONS

- Nursing mothers: Not recommended; can decrease milk production. (8.2)

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

Revised: 05/2019

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FULL PRESCRIBING INFORMATION

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

Cigarette smoking increases the risk of serious cardiovascular events from combination hormonal contraceptive (CHC) use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, CHCs, including Etonogestrel/Ethinyl Estradiol Vaginal Ring, should not be used by women who are over 35 years of age and smoke. [See *Contraindications (4)*.]

1 INDICATIONS AND USAGE

FOR VAGINAL USE ONLY

Etonogestrel/Ethinyl Estradiol Vaginal Ring is indicated for use by females of reproductive age to prevent pregnancy.

2 DOSAGE AND ADMINISTRATION

2.1 How to Use Etonogestrel/Ethinyl Estradiol Vaginal Ring

To achieve maximum contraceptive effectiveness, Etonogestrel/Ethinyl Estradiol Vaginal Ring must be used as directed [see *Dosage and Administration (2.2)*]. One Etonogestrel/Ethinyl Estradiol Vaginal Ring is inserted in the vagina. **The ring is to remain in place continuously for three weeks.** It is removed for a one-week break, during which a withdrawal bleed usually occurs. A new ring is inserted one week after the last ring was removed.

The user can choose the insertion position that is most comfortable to her, for example, standing with one leg up, squatting, or lying down. The ring is to be compressed and inserted into the vagina. The exact position of Etonogestrel/Ethinyl Estradiol Vaginal Ring inside the vagina is not critical for its function. The vaginal ring must be inserted on the appropriate day and left in place for three consecutive weeks. This means that the ring should be removed three weeks later on the same day of the week as it was inserted and at about the same time.

Etonogestrel/Ethinyl Estradiol Vaginal Ring can be removed by hooking the index finger under the forward rim or by grasping the rim between the index and middle finger and pulling it out. The used ring should be placed in the sachet (foil pouch) and discarded in a waste receptacle out of the reach of children and pets (do not flush in toilet).

After a one-week break, during which a withdrawal bleed usually occurs, a new ring is inserted on the same day of the week as it was inserted in the previous cycle. The withdrawal bleed usually starts on Day 2-3 after removal of the ring and may not have finished before the next ring is inserted. In order to maintain contraceptive effectiveness, the new ring must be inserted exactly one week after the previous one was removed even if menstrual bleeding has not finished.

2.2 How to Start Using Etonogestrel/Ethinyl Estradiol Vaginal Ring

IMPORTANT: Consider the possibility of ovulation and conception prior to the first use of Etonogestrel/Ethinyl Estradiol Vaginal Ring.

No Hormonal Contraceptive Use in the Preceding Cycle:

The woman should insert Etonogestrel/Ethinyl Estradiol Vaginal Ring on the first day of her menstrual bleeding. Etonogestrel/Ethinyl Estradiol Vaginal Ring may also be started on Days 2-5 of the woman's cycle, but in this case a barrier method, such as male condoms with spermicide, should be used for the first seven days of Etonogestrel/Ethinyl Estradiol Vaginal Ring use in the first cycle.

Changing From a CHC:

The woman may switch from her previous CHC on any day, but at the latest on the day following the usual hormone-free interval, if she has been using her hormonal method consistently and correctly, or if it is reasonably certain that she is not pregnant.

Changing From a Progestin-Only Method (progestin-only pill [POP], Implant, or Injection or a Progestin-Releasing Intrauterine System [IUS]):

The woman may switch from the POP on any day; instruct her to start using Etonogestrel/Ethinyl Estradiol Vaginal Ring on the day after she took her last POP. She should switch from an implant or the IUS on the day of its removal, and from an injectable on the day when the next injection would be due. In all of these cases, the woman should use an additional barrier method such as a male condom with spermicide, for the first seven days.

Use After Abortion or Miscarriage:

The woman may start using Etonogestrel/Ethinyl Estradiol Vaginal Ring within the first five days following a complete first trimester abortion or miscarriage, and she does not need to use an additional method of contraception. If use of Etonogestrel/Ethinyl Estradiol Vaginal Ring is not started within five days following a first trimester abortion or miscarriage, the woman should follow the instructions for “No Hormonal Contraceptive Use in the Preceding Cycle.” In the meantime, she should be advised to use a non-hormonal contraceptive method.

Start Etonogestrel/Ethinyl Estradiol Vaginal Ring no earlier than four weeks after a second trimester abortion or miscarriage, due to the increased risk of thromboembolism. [See *Contraindications (4) and Warnings and Precautions (5.1).*]

Following Childbirth:

The use of Etonogestrel/Ethinyl Estradiol Vaginal Ring may be initiated no sooner than four weeks postpartum in women who elect not to breastfeed, due to the increased risk of thromboembolism in the postpartum period. [See *Contraindications (4) and Warnings and Precautions (5.1).*]

Advise women who are breastfeeding not to use Etonogestrel/Ethinyl Estradiol Vaginal Ring but to use other forms of contraception until the child is weaned.

If a woman begins using Etonogestrel/Ethinyl Estradiol Vaginal Ring postpartum, instruct her to use an additional method of contraception, such as male condoms with spermicide, for the first seven days. If she has not yet had a period, consider the possibility of ovulation and conception occurring prior to initiation of Etonogestrel/Ethinyl Estradiol Vaginal Ring.

2.3 Deviations from the Recommended Regimen

To prevent loss of contraceptive efficacy, advise women not to deviate from the recommended regimen. Etonogestrel/Ethinyl Estradiol Vaginal Ring should be left in the vagina for a continuous period of three weeks. Advise women to regularly check for the presence of Etonogestrel/Ethinyl Estradiol Vaginal Ring in the vagina (for example, before and after intercourse).

Inadvertent Removal or Expulsion

Etonogestrel/Ethinyl Estradiol Vaginal Ring can be accidentally expelled, for example, while removing a tampon, during intercourse, or with straining during a bowel movement. Etonogestrel/Ethinyl Estradiol Vaginal Ring should be left in the vagina for a continuous period of three weeks. If the ring is accidentally expelled and is left outside of the vagina for **less than three hours**, contraceptive efficacy is not reduced. Etonogestrel/Ethinyl Estradiol Vaginal Ring can be rinsed with cool to lukewarm (not hot) water and **reinserted as soon as possible**, but at the latest within three hours. If Etonogestrel/Ethinyl Estradiol Vaginal Ring is lost, a new vaginal ring should be inserted and the regimen should be continued without alteration.

If Etonogestrel/Ethinyl Estradiol Vaginal Ring is out of the vagina **for more than three continuous hours**:

During Weeks 1 and 2: Contraceptive efficacy may be reduced. The woman should reinsert the ring as soon as she remembers. A barrier method such as male condoms with spermicides must be used until the ring has been used continuously for seven days.

During Week 3: The woman should discard that ring. One of the following two options should be chosen:

1. Insert a new ring immediately. Inserting a new ring will start the next three-week use period. The woman may not experience a withdrawal bleed from her previous cycle. However, breakthrough spotting or bleeding may occur.
2. Insert a new ring no later than seven days from the time the previous ring was removed or expelled, during which time she may have a withdrawal bleed. This option should only be chosen if the ring was used continuously for at least seven days prior to inadvertent removal/expulsion.

In either case, a barrier method such as male condoms with spermicides must be used until the new ring has been used continuously for seven days.

If Etonogestrel/Ethinyl Estradiol Vaginal Ring was out of the vagina for an unknown amount of time, the possibility of pregnancy should be considered. A pregnancy test should be performed prior to inserting a new ring.

Prolonged Ring-Free Interval

If the ring-free interval has been extended beyond one week, consider the possibility of pregnancy, and an additional method of contraception, such as male condoms with spermicide, **MUST** be used until Etonogestrel/Ethinyl Estradiol Vaginal Ring has been used **continuously for seven days**.

Prolonged Use of Etonogestrel/Ethinyl Estradiol Vaginal Ring

If Etonogestrel/Ethinyl Estradiol Vaginal Ring has been left in place for up to one extra week (i.e., up to four weeks total), the woman will remain protected. Etonogestrel/Ethinyl Estradiol Vaginal Ring should be removed and the woman should insert a new ring after a one-week ring-free interval.

If Etonogestrel/Ethinyl Estradiol Vaginal Ring has been left in place for longer than four weeks, instruct the woman to remove the ring, and rule out pregnancy. If pregnancy is ruled out, Etonogestrel/Ethinyl Estradiol Vaginal Ring may be restarted, and an additional method of contraception, such as male condoms with spermicide, **MUST** be used until a new Etonogestrel/Ethinyl Estradiol Vaginal Ring has been used **continuously for seven days**.

Ring Breakage

There have been reported cases of Etonogestrel/Ethinyl Estradiol Vaginal Ring disconnecting at the weld joint. This is not expected to affect the contraceptive effectiveness of Etonogestrel/Ethinyl Estradiol Vaginal Ring. In the event of a disconnected ring, vaginal discomfort or expulsion (slipping out) is more likely to occur. Vaginal injury associated with ring breakage has been reported [*see Adverse Reactions (6.2)*].

If a woman discovers that her Etonogestrel/Ethinyl Estradiol Vaginal Ring has disconnected, she should discard the ring and replace it with a new ring.

2.4 In the Event of a Missed Menstrual Period

1. If the woman has not adhered to the prescribed regimen (Etonogestrel/Ethinyl Estradiol Vaginal Ring has been out of the vagina for more than three hours or the preceding ring-free interval was extended beyond one week), consider the possibility of pregnancy at the time of the first

missed period and discontinue Etonogestrel/Ethinyl Estradiol Vaginal Ring use if pregnancy is confirmed.

2. If the woman has adhered to the prescribed regimen and misses two consecutive periods, rule out pregnancy.
3. If the woman has retained one Etonogestrel/Ethinyl Estradiol Vaginal Ring for longer than four weeks, rule out pregnancy.

2.5 Use with Other Vaginal Products

Etonogestrel/Ethinyl Estradiol Vaginal Ring may interfere with the correct placement and position of certain female barrier methods such as a diaphragm, cervical cap or female condom. These methods are not recommended as back-up methods with Etonogestrel/Ethinyl Estradiol Vaginal Ring use.

Pharmacokinetic data show that the use of tampons has no effect on the systemic absorption of the hormones released by Etonogestrel/Ethinyl Estradiol Vaginal Ring.

3 DOSAGE FORMS AND STRENGTHS

Etonogestrel/Ethinyl Estradiol Vaginal Ring is a non-biodegradable, flexible, transparent, colorless to almost colorless, combination contraceptive vaginal ring, with an outer diameter of 54 mm and a cross-sectional diameter of 4 mm. It is made of ethylene vinylacetate copolymers and magnesium stearate, and contains 11.7 mg etonogestrel and 2.7 mg ethinyl estradiol. When placed in the vagina, each ring releases on average 0.120 mg/day of etonogestrel and 0.015 mg/day of ethinyl estradiol over a three-week period of use. Etonogestrel/Ethinyl Estradiol Vaginal Ring is not made with natural rubber latex.

4 CONTRAINDICATIONS

Do not prescribe Etonogestrel/Ethinyl Estradiol Vaginal Ring to women who are known to have or use the following:

- 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 cerebrovascular disease [*see Warnings and Precautions (5.1)*]
 - Have coronary artery disease [*see Warnings and Precautions (5.1)*]
 - Have thrombotic valvular or thrombotic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease, or atrial fibrillation) [*see Warnings and Precautions (5.1)*]
 - Have inherited or acquired hypercoagulopathies [*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 (5.9)*]
 - Have headaches with focal neurological symptoms or migraine headaches with aura [*see Warnings and Precautions (5.10)*]
 - Women over age 35 with any migraine headaches [*see Warnings and Precautions (5.10)*]
- Liver tumors, benign or malignant or liver disease [*see Warnings and Precautions (5.3) and Use in Specific Populations (8.6)*]

- Undiagnosed abnormal uterine bleeding [*see Warnings and Precautions (5.11)*]
- Pregnancy, because there is no reason to use CHCs during pregnancy [*see Use in Specific Populations (8.1)*]
- Breast cancer or other estrogen- or progestin-sensitive cancer, now or in the past [*see Warnings and Precautions (5.14)*]
- Hypersensitivity reactions, including anaphylaxis and angioedema, to any of the components of Etonogestrel/Ethinyl Estradiol Vaginal Ring [*see Warnings and Precautions (5.6) and Adverse Reactions (6)*]
- Use of Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to potential for ALT elevations [*see Warnings and Precautions (5.4)*]

5 WARNINGS AND PRECAUTIONS

5.1 Thromboembolic Disorders and Other Vascular Problems

Stop Etonogestrel/Ethinyl Estradiol Vaginal Ring use if an arterial thrombotic or venous thromboembolic event (VTE) occurs. Stop Etonogestrel/Ethinyl Estradiol Vaginal Ring use if there is unexplained loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions. Evaluate for retinal vein thrombosis immediately. [*See Adverse Reactions (6).*]

If feasible, stop Etonogestrel/Ethinyl Estradiol Vaginal Ring at least four weeks before and through two weeks after major surgery or other surgeries known to have an elevated risk of thromboembolism, and during and following prolonged immobilization.

Start Etonogestrel/Ethinyl Estradiol Vaginal Ring no earlier than 4 weeks after delivery, in women who are not breastfeeding. The risk of postpartum thromboembolism decreases after the third postpartum week, whereas the risk of ovulation increases after the third postpartum week.

The use of 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)*].

Two epidemiologic studies^{1, 2, 3} that assessed the risk of VTE associated with the use of Etonogestrel/Ethinyl Estradiol Vaginal Ring are described below.

In these studies, which were required or sponsored by regulatory agencies, Etonogestrel/Ethinyl Estradiol Vaginal Ring users had a risk of VTE similar to Combined Oral Contraceptives (COCs) users (see Table 1 for adjusted hazard ratios). A large prospective, observational study, the Transatlantic Active Surveillance on Cardiovascular Safety of Etonogestrel/Ethinyl Estradiol Vaginal Ring (TASC), investigated the risk of VTE for new users, and women who were switching to or restarting Etonogestrel/Ethinyl Estradiol Vaginal Ring or COCs in a population that is representative of routine clinical users. The women were followed for 24 to 48 months. The results showed a similar risk of VTE among Etonogestrel/Ethinyl Estradiol Vaginal Ring users (VTE incidence 8.3 per 10,000 WY) and women using COCs (VTE incidence 9.2 per 10,000 WY). For women using COCs that did not contain the progestins desogestrel (DSG) or gestodene (GSD), VTE incidence was 8.9 per 10,000 WY.

A retrospective cohort study using data from 4 health plans in the US (FDA-funded Study in Kaiser Permanente and Medicaid databases) showed the VTE incidence for new users of Etonogestrel/Ethinyl Estradiol Vaginal Ring to be 11.4 events per 10,000 WY, for new users of a levonorgestrel (LNG)-

containing COC 9.2 events per 10,000 WY, and for users of other COCs available during the course of the study 8.2 events per 10,000 WY.

Table 1: Estimates (Hazard Ratios) of Venous Thromboembolism Risk in Users of Etonogestrel/Ethinyl Estradiol Vaginal Ring Compared to Users of Combined Oral Contraceptives (COCs)

Epidemiologic Study (Author, Year of Publication) Population Studied	Comparator Product(s)	Hazard Ratios (HR) (95% CI)
<p>TASC (Dinger, 2012)</p> <p>Initiators, including new users, switchers and restarters</p>	<p>All COCs available during the course of the study *</p> <p>COCs available excluding DSG- or GSD -containing OCs</p>	<p>HR[†]: 0.8 (0.5-1.5)</p> <p>HR[†]: 0.8 (0.4-1.7)</p>
<p>FDA-funded Study in Kaiser Permanente and Medicaid databases (Sidney, 2011)</p> <p>First use of a combined hormonal contraceptive (CHC) during the study period</p>	<p>COCs available during the course of the study[‡]</p> <p>LNG/0.03 mg ethinyl estradiol</p>	<p>HR[§]: 1.1 (0.6-2.2)</p> <p>HR[§]: 1.0 (0.5-2.0)</p>

* Includes low-dose COCs containing the following progestins: chlormadinone acetate, cyproterone acetate, desogestrel, dienogest, drospirenone, ethynodiol diacetate, gestodene, levonorgestrel, norethindrone, norgestimate, or norgestrel

† Adjusted for age, BMI, duration of use, VTE history

‡ Includes low-dose COCs containing the following progestins: norgestimate, norethindrone, or levonorgestrel

§ Adjusted for age, site, year of entry into study

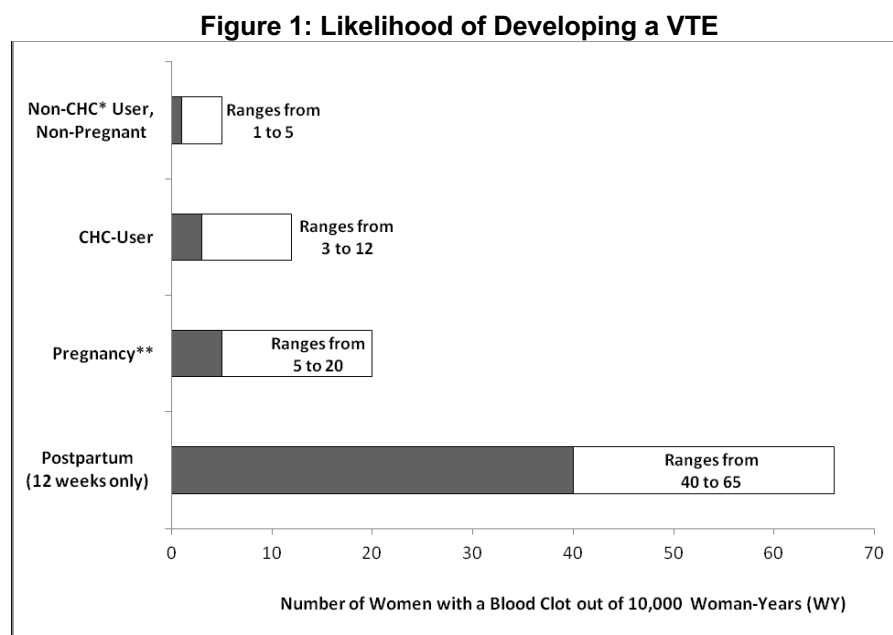
An increased risk of thromboembolic and thrombotic disease associated with the use of CHCs is well-established. Although the absolute VTE rates are increased for users of CHCs compared to non-users, the rates associated with pregnancy are even greater, especially during the post-partum period (see Figure 1).

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

* Includes low-dose COCs containing the following progestins: norgestimate, norethindrone, or levonorgestrel.

The risk of VTE is highest during the first year of CHC use and after restarting a CHC following a break of at least four weeks. The risk of VTE due to CHCs gradually disappears after use is discontinued.

Figure 1 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.



*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.

Several epidemiology studies indicate that third generation oral contraceptives, including those containing desogestrel (etonogestrel, the progestin in Etonogestrel/Ethinyl Estradiol Vaginal Ring, is the biologically active metabolite of desogestrel), may be associated with a higher risk of VTE than oral contraceptives containing other progestins. Some of these studies indicate an approximate two-fold increased risk. However, data from other studies have not shown this two-fold increase in risk.

Use of CHCs also increases the risk of arterial thromboses such as strokes and myocardial infarctions, especially in women with other risk factors for these events. CHCs have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes). In general, the risk is greatest among older (>35 years of age), hypertensive women who also smoke.

Use Etonogestrel/Ethinyl Estradiol Vaginal Ring with caution in women with cardiovascular disease risk factors.

5.2 Toxic Shock Syndrome (TSS)

Cases of TSS have been reported by Etonogestrel/Ethinyl Estradiol Vaginal Ring users. TSS has been associated with tampons and certain barrier contraceptives, and, in some cases the Etonogestrel/Ethinyl Estradiol Vaginal Ring users were also using tampons. A causal relationship between the use of Etonogestrel/Ethinyl Estradiol Vaginal Ring and TSS has not been established. If a

patient exhibits signs or symptoms of TSS, consider the possibility of this diagnosis and initiate appropriate medical evaluation and treatment.

5.3 Liver Disease

Impaired Liver Function

Do not use Etonogestrel/Ethinyl Estradiol Vaginal Ring in women with liver disease such as acute viral hepatitis or severe (decompensated) cirrhosis of the liver [see *Contraindications (4)*]. 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 [see *Use in Specific Populations (8.6)*]. Discontinue Etonogestrel/Ethinyl Estradiol Vaginal Ring use if jaundice develops.

Liver Tumors

Etonogestrel/Ethinyl Estradiol Vaginal Ring 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 per 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 attributable 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 and 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 Etonogestrel/Ethinyl Estradiol Vaginal Ring prior to starting therapy with the combination drug regimen ombitasvir/paritaprevir/ritonavir, with or without dasabuvir [see *Contraindications (4)*]. Etonogestrel/Ethinyl Estradiol Vaginal Ring can be restarted approximately 2 weeks following completion of treatment with the Hepatitis C combination drug regimen.

5.5 High Blood Pressure

Etonogestrel/Ethinyl Estradiol Vaginal Ring 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 Etonogestrel/Ethinyl Estradiol Vaginal Ring use if blood pressure rises significantly.

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

5.6 Hypersensitivity Reactions

Hypersensitivity reactions of anaphylaxis and angioedema have been reported during use of Etonogestrel/Ethinyl Estradiol Vaginal Ring. If anaphylaxis and/or angioedema is suspected, Etonogestrel/Ethinyl Estradiol Vaginal Ring should be discontinued and appropriate treatment administered. [See *Contraindications (4)*.]

5.7 Vaginal Use

Etonogestrel/Ethinyl Estradiol Vaginal Ring may not be suitable for women with conditions that make the vagina more susceptible to vaginal irritation or ulceration. Vaginal/cervical erosion or ulceration in women using Etonogestrel/Ethinyl Estradiol Vaginal Ring has been reported. In some cases, the ring adhered to vaginal tissue, necessitating removal by a healthcare provider and in some instances (i.e., when the tissue had grown over the ring), removal was achieved by cutting the ring without incising the overlying vaginal tissue.

Some women are aware of the ring on occasion during the 21 days of use or during intercourse, and sexual partners may feel Etonogestrel/Ethinyl Estradiol Vaginal Ring in the vagina.

5.8 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.

5.9 Carbohydrate and Lipid Metabolic Effects

Carefully monitor prediabetic and diabetic women who are using Etonogestrel/Ethinyl Estradiol Vaginal Ring. CHCs may decrease glucose tolerance.

Consider alternative contraception for women with uncontrolled dyslipidemia. Some women will have adverse lipid changes while on CHCs.

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

5.10 Headache

If a woman using Etonogestrel/Ethinyl Estradiol Vaginal Ring develops new headaches that are recurrent, persistent, or severe, evaluate the cause and discontinue Etonogestrel/Ethinyl Estradiol Vaginal Ring if indicated.

Consider discontinuation of Etonogestrel/Ethinyl Estradiol Vaginal Ring in the case of an increased frequency or severity of migraine during CHC use (which may be prodromal of a cerebrovascular event) [see *Contraindications (4)*].

5.11 Bleeding Irregularities and Amenorrhea

Unscheduled Bleeding and Spotting

Unscheduled bleeding (breakthrough or intracyclic) bleeding and spotting sometimes occur in women using CHCs, especially during the first three months of use. If bleeding persists or occurs after previously regular cycles, check for causes such as pregnancy or malignancy. If pathology and pregnancy are excluded, bleeding irregularities may resolve over time or with a change to a different CHC.

Bleeding patterns were evaluated in three large clinical studies. In the North American study (US and Canada, N=1,177), the percentages of subjects with breakthrough bleeding/spotting ranged from 7.2% to 11.7% during cycles 1-13. In the two non-US studies, the percentages of subjects with breakthrough bleeding/spotting ranged from 2.6% to 6.4% (Europe, N=1,145) and from 2.0% to 8.7% (Europe, Brazil, Chile, N=512).

Amenorrhea and Oligomenorrhea

If scheduled (withdrawal) bleeding does not occur, consider the possibility of pregnancy. If the patient has not adhered to the prescribed dosing schedule, consider the possibility of pregnancy at the time of the first missed period and take appropriate diagnostic measures.

Occasional missed periods may occur with the appropriate use of Etonogestrel/Ethinyl Estradiol Vaginal Ring. In the clinical studies, the percent of women who did not have withdrawal bleeding in a given cycle ranged from 0.3% to 3.8%.

If the patient has adhered to the prescribed regimen and misses two consecutive periods, rule out pregnancy.

Some women may experience amenorrhea or oligomenorrhea after discontinuing CHC use, especially when such a condition was pre-existent.

5.12 Inadvertent Urinary Bladder Insertion

There have been reports of inadvertent insertions of Etonogestrel/Ethinyl Estradiol Vaginal Ring into the urinary bladder, which required cystoscopic removal. Assess for ring insertion into the urinary bladder in Etonogestrel/Ethinyl Estradiol Vaginal Ring users who present with persistent urinary symptoms and are unable to locate the ring.

5.13 Depression

Carefully observe women with a history of depression and discontinue Etonogestrel/Ethinyl Estradiol Vaginal Ring use if depression recurs to a serious degree.

5.14 Carcinoma of the Breasts and Cervix

Etonogestrel/Ethinyl Estradiol Vaginal Ring is contraindicated in women who currently have or have had breast cancer because breast cancer is a hormonally-sensitive tumor [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 CHCs are associated with an increase in the risk of cervical cancer or intraepithelial neoplasia. However, there is controversy about the extent to which these findings may be due to differences in sexual behavior and other factors.

5.15 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 hormones or cortisol therapy may need to be increased.

5.16 Monitoring

A woman who is using Etonogestrel/Ethinyl Estradiol Vaginal Ring should have a yearly visit with her healthcare provider for a blood pressure check and for other indicated healthcare.

5.17 Hereditary Angioedema

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

5.18 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 Etonogestrel/Ethinyl Estradiol Vaginal Ring.

6 ADVERSE REACTIONS

The following serious adverse reactions with the use of CHCs are discussed elsewhere in the labeling.

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

Adverse reactions commonly reported by CHC users 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 practice.

Trials with a duration of 6 to 13 28-day cycles provided safety data. In total, 2,501 women, aged 18 to 41 contributed 24,520 cycles of exposure.

Common Adverse Reactions (≥ 2%): vaginitis (13.8%), headache (including migraine) (11.2%), mood changes (e.g., depression, mood swings, mood altered, depressed mood, affect lability) (6.4%), device-related events (e.g., expulsion/discomfort/foreign body sensation) (6.3%), nausea/vomiting (5.9%), vaginal discharge (5.7%), increased weight (4.9%), vaginal discomfort (4.0%), breast pain/discomfort/tenderness (3.8%), dysmenorrhea (3.5%), abdominal pain (3.2%), acne (2.4%), and decreased libido (2.0%).

Adverse Reactions (≥ 1%) Leading to Study Discontinuation: 13.0% of the women discontinued from the clinical trials due to an adverse reaction; the most common adverse reactions leading to discontinuation were device-related events (2.7%), mood changes (1.7%), headache (including migraine) (1.5%) and vaginal symptoms (1.2%).

Serious Adverse Reactions: deep vein thrombosis [see *Warnings and Precautions (5.1)*], anxiety, cholelithiasis, and vomiting.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Etonogestrel/Ethinyl Estradiol Vaginal Ring. 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.

Immune system disorders: hypersensitivity reactions, including anaphylaxis and angioedema

Nervous system disorders: stroke/cerebrovascular accident

Vascular disorders: arterial events (including arterial thromboembolism and myocardial infarction), aggravation of varicose veins

Skin and subcutaneous tissue disorders: urticaria, chloasma

Reproductive system and breast disorders: penile disorders, including local reactions on penis (in male partners of women using Etonogestrel/Ethinyl Estradiol Vaginal Ring), galactorrhea

General Disorders and Administration Site Conditions: device breakage (including with concomitant use of intravaginal antimycotic, antibiotic, and lubricant products)

Injury, poisoning and procedural complications: vaginal injury (including associated pain, discomfort, and bleeding) associated with ring breakage

7 DRUG INTERACTIONS

Consult the labeling of all 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 CHCs

Substances decreasing the plasma concentrations of CHCs and potentially diminishing the effectiveness 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 CHCs and other drugs may lead to breakthrough bleeding and/or contraceptive failure.

Counsel women to use an alternative non-hormonal method of contraception or a back-up method when enzyme inducers are used with Etonogestrel/Ethinyl Estradiol Vaginal Ring, and to continue back-up non-hormonal contraception for 28 days after discontinuing the enzyme inducer to ensure contraceptive reliability.

Note: Etonogestrel/Ethinyl Estradiol Vaginal Ring may interfere with the correct placement and position of certain female barrier methods such as a diaphragm or female condom. These methods are not recommended as back-up methods with Etonogestrel/Ethinyl Estradiol Vaginal Ring use [see *Dosage and Administration (2.5)*].

The serum concentrations of etonogestrel and ethinyl estradiol were not affected by concomitant administration of oral amoxicillin or doxycycline in standard dosages during 10 days of antibiotic treatment. The effects of other antibiotics on etonogestrel or ethinyl estradiol concentrations have not been evaluated.

Substances increasing the plasma concentrations of CHCs

Co-administration of atorvastatin and certain CHCs containing ethinyl estradiol increase AUC values for ethinyl estradiol by approximately 20-25%. Ascorbic acid and acetaminophen may increase plasma ethinyl estradiol concentrations, possibly by inhibition of conjugation. Concomitant administration of strong or moderate CYP3A4 inhibitors such as itraconazole, voriconazole, fluconazole, grapefruit juice, or ketoconazole may increase plasma estrogen and/or progestin concentrations. Co-administration of vaginal miconazole nitrate and Etonogestrel/Ethinyl Estradiol Vaginal Ring increases the serum concentrations of etonogestrel and ethinyl estradiol by up to 40% [see *Clinical Pharmacology (12.3)*].

Human immunodeficiency virus (HIV) / Hepatitis C Virus (HCV) protease inhibitors and non-nucleoside reverse transcriptase inhibitors

Significant changes in the plasma concentrations of the 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 (decrease [e.g., boceprevir and telaprevir]) or with non-nucleoside reverse transcriptase inhibitors (decrease [e.g., efavirenz, nevirapine] or increase [e.g., etravirine]). These changes may be clinically relevant in some cases.

7.2 Effects of CHCs on Other Drugs

CHCs containing ethinyl estradiol 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. A significant decrease in the plasma concentrations 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 concentrations of thyroid-binding globulin increase with use of CHCs.

7.3 Concomitant Use with HCV Combination Therapy – Liver Enzyme Elevation

Do not co-administer Etonogestrel/Ethinyl Estradiol Vaginal Ring 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

Risk Summary

Etonogestrel/Ethinyl Estradiol Vaginal Ring is contraindicated during pregnancy because there is no need for pregnancy prevention in a woman who is already pregnant. Epidemiologic studies and meta-analyses have not shown an increased risk of genital or non-genital birth defects (including cardiac anomalies and limb-reduction defects) following maternal exposure to low dose CHCs prior to conception or during early pregnancy. No adverse developmental outcomes were observed in pregnant rats and rabbits with the administration of etonogestrel during organogenesis at doses approximately 300 times the anticipated daily vaginal human dose (~0.002 mg/kg/day).

No adverse developmental outcomes were observed in pregnant rats and rabbits with the co-administration of the combination desogestrel/ethinyl estradiol during organogenesis at desogestrel/ethinyl estradiol doses at least 2/5 times, respectively, the anticipated daily vaginal human dose (~0.002 desogestrel/0.00025 ethinyl estradiol mg/kg/day).

Discontinue Etonogestrel/Ethinyl Estradiol Vaginal Ring use if pregnancy is confirmed.

Data

Animal Data

In rats and rabbits at dosages up to 300 times the anticipated dose, etonogestrel is neither embryotoxic nor teratogenic. Co-administration of a maternally toxic dose of desogestrel/ethinyl estradiol to pregnant rats was associated with embryoletality and wavy ribs at a desogestrel/ethinyl estradiol dose that was 40/130 times, respectively, the anticipated vaginal human dose (0.002 desogestrel/0.00025 ethinyl estradiol mg/kg/day). No adverse embryofetal effects were observed when the combination was administered to pregnant rats at a desogestrel/ethinyl estradiol dose that was 4/13 times, respectively, the anticipated vaginal human dose. When desogestrel/ethinyl estradiol was given to pregnant rabbits, pre-implantation loss was observed at a desogestrel/ethinyl estradiol dose that was 3/10 times, respectively, the anticipated vaginal human dose. No adverse embryofetal effects were observed when the combination was administered to pregnant rabbits at a desogestrel/ethinyl estradiol dose that was 2/5 times the anticipated vaginal human dose.

8.2 Lactation

Risk Summary

Small amounts of contraceptive steroids and/or metabolites, including etonogestrel and ethinyl estradiol are transferred to human milk. Harmful effects have not been observed in breastfed infants exposed to CHCs through breast milk. 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.

When possible, advise the nursing mother to use non-estrogen-containing contraception until she has completely weaned her child. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Etonogestrel/Ethinyl Estradiol Vaginal Ring and any potential adverse effects on the breastfed child from Etonogestrel/Ethinyl Estradiol Vaginal Ring or from the underlying maternal condition.

8.4 Pediatric Use

Safety and efficacy of Etonogestrel/Ethinyl Estradiol Vaginal Ring have been established in women of reproductive age. Efficacy is expected to be the same for postpubertal 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

Etonogestrel/Ethinyl Estradiol Vaginal Ring has not been studied in postmenopausal women and is not indicated in this population.

8.6 Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of Etonogestrel/Ethinyl Estradiol Vaginal Ring has not been studied. Steroid hormones may be poorly metabolized in patients with impaired liver function. Acute or chronic disturbances of liver function may necessitate the discontinuation of CHC use until markers of liver function return to normal. [See *Contraindications (4) and Warnings and Precautions (5.3).*]

8.7 Renal Impairment

The effect of renal impairment on the pharmacokinetics of Etonogestrel/Ethinyl Estradiol Vaginal Ring has not been studied.

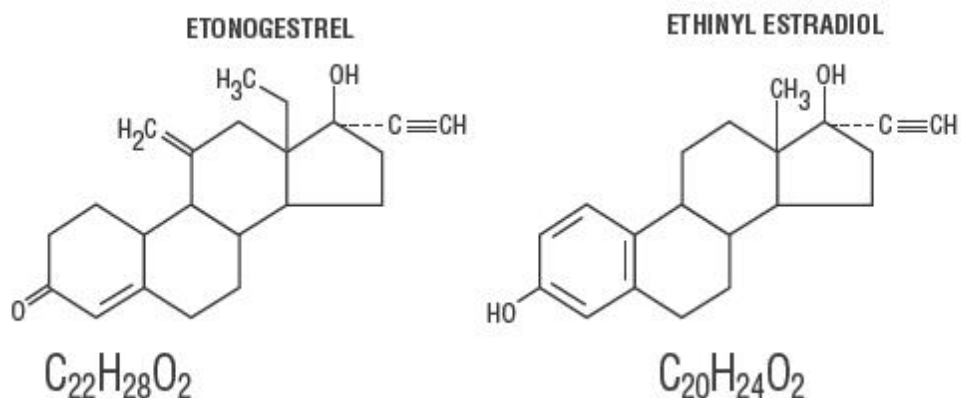
10 OVERDOSAGE

There have been no reports of serious ill effects from overdose of CHCs. Overdosage may cause withdrawal bleeding in females and nausea. If the ring breaks, it does not release a higher dose of hormones. In case of suspected overdose, all Etonogestrel/Ethinyl Estradiol Vaginal Ring rings should be removed and symptomatic treatment given.

11 DESCRIPTION

Etonogestrel/Ethinyl Estradiol Vaginal Ring is a non-biodegradable, flexible, transparent, colorless to almost colorless, combination contraceptive vaginal ring containing two active components, a progestin, etonogestrel (13-ethyl-17-hydroxy-11-methylene-18,19-dinor-17 α -pregn-4-en-20-yn-3-one) and an estrogen, ethinyl estradiol (19-nor-17 α -pregna-1,3,5(10)-trien-20-yne-3,17-diol). When placed in the vagina, each ring releases on average 0.120 mg/day of etonogestrel and 0.015 mg/day of ethinyl estradiol over a three-week period of use. Etonogestrel/Ethinyl Estradiol Vaginal Ring is made of ethylene vinylacetate copolymers (28% and 9% vinylacetate) and magnesium stearate and contains 11.7 mg etonogestrel and 2.7 mg ethinyl estradiol. Etonogestrel/Ethinyl Estradiol Vaginal Ring is not made with natural rubber latex. Etonogestrel/Ethinyl Estradiol Vaginal Ring has an outer diameter of 54 mm and a cross-sectional diameter of 4 mm. The molecular weights for etonogestrel and ethinyl estradiol are 324.46 and 296.40, respectively.

The structural formulas are as follows:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Combination hormonal contraceptives act by suppression of gonadotropins. Although the primary effect 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).

12.3 Pharmacokinetics

Absorption

Etonogestrel: Etonogestrel released by Etonogestrel/Ethinyl Estradiol Vaginal Ring is rapidly absorbed. The bioavailability of etonogestrel after vaginal administration is approximately 100%. The serum etonogestrel and ethinyl estradiol concentrations observed during three weeks of Etonogestrel/Ethinyl Estradiol Vaginal Ring use are summarized in Table 2.

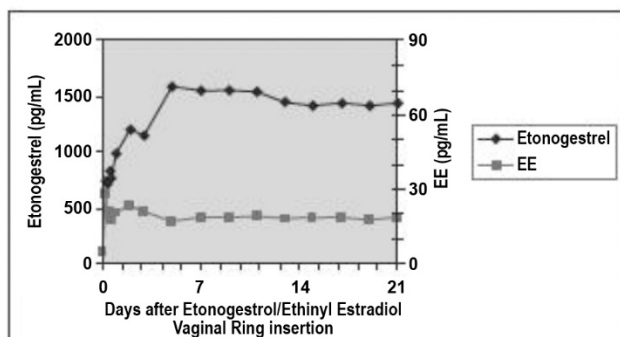
Ethinyl estradiol: Ethinyl estradiol released by Etonogestrel/Ethinyl Estradiol Vaginal Ring is rapidly absorbed. The bioavailability of ethinyl estradiol after vaginal administration is approximately 56%, which is comparable to that with oral administration of ethinyl estradiol. The serum ethinyl estradiol concentrations observed during three weeks of Etonogestrel/Ethinyl Estradiol Vaginal Ring use are summarized in Table 2.

Table 2: Mean (SD) Serum Etonogestrel and Ethinyl Estradiol Concentrations (n=16)

	1 week	2 weeks	3 weeks
etonogestrel (pg/mL)	1578 (408)	1476 (362)	1374 (328)
ethinyl estradiol (pg/mL)	19.1 (4.5)	18.3 (4.3)	17.6 (4.3)

The pharmacokinetic profile of etonogestrel and ethinyl estradiol during use of Etonogestrel/Ethinyl Estradiol Vaginal Ring is shown in Figure 2.

Figure 2: Mean Serum Concentration-Time Profile of Etonogestrel and Ethinyl Estradiol during Three Weeks of Etonogestrel/Ethinyl Estradiol Vaginal Ring Use



The pharmacokinetic parameters of etonogestrel and ethinyl estradiol were determined during one cycle of Etonogestrel/Ethinyl Estradiol Vaginal Ring use in 16 healthy female subjects and are summarized in Table 3.

Table 3: Mean (SD) Pharmacokinetic Parameters of Etonogestrel/Ethinyl Estradiol Vaginal Ring (n=16)

Hormone	C _{max} pg/mL	T _{max} hr	t _{1/2} hr	CL L/hr
etonogestrel	1716 (445)	200.3 (69.6)	29.3 (6.1)	3.4 (0.8)
ethinyl estradiol	34.7 (17.5)	59.3 (67.5)	44.7 (28.8)	34.8 (11.6)

C_{max}- maximum serum drug concentration
T_{max}- time at which maximum serum drug concentration occurs
t_{1/2} - elimination half-life, calculated by 0.693/K_{elim}
CL - apparent clearance

Prolonged use of Etonogestrel/Ethinyl Estradiol Vaginal Ring: The mean serum etonogestrel concentration at the end of the fourth week of continuous use of Etonogestrel/Ethinyl Estradiol Vaginal Ring was 1272 ± 311 pg/mL compared to a mean concentration range of 1578 ± 408 to 1374 ± 328 pg/mL at the end of weeks one to three. The mean serum ethinyl estradiol concentration at the end of the fourth week of continuous use of Etonogestrel/Ethinyl Estradiol Vaginal Ring was 16.8 ± 4.6 pg/mL compared to a mean concentration range of 19.1 ± 4.5 to 17.6 ± 4.3 pg/mL at the end of weeks one to three.

Distribution

Etonogestrel: Etonogestrel is approximately 32% bound to sex hormone-binding globulin (SHBG) and approximately 66% bound to albumin in blood.

Ethinyl estradiol: Ethinyl estradiol is highly but not specifically bound to serum albumin (98.5%) and induces an increase in the serum concentrations of SHBG.

Metabolism

In vitro data shows that both etonogestrel and ethinyl estradiol are metabolized in liver microsomes by the cytochrome P450 3A4 isoenzyme. Ethinyl estradiol is primarily metabolized by aromatic hydroxylation, but a wide variety of hydroxylated and methylated metabolites are formed. These are

present as free metabolites and as sulfate and glucuronide conjugates. The hydroxylated ethinyl estradiol metabolites have weak estrogenic activity. The biological activity of etonogestrel metabolites is unknown.

Excretion

Etonogestrel and ethinyl estradiol are primarily eliminated in urine, bile and feces.

Drug Interactions

[See also Drug Interactions (7).]

The drug interactions of Etonogestrel/Ethinyl Estradiol Vaginal Ring were evaluated in several studies.

A single-dose vaginal administration of an oil-based 1200-mg miconazole nitrate capsule increased the serum concentrations of etonogestrel and ethinyl estradiol by approximately 17% and 16%, respectively. Following multiple doses of 200 mg miconazole nitrate by vaginal suppository or vaginal cream, the mean serum concentrations of etonogestrel and ethinyl estradiol increased by up to 40%.

A single-dose vaginal administration of 100-mg water-based nonoxynol-9 spermicide gel did not affect the serum concentrations of etonogestrel or ethinyl estradiol.

The serum concentrations of etonogestrel and ethinyl estradiol were not affected by concomitant administration of oral amoxicillin or doxycycline in standard dosages during 10 days of antibiotic treatment.

Tampon Use

The use of tampons had no effect on serum concentrations of etonogestrel and ethinyl estradiol during use of Etonogestrel/Ethinyl Estradiol Vaginal Ring *[see Dosage and Administration (2.5)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In a 24-month carcinogenicity study in rats with subdermal implants releasing 10 and 20 mcg etonogestrel per day, (approximately 0.3 and 0.6 times the systemic steady-state exposure of women using Etonogestrel/Ethinyl Estradiol Vaginal Ring), no drug-related carcinogenic potential was observed.

Mutagenesis

Etonogestrel was not genotoxic in the in vitro Ames/Salmonella reverse mutation assay, the chromosomal aberration assay in Chinese hamster ovary cells or in the in vivo mouse micronucleus test.

Impairment of Fertility

A fertility study was conducted with etonogestrel in rats at approximately 600 times the anticipated daily vaginal human dose (~0.002 mg/kg/day). Treatment did not have any adverse effect on resulting litter parameters after cessation of treatment supporting the return to fertility after suppression with etonogestrel.

14 CLINICAL STUDIES

In three large one-year clinical trials enrolling 2,834 women aged 18-40 years, in North America, Europe, Brazil, and Chile, the racial distribution was 93% Caucasian, 5.0% Black, 0.8% Asian, and 1.2% Other. Women with BMI \geq 30 kg/m² were excluded from these studies.

Based on pooled data from the three trials, 2,356 women aged < 35 years completed 23,515 evaluable cycles of Etonogestrel/Ethinyl Estradiol Vaginal Ring use (cycles in which no back-up

contraception was used). The pooled pregnancy rate (Pearl Index) was 1.28 (95% CI [0.8, 1.9]) per 100 women-years of Etonogestrel/Ethinyl Estradiol Vaginal Ring use. In the US study, the Pearl Index was 2.02 (95% CI [1.1, 3.4]) per 100 women-years of Etonogestrel/Ethinyl Estradiol Vaginal Ring use.

Study data indicate the return of ovulation and spontaneous menstrual cycles in most women within a month after discontinuation of Etonogestrel/Ethinyl Estradiol Vaginal Ring use.

15 REFERENCES

1. Dinger, J et. al., Cardiovascular risk associated with the use of an etonogestrel-containing vaginal ring. *Obstetrics & Gynecology* 2013; 122(4): 800-808.
2. Sidney, S. et. al., Recent combined hormonal contraceptives (CHCs) and the risk of thromboembolism and other cardiovascular events in new users. *Contraception* 2013; 87: 93–100.
3. Combined hormonal contraceptives (CHCs) and the risk of cardiovascular endpoints. Sidney, S. (primary author) <http://www.fda.gov/downloads/Drugs/DrugSafety/UCM277384.pdf>, accessed 23-Aug-2013.

16 HOW SUPPLIED/STORAGE AND HANDLING

Each Etonogestrel/Ethinyl Estradiol Vaginal Ring is individually packaged in a reclosable aluminum laminate sachet consisting of three layers, from outside to inside: polyester, aluminum foil, and low-density polyethylene. The ring should be replaced in this reclosable sachet after use and discarded in a waste receptacle out of the reach of children and pets. It should not be flushed down the toilet.

Box of 3 sachets NDC 66993-605-36

16.1 Storage

Prior to dispensing to the user, store refrigerated 2-8°C (36-46°F). After dispensing to the user, Etonogestrel/Ethinyl Estradiol Vaginal Ring can be stored for up to 4 months at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Avoid storing Etonogestrel/Ethinyl Estradiol Vaginal Ring in direct sunlight or at temperatures above 30°C (86°F).

For the Dispenser: When Etonogestrel/Ethinyl Estradiol Vaginal Ring is dispensed to the user, place an expiration date on the label. The date should not exceed either 4 months from the date of dispensing or the expiration date, whichever comes first.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Counsel patients regarding the following:

Increased risk of cardiovascular events

- Advise patients that cigarette smoking increases the risk of serious cardiovascular events from use of Etonogestrel/Ethinyl Estradiol Vaginal Ring, and women who are over 35 years old and smoke should not use Etonogestrel/Ethinyl Estradiol Vaginal Ring [see *Boxed Warning*].
- Inform patients that the increased risk of VTE compared to non-users of CHCs is greatest after initially starting a CHC or restarting (following a 4-week or greater CHC-free interval) the same or a different CHC [see *Warnings and Precautions (5.1)*].

Use and administration

- Inform patients that Etonogestrel/Ethinyl Estradiol Vaginal Ring does not protect against HIV infection (AIDS) and other sexually transmitted infections.
- Advise patients on the proper usage of Etonogestrel/Ethinyl Estradiol Vaginal Ring and what to do if she does not comply with the labeled timing of insertion and removal [see *Dosage and Administration* (2)].
- Advise patients to regularly check for the presence of Etonogestrel/Ethinyl Estradiol Vaginal Ring in the vagina (for example, before and after intercourse) [see *Dosage and Administration* (2.3)].

Pregnancy

- Inform patients that Etonogestrel/Ethinyl Estradiol Vaginal Ring is not to be used during pregnancy. If pregnancy is planned or occurs during treatment with Etonogestrel/Ethinyl Estradiol Vaginal Ring, instruct the patient to discontinue Etonogestrel/Ethinyl Estradiol Vaginal Ring use [see *Use in Specific Populations* (8.1)].

Use of additional contraception

- Inform patients that they need to use a barrier method of contraception when the ring is out for more than three continuous hours until Etonogestrel/Ethinyl Estradiol Vaginal Ring has been used continuously for at least seven days [see *Dosage and Administration* (2.3)].
- Advise patients to use a back-up or alternative method of contraception when enzyme inducers are used with Etonogestrel/Ethinyl Estradiol Vaginal Ring [see *Drug Interactions* (7.1)].
- Inform patients who start Etonogestrel/Ethinyl Estradiol Vaginal Ring postpartum and have not yet had a normal period that they should use an additional non-hormonal method of contraception for the first seven days [see *Dosage and Administration* (2.2)].

Lactation

- Inform patients that CHCs may reduce breast milk production. This is less likely to occur if breastfeeding is well established [see *Use in Specific Populations* (8.2)].

Amenorrhea

- Inform patients that amenorrhea may occur. Rule out pregnancy in the event of amenorrhea if Etonogestrel/Ethinyl Estradiol Vaginal Ring has been out of the vagina for more than three consecutive hours, if the ring-free interval was extended beyond one week, if the woman has missed a period for two or more consecutive cycles, and if the ring has been retained for longer than four weeks [see *Warnings and Precautions* (5.11)].

Disposal

- Advise patients on the proper disposal of a used Etonogestrel/Ethinyl Estradiol Vaginal Ring [see *How Supplied/Storage and Handling* (16)].



Manufactured for: **Prasco Laboratories**, Mason, OH 45040, USA

Manufactured by: N.V. Organon, Oss, The Netherlands, a subsidiary of

Merck & Co., Inc., Whitehouse Station, NJ 08889, USA

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