PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]NUVARING

etonogestrel/ethinyl estradiol slow release vaginal ring

(11.4 mg/2.6 mg) to deliver

120 mcg etonogestrel/15 mcg ethinyl estradiol per day

Contraceptive Vaginal Ring

Organon Canada Inc.
16766 route Transcanadienne
Kirkland, QC Canada H9H 4M7
www.organon.ca

Date of Initial Authorization:
DEC 12, 2004

Date of Revision:
NOV 15, 2024

Submission Control Number: 286307

RECENT MAJOR LABEL CHANGES

None at time of most recent authorization	

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

NUVARING® (etonogestrel/ethinyl estradiol slow release vaginal ring) is indicated for:

- Conception control

1.1 Pediatrics

Pediatrics (<18 years of age): The safety and efficacy of NUVARING in adolescents under the age of 18 have not been studied. Use of this product before menarche is not indicated.

1.2 Geriatrics

Geriatrics: NUVARING has not been studied in postmenopausal women and is not indicated in this population.

2 CONTRAINDICATIONS

NUVARING should not be used in the presence of any of the conditions listed below. Should any of the conditions appear for the first time during the use of NUVARING, it should be removed immediately.

- Presence or history of venous thrombosis, with or without pulmonary embolism.
- Presence or history of arterial thrombosis (e.g., cerebrovascular accident, myocardial infarction) or prodromi of a thrombosis (e.g., angina pectoris or transient ischemic attack).
- Valvular heart disease with complications.
- Presence of a severe or multiple risk factor(s) for arterial or venous thrombosis (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular and Hematologic):
    - Severe hypertension (persistent values of ≥160/110 mmHg).
    - Known predisposition for venous or arterial thrombosis, with or without hereditary involvement such as Activated Protein C (APC-) resistance (including Factor V Leiden), antithrombin-III deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinemia and antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant).
    - Severe dyslipoproteinemia.
    - Smoking, if over age 35.
    - Diabetes mellitus with vascular involvement (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Diabetes).
    - Major surgery with prolonged immobilization (see 7 WARNINGS AND PRECAUTIONS, General).
- History of migraine with focal neurological symptoms (see 7 WARNINGS AND PRECAUTIONS, Neurologic, Migraine and Headache).
- Any ocular lesion arising from ophthalmic vascular disease, such as partial or complete loss of vision or defect in visual fields.

- Pancreatitis or a history thereof if associated with severe hypertriglyceridemia.
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal.
- Use with the Hepatitis C virus (HCV) combination drug regimen ombitasvir/ paritaprevir/ ritonavir with or without dasabuvir or medicinal products containing glecaprevir/pibrentasvir (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, Hepatitis C and 9.4 Drug-Drug Interactions).
- Presence or history of liver tumors (benign or malignant).
- Known or suspected malignant conditions of the genital organs or the breasts, if sex steroid-influenced.
- Undiagnosed vaginal bleeding.
- Known or suspected pregnancy.
- Hypersensitivity to NUVARING or to any ingredient in the formulation or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- 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 NUVARING, should not be used by women who are over 35 years of age and smoke (see **7 WARNINGS AND PRECAUTIONS, Cardiovascular**).
- Women should be counselled that NUVARING **DOES NOT PROTECT** against sexually transmitted infections (STIs) including HIV/AIDS. For protection against STIs, it is advisable to use latex or polyurethane condoms **IN COMBINATION WITH** NUVARING.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Pregnant women: NUVARING should not be used in women who are pregnant.
- Concomitant medications: Please see 9.4 DRUG-DRUG INTERACTION section.
- Discontinue medication: Please see 7 WARNINGS AND PRECAUTIONS section.

4.2 Recommended Dose and Dosage Adjustment

To achieve maximum contraceptive effectiveness, NUVARING must be used as directed (see When to Start NUVARING below). One NUVARING is inserted in the vagina by the woman herself. As NUVARING is designed to be a once-a-month contraceptive regimen 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 no more than one week after removal of the last ring.

Advise women to regularly check for the presence of NUVARING in the vagina (for example, before and after intercourse). If NUVARING is accidentally expelled, the woman should follow the instructions given below (4.5 Missed Dose, Inadvertent removal, expulsion, or prolonged ring-free interval) (for more information, see also 9 DRUG INTERACTIONS, 9.3 Drug-Behavioural Interactions, Expulsion).

Health Canada has not authorized an indication for pediatric and geriatric use.

4.4 Administration

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 until it feels comfortable. The exact position of NUVARING inside the vagina is not critical for the contraceptive effect of the ring. The vaginal ring must be inserted on the appropriate day and left in place for three consecutive weeks. This means that the ring is removed three weeks later on the same day of the week as it was inserted and at about the same time. NUVARING 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). The withdrawal bleeding usually starts 2-3 days 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 one week after the previous one was removed even if menstrual bleeding has not finished. For example, if NUVARING is inserted on Wednesday at 22:00 h the ring should be removed again on the Wednesday 3 weeks later at about 22:00 h. The following Wednesday a new ring should be inserted.

When to Start NUVARING

IMPORTANT: The possibility of ovulation and conception prior to the first use of NUVARING should be considered.

No hormonal contraceptive use in the preceding cycle

The woman may start using NUVARING within the first five days of her natural cycle (i.e., Day 1-5 of her menstrual bleeding). During the first seven days of NUVARING use in the first cycle, an additional barrier method, such as male condoms or spermicide, is recommended.

Switching from another CHC

The woman may switch from her previous combined hormonal contraceptive on any day of the cycle, if she has been using this method consistently and correctly, and if it is reasonably certain that she is not pregnant. Otherwise, the woman should insert NUVARING at the latest on the day following the usual tablet-free, patch-free or placebo tablet interval of her previous combined hormonal contraceptive. The hormone-free interval of the previous method should never be extended beyond its recommended length.

Switching from a progestin-only method

There are several types of progestin-only methods. Women should insert the first NUVARING as follows:

- Any day of the month when switching from a progestin-only pill; do not skip any days between the last pill and the first day of NUVARING use
- On the same day as contraceptive implant removal
- On the same day as removal of a progestin-containing IUD, or
- On the day when the next contraceptive injection would be due

In all of these cases, the patient should be advised to use an additional method of contraception, such as a male condom and/or spermicide, for the first seven days after insertion of the ring.

Following complete first-trimester abortion

The woman may start using NUVARING within the first five days following a complete first trimester abortion and does not need to use an additional method of contraception. If use of NUVARING is not started within five days following a first trimester abortion, the woman should follow the instructions for "No preceding hormonal contraceptive use in the preceding cycle." In the meantime she should be advised to use a non-hormonal contraceptive method.

Following delivery or second-trimester abortion

The use of NUVARING for contraception may be initiated four weeks after a second trimester abortion or four weeks postpartum in women who elect not to breastfeed. When NUVARING is used postpartum or postabortion, the increased risk of thromboembolic disease must be considered. (See 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS, Hematologic. Also see 7 WARNINGS AND PRECAUTIONS, Special Populations, Breast-feeding.) If a woman begins using NUVARING postpartum, she should be instructed to use an additional method of contraception, such as male condoms or spermicide for the first seven days. If she has not yet had a period, the possibility of ovulation and conception occurring prior to initiation of NUVARING should be considered.

The increased risk of venous thromboembolism (VTE) during postpartum period should be considered when restarting NUVARING (see 7 WARNING AND PRECAUTIONS, Hematologic)

Deviations from the Recommended Regimen

To prevent loss of contraceptive efficacy patients should not deviate from the recommended regimen.

Prolonged Use of NUVARING

If NUVARING has been left in place for up to one extra week (i.e., up to four weeks total), the woman will remain protected. NUVARING should be removed and the woman should insert a new ring after a one-week ring-free interval. The mean serum etonogestrel concentration during the fourth week of continuous use of NUVARING was 1,272 ± 311 pg/mL compared to a mean concentration range of 1,578 ± 408 to 1,374 ± 328 pg/mL during Weeks 1 to 3. The mean serum ethinyl estradiol concentration during the fourth week of continuous use of NUVARING 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 during Weeks 1 to 3. If NUVARING has been left in place for longer than four weeks, contraceptive efficacy may be reduced. Pregnancy should be ruled out before inserting a new NUVARING, and an additional method of contraception, such as a male condom and/or spermicide, MUST be used until the new NUVARING has been used continuously for seven days.

In the Event of a Missed Menstrual Period

1. If the patient has not adhered to the prescribed regimen (NUVARING has been out of the vagina for more than three hours or the preceding ring-free interval was extended beyond one week) the possibility of pregnancy should be considered at the time of the first missed period and NUVARING use should be discontinued if pregnancy is confirmed.
2. If the patient has adhered to the prescribed regimen and misses two consecutive periods, pregnancy should be ruled out.
3. If the patient has retained one NUVARING for longer than four weeks, pregnancy should be ruled out.

How to Change the NUVARING Start Day to another Day of the Week

If the woman wishes to change the day on which she starts a new NUVARING cycle, she should complete the current cycle, removing NUVARING on the same day of the week as the one on which she started. During the ring-free period, a new start day may be selected by inserting the new NUVARING on the first occurrence of the desired day. In no case should there be more than 7 consecutive ring-free days. The shorter the ring-free interval, the higher the risk that she does not have a withdrawal bleed and may experience breakthrough bleeding and spotting during the use of the next ring. This practice is for a one-time only change and should not to be used as a standard dosing regimen, as there are no long-term safety data available on the continuous use of NUVARING.

4.5 Missed Dose

Inadvertent removal, expulsion, or prolonged ring-free interval

NUVARING should be left in the vagina for a continuous period of 3 weeks. If the ring is accidentally expelled and is left outside of the vagina for less than 3 hours contraceptive efficacy is not reduced i.e., the woman should still be protected from pregnancy. NUVARING should be rinsed with cool to lukewarm (not hot) water and re-inserted as soon as possible, but at the latest within 3 hours. If NUVARING is lost, a new vaginal ring should be inserted and the regimen should be continued without alteration.

If NUVARING is out of the vagina for more than 3 continuous hours:

During Weeks 1 and 2: If NUVARING has been out of the vagina for more than 3 continuous hours during the 1st or 2nd week of use, contraceptive efficacy may be reduced. The woman should reinsert the ring as soon as she remembers. A barrier method, such as a male condom and/or spermicide, must be used in addition until NUVARING has been in the vagina continuously for 7 days. The longer the time NUVARING has been out of the vagina and the closer this is to the ring-free interval, the higher the risk of pregnancy.

During Week 3: If NUVARING has been out of the vagina for more than 3 continuous hours during the 3rd week of the three-week use period, contraceptive efficacy may be reduced. The woman should discard that ring, and 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. Have a withdrawal bleeding and insert a new ring no later than 7 days (7x24 hours) from the time the previous ring was removed or expelled. This option should only be chosen if the ring was used continuously for the preceding 7 days.

A barrier method such as male condoms and/or spermicides must be used until the new ring has been used continuously for seven days.

If the ring-free interval has been extended beyond one week, the possibility of pregnancy should be considered, and an additional method of contraception, such as a male condom and/or spermicide, **MUST** be used until NUVARING has been used **continuously for seven days**. The longer the ring-free interval, the higher the risk of pregnancy.

If NUVARING 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.

5 OVERDOSAGE

Overdosage of CHCs may cause nausea, vomiting, vaginal bleeding, or other menstrual irregularities.

Given the nature and design of NUVARING it is unlikely that overdosage will occur. If a NUVARING is broken, it does not release a higher dose of hormones. Serious ill effects have not been reported following acute ingestion of large doses of oral contraceptives by young children. There are no antidotes and further treatment should be symptomatic.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Vaginal	Slow release vaginal ring / 11.4 mg etonogestrel / 2.6 mg ethinyl estradiol (120 mcg etonogestrel/15 mcg ethinyl estradiol per day)	Ethylene vinylacetate copolymers (28% and 9% vinylacetate) and magnesium stearate.

Each NUVARING is individually packaged in a reclosable aluminum laminate sachet consisting of three layers, from outside to inside: Polyethylene terephthalate (PET), aluminum foil, and low-density polyethylene.

NUVARING has an outer diameter of 54 mm and a cross-sectional diameter of 4 mm.

Each ring contains 11.4 mg etonogestrel and 2.6 mg ethinyl estradiol Ph.Eur. and delivers 120 mcg etonogestrel and 15 mcg ethinyl estradiol per day.

NUVARING is not made with natural rubber latex.

NUVARING is available in: Boxes of 3 sachets and boxes of 1 sachet.

7 WARNINGS AND PRECAUTIONS

*Please see **3 SERIOUS WARNINGS AND PRECAUTIONS BOX**.*

General

Discontinue medication at the earliest manifestation of:

A. **Thromboembolic and Cardiovascular Disorders** such as: Thrombophlebitis, pulmonary embolism, cerebrovascular disorders, myocardial ischemia, mesenteric thrombosis, and retinal thrombosis.

B. **Conditions which Predispose to Venous Stasis and to Vascular Thrombosis**, e.g., immobilization after accidents or confinement to bed during long-term illness. Other non-hormonal methods of contraception should be used until regular activities are resumed. For use of combination hormonal contraceptives when surgery is contemplated, see **Peri-Operative Considerations**.

C. **Visual Defects, Partial or Complete**.

D. **Papilledema, or Ophthalmic Vascular Lesions**.

E. **Severe Headache of Unknown Etiology or Worsening of Pre-existing Migraine Headache**.

F. **Increase in Epileptic Seizures,** see 9 DRUG INTERACTIONS, Table 5, Anticonvulsants.

NUVARING and other contraceptives that contain both an estrogen and a progestin are called CHCs. Most of the warnings below are based on data obtained from the oral route of administration.

The use of CHCs is associated with increased risks of several serious conditions including myocardial infarction, thromboembolism, stroke, although the risk of serious morbidity or mortality is small in healthy women without underlying risk factors. The risk of morbidity and mortality increases significantly if associated with the presence of other risk factors such as hypertension, hyperlipidemias, obesity and diabetes. The excess risk of VTE is highest during the first year a woman ever uses a combined hormonal contraceptive. Other medical conditions which have been associated with adverse circulatory events include systemic lupus erythematosus, hemolytic uremic syndrome, chronic inflammatory bowel disease, (Crohn's disease or ulcerative colitis), sickle cell disease, valvular heart disease, and atrial fibrillation.

The following conditions have been reported to occur or deteriorate with both pregnancy and CHC use, although a direct association with CHCs has not been firmly established: porphyria, systemic lupus erythematosus, hemolytic uremic syndrome, Sydenham's chorea, herpes gestationis, and otosclerosis-related hearing loss.

If any of the conditions/risk factors mentioned below is present, the benefits of the use of NUVARING should be weighed against the possible risks for each individual woman and discussed with the woman before she decides to start using it. In the event of aggravation, exacerbation or first appearance of any of these conditions or risk factors, the woman should contact her physician. The physician should then decide on whether NUVARING use should be discontinued.

Carcinogenesis and Mutagenesis

Breast Cancer

Increasing age and a strong family history are the most significant risk factors for the development of breast cancer. Other established risk factors include obesity, nulliparity and late age at first full-term pregnancy. The identified groups of women that may be at increased risk of developing breast cancer before menopause are long-term users (more than 8 years) of CHCs (including NUVARING) and starters at early age. In a few women, the use of CHCs (including NUVARING) may accelerate the growth of an existing but undiagnosed breast cancer. Since any potential increased risk related to CHCs (including NUVARING) use is small, there is no reason to change prescribing habits at present.

Women receiving CHCs (including NUVARING) should be instructed in self-examination of their breasts. Their physicians should be notified whenever any masses are detected. A yearly clinical breast examination is also recommended because, if a breast cancer should develop, estrogen-containing drugs may cause a rapid progression.

Cervical Cancer

Persistent infection with the Human Papilloma Virus (HPV) is believed to be the most important risk factor for cervical cancer. Some epidemiological studies indicated that long-term use of combination oral contraceptives (COCs) may further contribute to this increased risk, but there continues to be controversy about the extent to which this finding may be confounded by other factors, e.g., cervical screening bias and sexual behaviour. It is unknown how this effect relates to NUVARING.

Hepatocellular Carcinoma

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.

Cardiovascular

Predisposing Factors for Coronary Artery Disease

Cigarette smoking increases the risk of serious cardiovascular side effects and mortality. CHCs (including NUVARING), increase this risk, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, CHCs, including NUVARING, should not be used by women who are over 35 years of age and smoke.

Convincing data are available to support an upper age limit of 35 years for CHC use in women who smoke.

Other women who are independently at high risk for cardiovascular disease include those with diabetes, hypertension, abnormal lipid profile, or a family history of these. Whether CHCs, accentuate this risk is unclear.

In low-risk, non-smoking women of any age, the benefits of CHCs use outweigh the possible cardiovascular risks associated with low-dose formulations.

Consequently, CHCs may be prescribed for these women up to the age of menopause.

Hypertension

Patients with essential hypertension whose blood pressure is well-controlled may be prescribed CHCs (including NUVARING) but only under close supervision. If a significant elevation of blood pressure in previously normotensive or hypertensive subjects occurs at any time during the administration of the drug, cessation of medication is necessary.

Endocrine and Metabolism

Diabetes

Current low-dose CHCs (including NUVARING) exert minimal impact on glucose metabolism. Diabetic patients, or those with a family history of diabetes, should be observed closely to detect any worsening of carbohydrate metabolism. Patients predisposed to diabetes who can be kept under close supervision may be given CHCs. Young diabetic patients whose disease is of recent origin, well-controlled, and not associated with hypertension or other signs of vascular disease such as ocular fundal changes, should be monitored more frequently while using CHCs.

Lipid and Other Metabolic Effects

A small proportion of women will have adverse lipid changes while on CHCs. Alternative contraception should be used in women with uncontrolled dyslipidemia (see 2 CONTRAINDICATIONS). Elevations of plasma triglycerides may lead to pancreatitis and other complications.

Gastrointestinal

Published epidemiological studies indicate a possible association of COC use and the development of Crohn's disease and ulcerative colitis, although this has not been firmly established.

Genitourinary

If a woman has any of the following conditions, she may not be able to insert NUVARING correctly or may in fact lose the ring: prolapse of the uterine cervix, cystocele, and/or rectocele, severe or chronic constipation.

During the use of NUVARING, women may occasionally experience vaginitis. There are no indications

that the efficacy of NUVARING is affected by the treatment of vaginitis, nor that the use of NUVARING affects the treatment of vaginitis (see 9.4 Drug-Drug Interactions).

Vaginal Bleeding

Persistent irregular vaginal bleeding requires assessment to exclude underlying pathology.

NUVARING may not be suitable for women with conditions that make the vagina more susceptible to vaginal irritation or ulceration. Very rarely, vaginal tissue may grow over the ring, necessitating removal by a healthcare provider. In some cases when the tissue had grown over the ring, removal was achieved by cutting the ring without incising the overlying vaginal tissue.

Urethra

Very rarely it has been reported that NUVARING was inadvertently inserted in the urethra and possibly ended up in the bladder. Healthcare providers should assess for incorrect placement of NUVARING in the urethra or bladder in those users presenting with persistent urinary symptoms and who are unable to locate the ring.

Disconnected/Broken Ring

On rare occasions, NUVARING has been reported to disconnect/break at the weld joint. Since the core of NUVARING is solid, its contents will remain intact and release of hormone is unlikely to occur. Vaginal injury associated with ring breakage has been reported. In the event of a disconnected/broken ring, expulsion (slipping out) is likely to occur (see 9 DRUG INTERACTIONS, 9.4 Drug-Behavioural Interactions, Expulsion). If a woman discovers that her NUVARING has disconnected, she should discard the ring and replace it with a new ring**.**

Fibroids

Patients with fibroids (leiomyomata) should be carefully observed. Sudden enlargement, pain, or tenderness require discontinuation of the use of CHCs (including NUVARING).

Hematologic

Compared to nonusers, the use of CHCs has been associated with the increased risk of venous thrombosis (deep vein thrombosis and pulmonary embolism) and arterial thrombosis and associated complications. These events may sometimes be fatal.

As NUVARING is a contraceptive product with a vaginal route of administration delivering ethinyl estradiol and etonogestrel (the biological active metabolite of desogestrel) the following should be noted:

- Use of any CHCs carries an increased risk of VTE, compared with no use. The excess risk of VTE is highest during the first year a woman ever uses a CHC. Data from a large, prospective cohort safety study of new users of various COCs suggest that this increased risk, as compared to that in non-COC users, is greatest during the first 6 months of COC use and is present after initially starting a COC or restarting (following a 4 week or greater pill-free interval) the same or a different COC. This increased risk of VTE in COC users is two to three-fold higher than for nonusers of COCs who are not pregnant and remains less than the risk of VTE associated with pregnancy and delivery.

  The risk of developing a VTE for women who use CHCs is 3-12 per 10,000 women-years compared to 1 - 5 per 10,000 women-years in non CHC users.

- Several epidemiological studies indicate that third-generation oral contraceptives, including those containing desogestrel (etonogestrel, the progestin component released by NUVARING is the

biologically active metabolite of desogestrel) are associated with a higher risk of VTE than certain second-generation oral contraceptives. These studies indicate an approximate 2-fold difference in risk, which corresponds to 1-2 cases of VTE per 10,000 women-years of use. However, data from additional studies have not shown this difference in risk. It should be noted, however, that the incidence of VTE in oral contraceptive users is rare.

- Known risk factors for VTE include smoking, obesity and family history of VTE, in addition to other factors that contraindicate use of COCs (see 2 CONTRAINDICATIONS). VTE is fatal in 1-2% of cases.
- The increased risk of VTE with combined oral contraceptives gradually disappears after COC use is discontinued.

Three epidemiological studies have examined the risk of VTE with NUVARING versus combined oral contraceptives. A large, sponsor-funded, prospective cohort study has shown that the frequency of VTE diagnosis was estimated at about 8.3 events per 10,000 woman-years (WY) in new users of NUVARING, compared to 7.8 events per 10,000 WY in new users of levonorgestrel (LNG)-containing COC. The study also reported a VTE incidence of 5.0 events per 10,000 WY in non-pregnant, non COC users and 29.0 events per 10,000 WY in pregnant or postpartum women.

A retrospective cohort study conducted in the United States showed a VTE incidence rate for all users (including new users and continuous users) of NUVARING of 11.91 events per 10,000 WY and for all users of a LNG-containing COC of 6.64 events per 10,000 WY. The corresponding incidence rates for new users in the same study were 11.35 and 9.21 events per 10,000 WY for NUVARING and LNG, respectively.

A second retrospective cohort study using data from the Denmark National Registry showed a VTE incidence for all users of NUVARING of 7.8 events per 10,000 WY and for all users of a LNG-containing COC of 6.2 events per 10,000 WY. A new user analysis was not conducted in this study.

Epidemiological studies have inherent methodological issues making the interpretation of their results complex. Prescribers should consider the benefits and risks for specific women with respect to VTE risk given the results of epidemiological studies of both new and continuous users of CHCs (see 8 ADVERSE EVENTS, 8.5 Post-Market Adverse Reactions, Post-Market Epidemiological Cohort Studies).

Women using CHCs should be advised to contact their physician in case of possible symptoms of thrombosis. In case of suspected or confirmed thrombosis, CHC use should be discontinued. Adequate contraception should be initiated because of the teratogenicity of anti-coagulant therapy (coumarins).

Hepatic/Biliary/Pancreatic

Jaundice

Patients who have had jaundice including a history of cholestatic jaundice during pregnancy should be given CHCs (including NUVARING) with great care and under close observation.

The development of severe generalized pruritus or icterus requires that the medication be withdrawn until the problem is resolved.

If the jaundice should prove to be cholestatic in type, the use of CHCs should not be resumed. In patients taking CHCs, changes in the composition of the bile may occur and an increased incidence of gallstones has been reported.

Hepatic Nodules

Hepatic nodules (adenoma and focal nodular hyperplasia) have been reported, particularly in long-term users of CHCs. Although these lesions are extremely rare, they have caused fatal intra-abdominal

hemorrhage and should be considered in women presenting with an abdominal mass, acute abdominal pain, or evidence of intra-abdominal bleeding.

Hepatitis C

During clinical trials with some HCV combination drug regimens, alanine aminotransferase (ALT) elevations were observed in women using ethinylestradiol containing medications (see 9.4 Drug-Drug Interactions). For example, the HCV combination drug regimen ombitasvir/ paritaprevir/ ritonavir with and without dasabuvir, ALT elevations greater than 5 times the upper limit of normal were significantly more frequent in women using ethinylestradiol-containing medications such as CHCs. Additionally, in patients treated with glecaprevir/pibrentasvir, ALT elevations were observed in women using ethinylestradiol-containing medications such as CHCs. NUVARING must be discontinued prior to starting therapy with the combination drug regimen ombitasvir/ paritaprevir/ ritonavir with or without dasabuvir or medicinal products containing glecaprevir/pibrentasvir (see 2 CONTRAINDICATIONS and 9 DRUG INTERACTIONS). NUVARING can be restarted approximately 2 weeks following completion of treatment with the HCV combination drug regimen.

Immune

Hypersensitivity Reactions

Hypersensitivity reactions of angioedema and anaphylaxis have been reported during use of NUVARING. If angioedema and/or anaphylaxis are suspected, NUVARING should be discontinued and appropriate treatment administered.

Hereditary and Acquired Angioedema

Exogenous estrogens may induce or exacerbate symptoms of hereditary and acquired angioedema.

Monitoring and Laboratory Tests

Physical Examination and Follow-up

Before CHCs (including NUVARING) are used, a thorough history and physical examination should be performed, including a blood pressure determination. Breasts, liver, extremities and pelvic organs should be examined. A Papanicolaou smear should be taken if the patient has been sexually active.

The first follow-up visit should be done three months after CHCs are prescribed. Thereafter, examinations should be performed at least once a year or more frequently if indicated. At each annual visit, examination should include those procedures that were done at the initial visit as outlined above or per recommendations of the Canadian Task Force on the Periodic Health Examination.

Neurologic

Migraine and Headache

The onset or exacerbation of migraine or the development of headache of a new pattern which is recurrent, persistent or severe, requires discontinuation of CHCs (including NUVARING) and evaluation of the cause. Women with migraine headaches who take CHCs may be at increased risk of stroke (see 2 CONTRAINDICATIONS).

Ophthalmologic

Ocular Disease

Patients who are pregnant or are using CHCs (including NUVARING), may experience corneal edema that may cause visual disturbances and changes in tolerance to contact lenses, especially of the rigid type.

Soft contact lenses usually do not cause disturbances. If visual changes or alterations in tolerance to contact lenses occur, temporary or permanent cessation of wear may be advised.

Ocular Lesions

There have been clinical reports of retinal thrombosis associated with the use of CHCs. CHCs (including NUVARING) should be discontinued if there is unexplained transient, partial or complete loss of vision; onset of proptosis or diplopia; papilledema or retinal vascular lesions. Appropriate diagnostic and therapeutic measures should be undertaken immediately.

Peri-Operative Considerations

Thromboembolic Complications – Post-surgery

There is an increased risk of post-surgery thromboembolic complications in CHC (including NUVARING) users, after major surgery. If feasible, CHCs should be discontinued and an alternative method substituted at least one month prior to MAJOR elective surgery. CHCs should not be resumed until the first menstrual period after hospital discharge following surgery (see 2 CONTRAINDICATIONS).

Psychiatric

Emotional Disorders

Patients with a history of emotional disturbances, especially the depressive type, may be more prone to have a recurrence of depression while using CHCs (including NUVARING). In cases of a serious recurrence, a trial of an alternate method of contraception should be made which may help to clarify the possible relationship. Women with premenstrual syndrome (PMS) may have a varied response to CHCs, ranging from symptomatic improvement to worsening of the condition.

Reproductive Health: Female and Male Potential

NUVARING is contraindicated during pregnancy (See 2 CONTRAINDICATIONS, 7.1.1 Pregnant Women).

Return to Fertility

After discontinuing CHC (including NUVARING) therapy, the patient should delay pregnancy until at least one normal spontaneous cycle has occurred in order to date the pregnancy. An alternate contraceptive method should be used during this time.

Amenorrhea

In some women, withdrawal bleeding may not occur during the ring-free interval. If NUVARING has been used according to directions; it is unlikely that the woman is pregnant. However, if NUVARING has not been used according to directions prior to the first missed withdrawal bleed, or if two withdrawal bleeds are missed, pregnancy must be ruled out before NUVARING use is continued.

Women having a history of oligomenorrhea, secondary amenorrhea, or irregular cycles may remain anovulatory or become amenorrheic following discontinuation of estrogen-progestin combination therapy.

Amenorrhea, especially if associated with breast secretion, that continues for six months or more after withdrawal, warrants a careful assessment of hypothalamic-pituitary function.

Reduced Efficacy

The efficacy of NUVARING may be reduced in the event of non-compliance, or when concomitant medications that decrease the plasma concentration of ethinyl estradiol and/or etonogestrel are used (see 4 DOSAGE AND ADMINISTRATION and 9 DRUG INTERACTIONS).

Risk to the Partner

The extent and possible pharmacological role of exposure of male sexual partners to ethinyl estradiol and etonogestrel through absorption through the penis have not been determined.

Skin

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 NUVARING.

7.1 Special Populations

7.1.1 Pregnant Women

CHCs (including NUVARING) should not be used by pregnant women (see 2 CONTRAINDICATIONS). However, if conception accidentally occurs while using CHCs, there is no conclusive evidence that the estrogen and progestin contained in CHCs will damage the developing child.

The extent of exposure in pregnancy during clinical trials: Very Limited: individual cases only.

7.1.2 Breast-feeding

The effects of NUVARING in nursing mothers have not been evaluated and are unknown. In breastfeeding women, the use of CHCs results in the hormonal components being excreted in breast milk and may reduce its quantity and quality. If the use of CHCs is initiated after the establishment of lactation, there does not appear to be any effect on the quantity and quality of the milk. There is no evidence that low-dose CHCs are harmful to the nursing infant. However, women who are breast feeding should be advised not to use CHCs (including NUVARING) but to use other forms of contraception until the child is weaned.

7.1.3 Pediatrics

Pediatrics (<18 years of age): The safety and efficacy of NUVARING in adolescents under the age of 18 have not been studied. Use of this product before menarche is not indicated.

7.1.4 Geriatrics

Geriatrics: NUVARING has not been studied in postmenopausal women and is not indicated in this population.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

An increased risk of the following serious adverse reactions has been associated with the use of CHCs (including NUVARING):

- Arterial and venous thromboembolism (See 7 WARNINGS AND PRECAUTIONS)
- Thrombophlebitis (See 7 WARNINGS AND PRECAUTIONS)
- Pulmonary embolism (See 7 WARNINGS AND PRECAUTIONS; 2 CONTRAINDICATIONS)
- Mesenteric thrombosis (See 7 WARNINGS AND PRECAUTIONS)
- Neuro-ocular lesions, e.g., retinal thrombosis (See 7 WARNINGS AND PRECAUTIONS)

- Myocardial infarction
- Cerebral thrombosis
- Cerebral hemorrhage
- Hypertension (See 7 WARNINGS AND PRECAUTIONS; 2 CONTRAINDICATIONS)
- Benign and malignant hepatic tumors
- Gallbladder disease
- Congenital anomalies

The following adverse reactions also have been reported in patients receiving CHCs:

Nausea and vomiting constitute the most common adverse reactions and occur in approximately 10% of patients during the first cycle.

Other reactions, observed with a frequency of <10%, include:

- Gastrointestinal symptoms (such as abdominal cramps and bloating)
- Breakthrough bleeding
- Spotting
- Change in menstrual flow
- Dysmenorrhea
- Amenorrhea during and after treatment (See 7 WARNINGS AND PRECAUTIONS)
- Temporary infertility after discontinuance of treatment
- Edema
- Chloasma or melasma which may persist
- Breast changes: tenderness, enlargement, and secretion
- Change in weight (increase [5%] or decrease [0.1%])
- Endocervical hyperplasias
- Possible diminution in lactation when given immediately post-partum
- Cholestatic jaundice (See 7 WARNINGS AND PRECAUTIONS)
- Migraine (See 7 WARNINGS AND PRECAUTIONS; 2 CONTRAINDICATIONS)
- Increase in size of uterine leiomyomata
- Rash (allergic)
- Mental depression (See 7 WARNINGS AND PRECAUTIONS)
- Reduced tolerance to carbohydrates
- Vaginal candidiasis
- Premenstrual-like syndrome
- Intolerance to contact lenses (See 7 WARNINGS AND PRECAUTIONS)
- Change in corneal curvature (steepening)
- Cataracts
- Optic neuritis
- Changes in libido
- Chorea
- Changes in appetite
- Cystitis-like syndrome
- Rhinitis
- Headache (See 7 WARNINGS AND PRECAUTIONS)
- Nervousness
- Dizziness

- Hirsutism
- Loss of scalp hair
- Erythema multiforme
- Erythema nodosum
- Hemorrhagic eruption
- Vaginitis (See 7 WARNINGS AND PRECAUTIONS)
- Porphyria
- Impaired renal function
- Raynaud's phenomenon
- Auditory disturbances
- Hemolytic uremic syndrome
- Pancreatitis (See 7 WARNINGS AND PRECAUTIONS; 2 CONTRAINDICATIONS)

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The most common treatment-related adverse events seen in the two pivotal clinical studies were headache, vaginitis, and leukorrhea (Table 2). These adverse events as well as the incidence of acne, breast tenderness, and nausea which are typical of contraceptives were low.

Table 2 - Treatment related adverse events occurring in ≥1% of subjects in all pivotal clinical studies

System Organ Class	Adverse Event	n*	%
Skin and Appendages Disorders	Acne	46	2.0
Central & Peripheral Nervous System Disorders	Headache	135	5.8
	Migraine	24	1.0
Psychiatric Disorders	Emotional lability	64	2.8
	Libido decreased	31	1.3
	Depression	33	1.4
Gastrointestinal System Disorders	Nausea	74	3.2
	Abdominal pain	24	1.0
Metabolic and Nutritional Disorders	Weight increase	93	4.0
Reproductive Disorders, Female	Vaginitis	130	5.6
	Leukorrhea	111	4.8
	Device related problems	103	4.4
	Breast pain (female)	61	2.6

	Dysmenorrhea	60	2.6
	Vaginal discomfort	56	2.4
	Abdominal pain (gynecological)	**36**	**1.6**

*Total n=2,322 subjects

Cervical cytology was assessed in 2,039 women during treatment with NUVARING. For the majority of subjects, the cervical Pap smear result was Pap I at screening and at last assessment. A small number of subjects had a change from normal (Pap smear result of I, IIa, or IIb) at screening to a Pap result of III or IIIa at last assessment (n=33, 1.3%). Clinically relevant shifts of particular note occurred for 7 subjects with a Pap result of I at screening to a Pap result of IIIb/IV (high-grade SIL) at last assessment. In summary, changes to abnormal cervical cytology occurred in a low percentage of the subjects.

In the comparative metabolic studies, the incidence of adverse events was similar for the NUVARING and LNG/EE OC group (57.9% and 54.0%, respectively). The incidence of drug-related adverse events was higher in the NUVARING group than in the LNG/EE OC group (33.9% and 24.6%, respectively), partly due to the adverse events device-related events and vaginal discomfort, which were only reported in the NUVARING group. Medical and gynecologic examinations performed before and after the studies showed no clinically relevant changes in either group. Heart rate and blood pressure did not change significantly from baseline in either group. Overall, the tolerability of both contraceptives was good (Table 3).

Table 3 – Adverse Events (at Least Possibly Related) Occurring in ≥2% – Metabolic Comparative Studies (NUVARING n=121; COC n=126)

Adverse Event	**NUVARING** **n (%)**	**COC** **n (%)**
Acne	2 (1.7)	3 (2.4)
Breast tenderness	5 (4.1)	5 (4.0)
Decreased libido	10 (8.3)	0 (0.0)
Depression	0 (0.0)	6 (4.8)
Device-related events[1]	3 (2.5)	NA[2]
Headache	4 (3.3)	3 (2.4)
Leukorrhea	3 (2.5)	0 (0.0)
Nausea	6 (5.0)	4 (3.2)
Nervousness	3 (2.5)	2 (1.6)
Weight increase	4 (3.3)	2 (1.6)
Vaginal discomfort	3 (2.5)	0 (0.0)
Vaginitis	5 (4.1)	2 (1.6)

[1]Comprising foreign body feeling, coital problems, and expulsion (WHO terms)

[2]NA = Not applicable

8.3 Less Common Clinical Trial Adverse Reactions

Other rare adverse events which were observed in clinical trials were as follows:

Body as a whole: abdomen enlarged, allergic reaction, asthenia, back pain, chest pain, fatigue, hot flushes, influenza-like symptoms, leg pain, malaise, oedema, oedema peripheral, pain, temperature-changed sensation

Cardiovascular disorders, general: hypertension, hypotension, oedema dependent

Central & peripheral nervous system disorder: aphasia, cramps legs, dizziness, dysaesthesia, hypoesthesia, migraine aggravated, paraesthesia, vertigo

Endocrine disorders: estrogens increased, glucocorticoids increased, hypothyroidism

Gastrointestinal system disorders: anus disorder, change in bowel habits, colitis ulcerative aggravated, constipation, diarrhea, dyspepsia, flatulence, hemorrhoids, rectal disorder, tenesmus, vomiting

Heart rate and rhythm disorders: palpitation

Liver and biliary system disorders: cholelithiasis, SGOT increased

Metabolic and nutritional disorders: dehydration, hypercholesterolemia, hypertriglyceridemia, oedema generalised, xerophthalmia

Musculo-skeletal system disorders: arthralgia, muscle weakness

Neoplasm: breast fibroadenosis, breast neoplasm benign female, cervical smear test positive, cervical uterine polyp, hemangioma acquired, ovarian cyst, uterine fibroid, vaginal neoplasm benign

Platelet, bleeding & clotting disorders: hematoma, purpura

Psychiatric disorders: aggressive reaction, agitation, anorexia, anxiety, apathy, appetite increased, concentration impaired, depression aggravated, hallucination, insomnia, libido increased, nervousness

Red blood cell disorders: anemia

Reproductive disorders, female: amenorrhea, bleeding irregularity, breast enlargement, cervical dysplasia, cervicitis, cervix lesion, ectopy, endometritis, lactation nonpuerperal, mastitis, ovarian disorder, ovarian mass, ovarian pain, pelvic inflammation, premenstrual tension, uterine disorder nos, vulva discomfort, vulva disorder

Reproductive disorders, male: device-related problems, penis disorders including pain, rash, bruises and abrasions

Respiratory system disorders: asthma, dyspnea, rhinitis

Skin & appendages: alopecia, dermatitis fungal, eczema, photosensitivity reaction, pigmentation abnormal, pruritus, pruritus genital, rash, rash maculo-papular, seborrhea, skin discoloration, skin disorder, skin dry

Urinary system disorders: bladder discomfort, cystitis, dysuria, micturition frequency, micturition urgency, strangury, urinary incontinence, urinary tract infection

Vascular (extracardiac) disorders: thrombophlebitis, thrombophlebitis deep, thrombophlebitis superficial

Vision disorders: conjunctivitis, vision abnormal

Application site disorders: skin nodule

Resistance mechanism disorders: infection viral

Secondary terms: cervical smear test PAP II

Undefined system-organ class: cervical smear PAP II

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Not Applicable

8.5 Post-Market Adverse Reactions

In general, post-marketing data are in agreement with the expectations and conclusions based on the clinical development program, except for some unanticipated reports related to disconnected rings (<0.005%). Vaginal injury associated with ring breakage has also been reported (see 7 WARNINGS AND PRECAUTIONS, Genitourinary). In addition, hypersensitivity reactions including angioedema and anaphylaxis, as well as exacerbations of hereditary and acquired angioedema have been reported.

Post-Market Epidemiological Cohort Studies

NUVARING users had a risk of VTE similar to COC users (see table below for adjusted hazard ratios). A large prospective, observational study, the Transatlantic Active Surveillance on Cardiovascular Safety of NUVARING (TASC), investigated the risk of VTE for new users of NUVARING and 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 NUVARING users (VTE incidence 8.3 per 10,000 WY) and women using COCs (VTE incidence 9.2 per 10,000 WY). For women using levonorgestrel (LNG)-containing COCs, VTE incidence was 7.8 per 10,000 WY. Incidence of VTE was 5.0 per 10,000 woman-years in non-pregnant, non-COC and 29.0 per 10,000 woman-years in pregnant or postpartum women.

A retrospective cohort study using data from 4 health plans in the US ("FDA-funded study") showed a VTE incidence rate for all users (including new users and continuous users) of NUVARING of 11.91 events per 10,000 WY and for all users of a LNG-containing COC of 6.64 events per 10,000 WY. The corresponding incidence rates for new users in the same study were 11.35 and 9.21 events per 10,000 WY for NUVARING and LNG, respectively.

A second retrospective cohort study using data from the Denmark National Registry showed a VTE incidence for all users of NUVARING of 7.8 events per 10,000 WY and for all users of a LNG-containing COC of 6.2 events per 10,000 WY. A new user analysis was not conducted in this study.

Table 4 – Estimates (Hazard Ratios or Rate Ratios) of Venous Thromboembolism Risk in Users of NUVARING Compared to Users of Combined Oral Contraceptives (COCs)

Epidemiologic Study	Comparator Product(s)	Hazard Ratios (HR) (95% CI) New Users	Hazard Ratios (HR) or Rate Ratio (RR) (95% CI) All Users
TASC		HR[†]: 0.8 (0.5-1.5)	n/a

	All COCs available during the course of the study * COCs available excluding DSG-, GSD-, DRSP-containing OCs	HR[†]: 0.9 (0.4-2.0)	
FDA-funded study	COCs available during the course of the study[§] LNG/0.03 mg ethinyl estradiol	HR[¶]: 1.09 (0.55-2.16) HR[¶]: 0.96 (0.47-1.95)	HR[¶]: 1.56 (1.02-2.37) HR[¶]: 1.28 (0.83-1.99)
Danish Study	LNG/0.03-0.04 mg ethinyl estradiol	n/a	RR[¥]: 1.9 (1.34-2.7)

* 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

[¥] adjusted for age, calendar year and education

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Note: The prescribing information of concomitant medications should be consulted to identify potential interactions.

The concurrent administration of CHCs (including NUVARING) with other medicinal products may result in an altered response to either agent (see 9.4 Drug-Drug Interactions, Tables 5 and 6). Reduced effectiveness of CHCs (including NUVARING), is more likely with the low-dose formulations. This could result in unintended pregnancy or breakthrough bleeding. It is important to ascertain all drugs that a patient is taking, both prescription and non-prescription, before CHCs (including NUVARING) are prescribed.

Hepatic metabolism: Interactions can occur with medicinal or herbal products that induce microsomal enzymes, specifically cytochrome P450 enzymes (CYP), which can result in increased clearance reducing plasma concentrations of sex hormones and may decrease the effectiveness of CHCs, including NUVARING. These products are identified in 9.4 Drug-Drug Interactions and 9.6 Drug-Herb Interactions with an (*). Enzyme induction can occur after a few days of treatment. Maximum enzyme induction is generally observed within a few weeks. After drug therapy is discontinued, enzyme induction can last for about 28 days. For women on long-term therapy with enzyme-inducing medicinal products, an alternative method of contraception unaffected by enzyme-inducing medicinal products should be considered.

9.3 Drug-Behavioural Interactions

See **3 SERIOUS WARNINGS AND PRECAUTIONS BOX** about cigarette smoking.

Vaginal Use

NUVARING is designed to be a once-a-month contraceptive regimen, therefore, NUVARING should be left in the vagina for a continuous period of 3 weeks. Some women are aware of the ring at random times during the 21 days of use or during intercourse. During intercourse some sexual partners may feel NUVARING in the vagina. However, clinical studies revealed that 90% of couples did not find this to be a problem. NUVARING should not be removed during intercourse.

NUVARING may interfere with the correct placement and position of certain female barrier methods such as a diaphragm, cervical cap or female condom. These methods should not be used as back-up methods with NUVARING.

Tampon Use

The pharmacokinetics of NUVARING was evaluated in one cycle in 10 healthy female subjects randomized to tampon use (Kotex, regular strength) on Day 8, 9, 10 of the NUVARING cycle. The use of tampons had no effect on serum concentrations of etonogestrel and ethinyl estradiol during use of NUVARING. It is unknown how this affects the safety and efficacy of NUVARING.

Expulsion

NUVARING can be accidentally expelled, for example, when it has not been inserted properly, or while removing a tampon, during intercourse, or with straining during a bowel movement. Therefore, it is good habit for the woman to regularly verify the presence of NUVARING (for example, before and after intercourse). If NUVARING is accidentally expelled, the woman should follow the instructions given in sections 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment and 4.5 Missed Dose.

Clinical trial data indicate that expulsion of NUVARING is most common in the first few cycles of use when women are becoming accustomed to this method of contraception. In a retrospective analysis of four one-year NUVARING trials it was found that expulsion occurred in 0.5% of cycles (N=33,462) and this percentage decreased to zero with duration of use (1.1% at cycle 1; N=3,228 and 0% at cycle 13; N=2,071). Overall, 2.3% of subjects (N=3,333) experienced expulsion over 13 cycles of use.

If the ring is accidentally expelled and is left outside of the vagina for less than 3 hours, contraceptive efficacy is not reduced. The vaginal ring can be rinsed with cool to lukewarm (not hot) water and re-inserted as soon as possible, but at the latest within 3 hours (see 4 DOSAGE AND ADMINISTRATION, 4.5 Missed Dose and PATIENT MEDICATION INFORMATION, Missed Dose). If NUVARING is lost, a new vaginal ring should be inserted and the regimen should be continued without alteration.

If the ring has been out of the vagina for more than three hours during the 1st or 2nd week, contraceptive effectiveness may be reduced. The woman should reinsert the ring as soon as she remembers and an additional barrier method of contraception, such as a male condom and/or spermicide, **MUST** be used until the ring has been used **continuously for seven days**. The longer the time NUVARING has been out of the vagina and the closer this is to the ring-free interval, the higher the risk of a pregnancy.

If NUVARING has been out of the vagina for more than 3 hours during the 3rd week of the three-week use period contraceptive efficacy may be reduced. The woman should discard that ring, and one of the following two options should be chosen:

1. Insert a new ring immediately. Note: 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. Have a withdrawal bleeding and insert a new ring no later than 7 days (7x24 hours) from the time the previous ring was removed or expelled. Note: This option should only be chosen if the ring was used continuously for the preceding 7 days.

Women with conditions affecting the vagina, such as a prolapsed uterus, may be more likely to have NUVARING slip out of the vagina.

9.4 Drug-Drug Interactions

Interactions between contraceptive steroids and other drugs have been reported in the literature

The drugs listed in table 1 and 2 are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 5 - Drugs Which May Decrease the Efficacy of Combination Hormonal Contraceptives (CHC)

Class of Compound	Drug	Proposed Mechanism	Suggested Management
Antacids		Decreased intestinal absorption of progestins.	
Antibiotics	Chloramphenicol Neomycin Nitrofurantoin Sulfonamides	Induction of hepatic microsomal enzymes. Also disturbance of enterohepatic circulation.	For short course, use a barrier contraceptive method in addition to NUVARING during administration and for 28 days after discontinuation. NUVARING should not be used with a diaphragm, cervical cap or female condom. For long course of enzyme inducing drugs, use another method of contraception unaffected by enzyme induction.
	Troleandomycin	May retard metabolism of CHC increasing the risk of cholestatic jaundice.	

	Rifabutin(*) Rifampicin(*)	Increased metabolism of progestins. Suspected acceleration of estrogen metabolism.	Use another method. For short course, use a barrier contraceptive method in addition to NUVARING during administration and for 28 days after discontinuation. NUVARING should not be used with a diaphragm, cervical cap or female condom. For long course of enzyme inducing drugs, use another method of contraception unaffected by enzyme induction.
Anticonvulsants	Carbamazepine(*) Felbamate(*) Lamotrigine Oxcarbazepine(*) Phenobarbital(*) Phenytoin(*) Primidone(*) Topiramate(*)	Induction of hepatic microsomal enzymes: Rapid metabolism of estrogen and increased binding of progestin and ethinyl estradiol to SHBG.	For short course, use a barrier contraceptive method in addition to NUVARING during administration and for 28 days after discontinuation. NUVARING should not be used with a diaphragm, cervical cap or female condom. For long course of enzyme inducing drugs, use another method of contraception unaffected by enzyme induction.
Antifungals	Griseofulvin(*)	Stimulation of hepatic metabolism of contraceptive steroids may occur.	Use another method. For short course, use a barrier contraceptive method in addition to NUVARING during administration and for 28 days after discontinuation. NUVARING should not be used with a diaphragm, cervical cap or female condom. For long course of enzyme inducing drug, use another method of contraception unaffected by enzyme induction.

HCV protease inhibitors HIV protease inhibitors Non-nucleoside reverse transcriptase inhibitors	Boceprevir Telaprevir Nelfinavir(*) Ritonavir(*) Nevirapine Efavirenz(*)	HCV and HIV combination therapy may alter clearance of the sex hormones; decreased, increased or no change in the plasma concentrations of the progestin or estrogen component.	For short course, use a barrier contraceptive method in addition to NUVARING during administration and for 28 days after discontinuation. NUVARING should not be used with a diaphragm, cervical cap or female condom. For long course of enzyme inducing drug, use another method of contraception unaffected by enzyme induction.
Sedatives and Hypnotics	Barbiturates Glutethimide(*) Meprobamate(*)	Induction of hepatic microsomal enzymes.	For short course, use a barrier contraceptive method in addition to NUVARING during administration and for 28 days after discontinuation. NUVARING should not be used with a diaphragm, cervical cap or female condom. For long course of enzyme inducing drugs, use another method of contraception unaffected by enzyme induction.
Pulmonary arterial hypertension Drugs	Bosentan(*)	Induction of hepatic microsomal enzymes	For short course, use a barrier contraceptive method in addition to NUVARING during administration and for 28 days after discontinuation. NUVARING should not be used with a diaphragm, cervical cap or female condom. For long course of enzyme inducing drugs, use another method of contraception unaffected by enzyme induction
Other Drugs	Analgesics Antihistamines Antimigraine preparations Phenylbutazone Vitamin E	Reduced contraceptive efficacy has been reported. Remains to be confirmed.	

Hormonal contraceptives may interfere with the metabolism of other drugs. Accordingly, plasma and tissue concentrations may either increase (eg, cyclosporine) or decrease (eg, lamotrigine).

If concomitant drug administration runs beyond the 3 weeks of a ring cycle, the next ring should be inserted immediately, without having the usual ring-free interval.

Table 6 - Modification of Other Drug Action by Combined Hormone Contraceptives

Class of Compound	Drug	Modification of Other Drug Action	Suggested Management
Alcohol		Possible increased levels of ethanol or acetaldehyde.	Use with caution.
Alpha-II Adrenoreceptor Agents	Clonidine	Sedation effect increased.	Use with caution.
Anticoagulants	All	CHCs increase clotting factors, decrease efficacy. However CHC may potentiate action in some patients.	Use another method.
Anticonvulsants	All	Estrogens may increase risk of seizures.	Use another method.
	Lamotrigine	Decreased lamotrigine levels may lead to breakthrough seizures	Use another method
Antidiabetic Drugs	Oral Hypoglycemics and Insulin	CHCs may impair glucose tolerance and increase blood glucose.	Use low dose estrogen and progestin CHC or another method. Monitor blood glucose.
Antihypertensive Agents	Guanethidine and Methyldopa	Estrogen component cause sodium retention, progestin has no effect.	Use low estrogen CHC or use another method.
	Beta Blockers	Increased drug effect (decreased metabolism).	Adjust dose of drug if necessary. Monitor cardiovascular status.
Antipyretics	Acetaminophen	Increased metabolism and renal clearance.	Dose of drug may have to be increased.
	Antipyridine	Impaired metabolism.	Decrease dose of drug.
	Acetylsalicylic acid (ASA)	Effects of ASA may be decreased by the short-term use of CHCs.	Patients on chronic ASA therapy may require an increase in ASA dosage.

Aminocaproic Acid		Theoretically, a hypercoagulable state may occur because CHCs augment clotting factors.	Avoid concomitant use.
Betamimetic Agents	Isoproterenol	Estrogen causes decreased response to these drugs.	Adjust dose of drug as necessary. Discontinuing CHCs can result in excessive drug activity.
Caffeine		The actions of caffeine may be enhanced as CHCs may impair the hepatic metabolism of caffeine.	Use with caution.
Cholesterol Lowering Agents	Clofibrate	CHCs may increase the clearance of clofibrate leading to decreased level of clofibrate.	Use with caution.
Corticosteroids	Prednisone	Markedly increased serum levels.	Possible need for decrease in dose.
Cyclosporine		May lead to an increase in cyclosporine levels and hepatotoxicity.	Monitor hepatic function. The cyclosporine dose may have to be decreased.
Folic Acid		CHCs have been reported to impair folate metabolism.	
Meperedine		Possible increased analgesia and central nervous system depression due to decreased metabolism of meperidine.	Use combination with caution.
Phenothiazine Tranquilizers	All Phenothiazines, Reserpine and similar drugs	Estrogen potentiates the hyperprolactinemia effect of these drugs.	Use other drugs or lower dose CHCs. If galactorrhea or hyperprolactinemia, occurs use other method.
Sedatives and Hypnotics	Chlordiazepoxide Lorazepam Oxazepam Diazepam	Increased effect (increased metabolism).	Use with caution.

Theophylline	All	Decreased oxidation, leading to possible toxicity.	Use with caution. Monitor theophylline levels.
Tricyclic Antidepressants	Clomipramine (possibly others)	Increased side effects: i.e., depression.	Use with caution.
Vitamin B_{12}		CHCs have been reported to reduce serum levels of Vitamin B_{12}.	

Protease and Transcriptase Inhibitors

When co-administered with hormonal contraceptives, many combinations of HIV protease inhibitors (e.g., nelfinavir) and non-nucleoside reverse transcriptase inhibitors (e.g., nevirapine), and/or combinations with HCV medicinal products (e.g., boceprevir, telaprevir) can increase or decrease plasma concentrations of estrogens or progestins, including etonogestrel. The efficacy and safety of oral contraceptive products may be affected; it is unknown whether this applies to NUVARING. Healthcare providers should refer to the label of the individual anti-HIV/HCV protease inhibitors for further drug-drug interaction information.

During clinical trials with the HCV combination drug regimen ombitasvir/ paritaprevir/ ritonavir with and without dasabuvir, ALT elevations greater than 5 times the upper limit of normal were significantly more frequent in women using ethinylestradiol-containing medications such as CHCs. NUVARING must be discontinued prior to starting therapy with the combination drug regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir (see 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, Hepatitis C). NUVARING can be restarted approximately 2 weeks following completion of treatment with the HCV combination drug regimen.

Concomitant use with some other HCV antiviral medicinal products, such as those containing glecaprevir/pibrentasvir, may increase the risk of ALT elevations.

Strong and moderate CYP3A4 Inhibitors

Concomitant administration of strong (e.g., ketoconazole, itraconazole, clarithromycin) or moderate (e.g., fluconazole, diltiazem, erythromycin) CYP 3A4 inhibitors may increase the serum concentrations of estrogens or progestins, including etonogestrel.

Antibiotics

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 ethinylestradiol concentrations have not been evaluated.

Nonoxynol-9 spermicide gel and Miconazole nitrate capsule/suppository

The single dose of 100 mg vaginally administered, water-based nonoxyl-9 gel did not affect the serum concentrations of etonogestrel or ethinyl estradiol.

The single dose of 1,200 mg vaginally-administered, oil-based miconazole nitrate capsule increased the serum concentrations of etonogestrel and ethinyl estradiol by approximately 17% and 16% respectively. The clinical significance of these findings is unknown; however the contraceptive effectiveness of NUVARING is not expected to change.

Three consecutive daily doses of an oil-based 200 mg miconazole nitrate antimycotic suppository or a water-based 200 mg miconazole nitrate antimycotic vaginal cream resulted in mean serum concentrations of etonogestrel and ethinyl estradiol elevations of up to 40%. This effect was more pronounced with the oil-based suppository treatment than in the water-based cream treatment.

The effects of chronic administration of these products with NUVARING are unknown.

Intravaginal preparations

There have been reports of ring breakage during concomitant use of intravaginal preparations, including antimycotic, antibiotic and lubricant products (see 7 WARNINGS AND PRECAUTIONS, Genitourinary, Disconnected/Broken Ring).

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Herbal products containing St. John's wort(*) (Hypericum perforatum) may induce hepatic enzymes (cytochrome P450) and p-glycoprotein transporter and may reduce the effectiveness of contraceptive steroids. This may also result in breakthrough bleeding. For short course, a barrier contraceptive method should be used in addition to NUVARING during administration and for 28 days after discontinuation of the herbal product. For long course, use another method of contraception.

Physicians and other health care providers should be made aware of the non-prescription products concomitantly used by the patient, including herbal and natural products.

9.7 Drug-Laboratory Test Interactions

Results of laboratory tests should be interpreted in the light that the patient is on CHCs (including NUVARING). The following laboratory tests are modified.

A. Liver function tests

Aspartate serum transaminase (AST) – variously reported elevations. Alkaline phosphatase and gamma glutamine transaminase (GGT) – slightly elevated.

B. Coagulation tests

Minimal elevation of test values reported for such parameters as prothrombin and Factors VII, VIII, IX and X.

C. Thyroid function tests

Protein binding of thyroxine is increased as indicated by increased total serum thyroxine concentrations and decreased T3 resin uptake.

D. Lipoproteins

Small changes of unproven clinical significance may occur in lipoprotein cholesterol fractions.

E. Gonadotropins

LH and FSH levels are suppressed by the use of oral contraceptives. Wait two weeks after discontinuing the use of oral contraceptives before measurements are made.

Tissue Specimens

Pathologists should be advised of CHC (including NUVARING) therapy when specimens obtained from surgical procedures and Pap smears are submitted for examination.

10 CLINICAL PHARMACOLOGY

NUVARING is a non-biodegradable, flexible, transparent, colorless to almost colorless, combination contraceptive vaginal ring containing two active components, a progestin, etonogestrel and an estrogen, ethinyl estradiol. When placed in the vagina, each ring releases on average 120 µg/day of etonogestrel and 15 µg/day of ethinyl estradiol over a three-week period of use. NUVARING is made of ethylene vinylacetate copolymers and magnesium stearate and contains 11.4 mg etonogestrel and 2.6 mg ethinyl estradiol. NUVARING has an outer diameter of 54 mm and a cross-sectional diameter of 4 mm. It does not contain any latex.

10.1 Mechanism of Action

CHCs (including NUVARING) 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 reduces the likelihood of implantation).

10.2 Pharmacodynamics

Etonogestrel, the progestogen component of NUVARING, displays low androgenic activity in relation to its progestogenic effects and may increase the HDL1-, HDL2-, and HDL3-cholesterol and apoprotein A-1/B ratio without affecting LDL. Like other hormonal contraceptives, these changes in lipid profile can be associated with an increase in triglycerides.

Animal and in vitro pharmacology:

Animal pharmacology and in vitro receptor binding studies indicate that etonogestrel is a highly selective progestational agent (Table 7) with no estrogenic effects, and only residual androgenicity.

Table 7 – Comparison of Relative Binding Affinity of Desogestrel, Etonogestrel and Progesterone for the Progesterone Receptor in Uterine Cytosol*

	Rabbit myometrium	Human myometrium
desogestrel	5	2
etonogestrel	111	113
progesterone	32	18

*Binding affinities were determined at 4^{E}C using the reference standard 16α-ethyl-21-hydroxy-9-nor-pregn-4-ene-3,20-dione.

The binding affinity of etonogestrel is approximately 1/10 of 5α-dihydrotestosterone suggesting a low androgenic activity. The binding affinity for the androgen receptor in intact MCF-7 cells as displayed by etonogestrel was also significantly lower than that of other progestogens. As a result the "selectivity index" (progestogen/androgen receptor binding affinity ratio) for etonogestrel in intact MCF-7 cells is high.

10.3 Pharmacokinetics

The pharmacokinetic parameters of etonogestrel and ethinyl estradiol were determined during one cycle of NUVARING use in 16 healthy female subjects and are summarized in Table 8.

Table 8 - Summary of NUVARING's Pharmacokinetic Parameters in 16 healthy female subjects

	C_{max} mean (SD) pg/mL	$t_{½}$ (h)	T_{max} (h)	Clearance (L/h)
Etonogestrel	1,716 (445)	29.3 (6.1)	200.3 (69.9)	3.4 (0.8)
Ethinyl Estradiol	34.7 (17.5)	44.7 (28.8)	59.3 (67.5)	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

Absorption:

Etonogestrel: Etonogestrel released by NUVARING is rapidly absorbed. The bioavailability of etonogestrel after vaginal administration is approximately 100%. The serum etonogestrel and ethinyl estradiol concentrations (pg/mL) observed during three weeks of NUVARING use are summarized in Table 9.

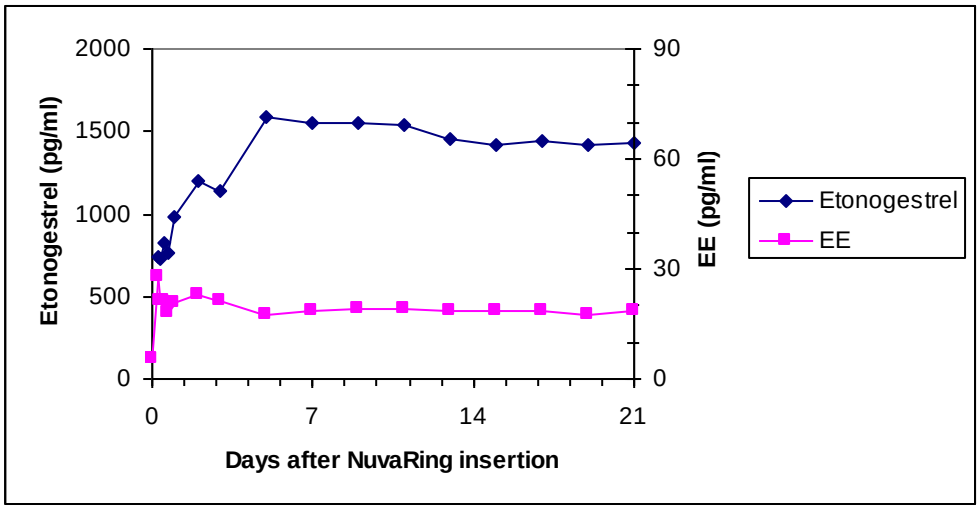
Ethinyl estradiol: Ethinyl estradiol released by NUVARING is rapidly absorbed. The bioavailability of ethinyl estradiol after vaginal administration is approximately 55.6%, which is comparable to that with oral administration of ethinyl estradiol. However, the overall systemic exposure to ethinyl estradiol with NUVARING was approximately 50% of that for a 30 mcg oral contraceptive reflecting the difference in daily doses (15 µg vs. 30 µg). The serum ethinyl estradiol concentrations observed during three weeks of NUVARING use are summarized in Table 9.

Table 9 – Mean (SD) Serum Etonogestrel and Ethinyl Estradiol Concentrations (n=16)

	1 week	2 weeks	3 weeks
Etonogestrel (pg/mL)	1,578 (408)	1,476 (362)	1,374 (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 NUVARING is shown in Figure 1.

Figure 1 – Mean serum concentration-time profile of etonogestrel and ethinyl estradiol during three weeks of NUVARING use



Serum ethinyl estradiol levels were measured in a comparative randomized trial (n=24) with NUVARING (daily vaginal EE release of 0.015 mg), a transdermal patch (norelgestromin/EE; daily EE release of 0.020 mg) and a COC (levonorgestrel/EE; daily EE release of 0.030 mg) during one cycle in healthy female subjects. The monthly systemic ethinyl estradiol exposure (AUC0-¥) of NUVARING was 10.9 ng·h/mL.

Distribution:

Etonogestrel: Etonogestrel was found to be 98% protein bound, primarily to albumin and sex hormone-binding globulin (SHBG). The apparent volume of distribution of etonogestrel is 2.3 L/kg.

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. An apparent volume of distribution of about 15 L/kg has been determined.

Metabolism:

In vitro data shows that both etonogestrel and ethinyl estradiol are metabolized in liver microsomes by the cytochrome P450 3A4 isoenzyme (see 9 DRUG INTERACTIONS). 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.

Elimination:

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

Special Populations and Conditions

- **Pediatrics:** The pharmacokinetics of NUVARING in healthy postmenarchal female adolescents under the age of 18 has not been studied.
- **Ethnic Origin:** No formal studies were conducted to evaluate the effect of race on the pharmacokinetics of NUVARING.
- **Hepatic Insufficiency:** No formal studies were conducted to evaluate the effect of hepatic disease on the pharmacokinetics, safety, and efficacy of NUVARING. 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 CHC use until markers of

liver function return to normal (see 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS).

- **Renal Insufficiency:** No formal studies were conducted to evaluate the effect of renal disease on the pharmacokinetics, safety, and efficacy of NUVARING.

11 STORAGE, STABILITY AND DISPOSAL

Prior to dispensing to the user, store refrigerated at 2-8°C. After dispensing to the user, NUVARING (etonogestrel/ethinyl estradiol slow release vaginal ring) can be stored for up to 4 months at 2-30°C. Avoid storing NUVARING at temperatures above 30°C. Protect from light.

For the Dispenser

When NUVARING 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. Store between 2-30°C.

Keep in a safe place out of the reach of children and pets.

12 SPECIAL HANDLING INSTRUCTIONS

After removal, NUVARING should be replaced in the reclosable sachet and disposed of with the normal household waste in a manner that avoids accidental contact with others. NUVARING should not be flushed down the toilet.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

I. Progestogen

Proper name: Etonogestrel

Chemical name: 1) 18,19-Dinor-17α-pregn-4-en-20-yn-3-one,13-ethyl-17-hydroxy-11-methylene-;

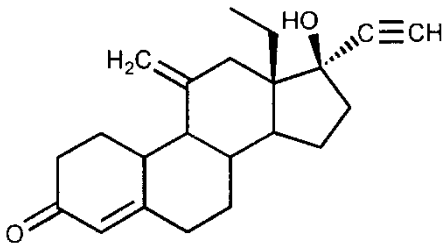
2) 13-Ethyl-17-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20yn-3-one.

3) (17α)13-ethyl-17-hydroxy-11-methylene-18,19- dinorpregn-4-en-20-yn-3-one.

Molecular formula: $C_{22}H_{28}O_2$

Molecular mass: 324.46

Structural formula:



Physicochemical properties:

Physical Form: White to practically white crystalline powder which may have a slight odour.

Solubility: At 22°C: n-Hexane - 2 mg/mL

Ethanol (96%) - 60 mg/mL

Ethyl acetate - 60 mg/mL

Water - practically insoluble

Melting Point: 197.6°C

II. Estrogen

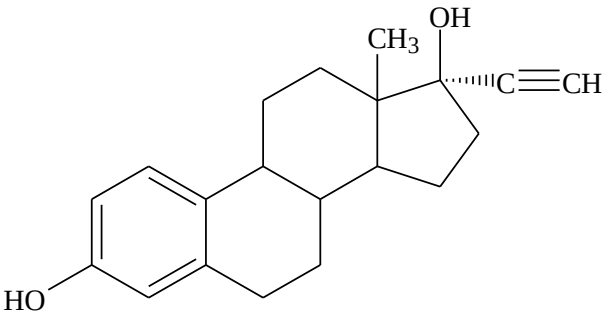
Proper name: Ethinyl Estradiol Ph.Eur.

Chemical name: 19-Nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol

Molecular formula: $C_{20}H_{24}O_2$

Molecular mass: 296.4

Structural formula:



Physicochemical properties:

Physical Form: White, crystalline powder

Solubility: Soluble in ethanol, ether, acetone, chloroform.

Practically insoluble in water.

Melting Point: 182-184°C

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Indication 1: Conception control

Table 10 - Summary of patient demographics for clinical trials in contraception

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Sex	Primary endpoint	Secondary endpoint
068003	Open-label, non-comparative, multicenter, efficacy, cycle control, safety	Declared daily release rate of 0.120 mg ENG and 0.015 mg EE, vaginal – 13 cycles	1,177	28.1 (18-41)	F	Contraception – Primary efficacy was based on contraceptive efficacy, ie, on the prevention of in-treatment pregnancies. Pearl indices (representing the expected number	Cycle control – The statistical analysis of the cycles focused on the following parameters: • occurrence of breakthrough bleeding/spotting • absence of withdrawal bleeding/spotting • occurrence of breakthrough bleeding • occurrence of
34219			1,145	28.2 (18-41)			

						of pregnancies per 100 women-years of exposure) and overall cumulative probability of in-treatment pregnancy are estimated to evaluate the contraceptive efficacy of NUVARING®.	breakthrough spotting (spotting only) • occurrence of early withdrawal bleeding • occurrence of continued withdrawal bleeding • number of breakthrough bleeding/spotting days • number of withdrawal bleeding (days) • occurrence of early withdrawal bleeding with only spotting days in the ring period • occurrence of continued withdrawal bleeding continued with spotting days only • occurrence of intended bleeding pattern

a) Contraceptive Efficacy – Pearl Index

Clinical studies were performed worldwide in women between the age of 18 and 40 years.

In 2 large pivotal clinical trials of 13 cycles of NUVARING (etonogestrel/ethinyl estradiol slow release vaginal ring) use, pregnancy rates were between 1 and 2 per 100 women-years of use.

b) Cycle Control

Relative frequencies of bleeding/spotting and bleeding days showed a consistent pattern throughout all 13 cycles for the pivotal studies combined. The majority of subjects were bleeding/spotting during the ring-free period. The relative frequencies of bleeding days were acceptable during almost all ring period days.

For the combined pivotal studies, incidences of bleeding variables over Cycles 1-13 were acceptable and comparable to that of other combined hormonal contraceptives (Table 11). The incidence of

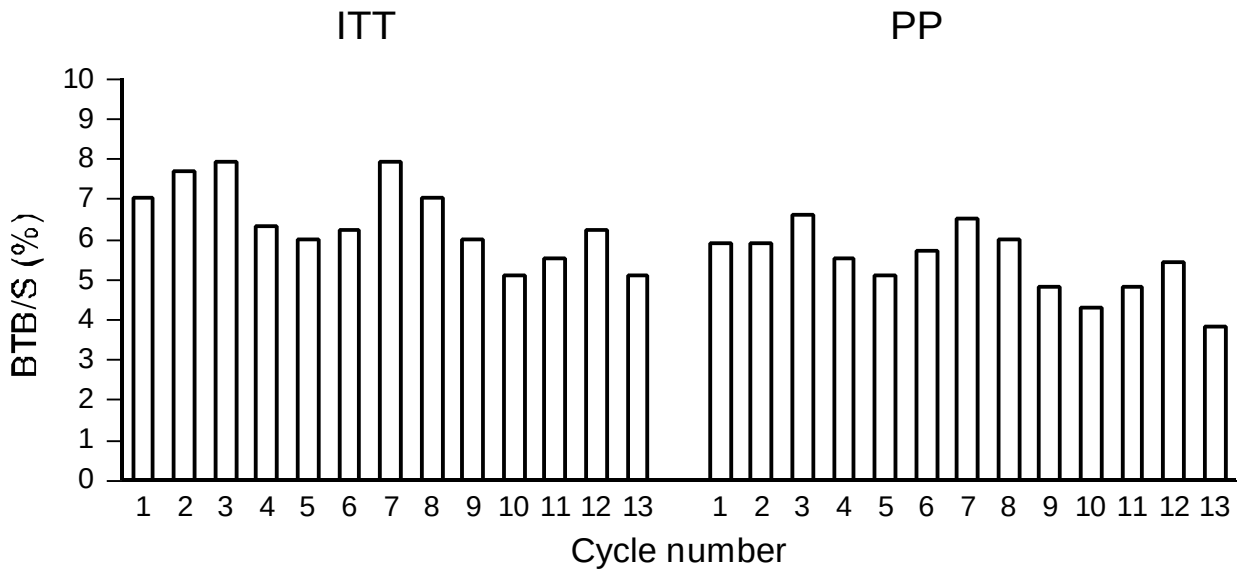
breakthrough bleeding/spotting ranged from 5.1% - 7.9% and the incidence of absence of withdrawal bleeding ranged from 1.5% - 2.9% of Intent-to-Treat (ITT) evaluable cycles. Per Protocol (PP) cycles exhibited lower incidences than ITT cycles (Figure 2). Early (ranges 5.6% - 8.8%) and continued withdrawal bleeding (ranges 19.5% to 25.2%) consisted mostly of spotting days only. The incidence of intended bleeding pattern, which is representative of an "ideal" bleeding pattern where bleeding occurs primarily during the ring-free period (without breakthrough bleeding/spotting, without absence of withdrawal bleeding, without absence of early and continued (in the next cycle) withdrawal bleeding), over Cycles 1-12 ranged from 59.9% - 68.5% of ITT evaluable cycles. The incidences of intended bleeding pattern were comparable between ITT and PP cycles.

Table 11 – Parameters of Bleeding Pattern during the First Year of use – Combined Pivotal Studies

Cycle	Number of Evaluable Cycles	Number of Evaluable Cycles	Incidence of Breakthrough Bleeding/Spotting (%)		Incidence of Absence of Withdrawal Bleeding (%)		Incidence of Intended Bleeding Pattern (%)	
	ITT	PP	ITT	PP	ITT	PP	ITT	PP
1	1,971	1,709	7	5.9	2.9	2.3	59.9	60
3	1,796	1,368	7.9	6.6	2.1	1	63.6	65.2
6	1,649	1,299	6.2	5.7	1.5	1.2	66.5	67.1
9	1,499	1,177	6.0	4.8	2.4	1.7	65.8	66.7
12	1,300	1,053	6.6	5.3	2.2	1.7	68.5	70.0
13	948	734	5.5	3.5	2.2	1.2	84.8	87.9

ITT = Intent-to-Treat; PP = Per Protocol

Figure 2 – Incidence of Breakthrough Bleeding/Spotting (BTB/S) – Combined Pivotal Studies



ITT = Intent-to-Treat; PP = Per Protocol

c) Tolerance

Acceptability of NUVARING was evaluated in the pivotal studies on the basis of answers to questions completed by each subject at different timepoints during the studies. Acceptability data from last assessment related to the use of NUVARING are presented in Table12. Nearly all women found the ring easy to insert and remove. Eighteen percent of women reported at least occasionally feeling the ring during intercourse. Although this response was higher for the question of partners feeling the ring, 94% of completers' partner and 83% of discontinuers' partner did not object to women using the ring.

Table 12 – Responses from Acceptability Questionnaire at Last Assessment – Combined Pivotal Studies

	Population	**Number of responders**	**Proportion of subjects responding**		
			Never/rarely **%**	**Occasionally** **%**	**Frequently/always** **%**
Was the ring easy	Completers	1,499	1	1	98
to insert?	Discontinuers	643	4	5	92
	Combined	2,142	2	2	96
Was the ring easy	Completers	1,499	0	1	98
to remove?	Discontinuers	642	2	3	95
	Combined	2,141	1	2	98
Could feel ring	Completers	1,498	85	12	3
during intercourse?	Discontinuers	630	77	13	10
	Combined	2,128	83	13	5
Could partner feel	Completers	1,498	71	22	7
ring during intercourse?	Discontinuers	631	63	21	16
	Combined	2,129	68	22	10
Did partner mind	Completers	1,498	94	4	2
you using the ring?	Discontinuers	635	83	6	10
	Combined	2,133	91	5	5

Ninety-six percent (96%) of completers at cycle 13 reported that they were satisfied with the ring and 97% would recommend this method to others. Eighty-five percent (85%) of all women (completers and premature study discontinuers) were satisfied with the use of NUVARING and 90% would recommend this method to others.

d) Safety

In the combined pivotal non-controlled open-label studies 351/2322 (15.1%) treated subjects discontinued due to adverse events; most were drug-related adverse events. The most common adverse events leading to discontinuation of women were device related events (2.5%): foreign-body sensation, coital problems, device expulsion, vaginal symptoms (discomfort/vaginitis/leukorrhea), headache (1.3%), emotional lability (1.2%), and weight increase (1.0%).

Over the 13 cycles of treatment, the mean increase in body weight from baseline was 0.84 kg. Similarly, there was no clinically relevant change from baseline in blood pressure (Table 13).

Table 13 – Mean Change (± standard deviation) in Blood Pressure and Body Weight from Baseline – Combined Pivotal Studies (ITT)

	Cycle			
	3	**6**	**9**	**13**
Diastolic (mmHg)	-0.1 ± 8.4	-0.3 ± 8.9	0.0 ± 8.7	0.5 ± 8.9
Systolic (mmHg)	-0.2 ± 10.3	-0.1 ± 11.0	-0.2 ± 11.0	0.6 ± 11.2
Body weight (kg)	0.02 ± 2.29	0.05 ± 3.12	0.47 ± 3.40	0.84 ± 3.81

Subjects withdrew at a rate of <1.0% for the following reasons: bleeding irregularities, vaginal discomfort, vaginitis, nausea, and leukorrhea.

Comparative Trials – Cycle Control

In 3 metabolic studies, the secondary objective was to examine cycle control and tolerability in NUVARING users compared to a 150 µg levonorgestrel/30 µg ethinyl estradiol combined oral contraceptive group (COC). All three trials were of similar design to permit pooling of the data for all 6 cycles.

Relative frequencies of bleeding/spotting and bleeding days showed a consistent pattern throughout all 6 cycles for both treatment groups, except for Cycle 1 in the COC group. In the NUVARING group, the relative frequencies of bleeding/spotting during the ring-free periods reached a maximum of at least 92.6% per cycle in the ITT analysis. In the COC group, the relative frequencies of bleeding/spotting during the ring-free periods reached a maximum of at least 91.8% per cycle. The relative frequencies of bleeding/spotting days are low during the ring/pill period beginning from the second half of the first week onwards while the relative frequencies of bleeding days are extremely low during almost all ring/pill period days.

Withdrawal bleeding occurred in nearly all cycles for both groups, 98.2 - 100%. Incidences of early withdrawal bleeding (Cycles 1-6) were low in both groups (1.3% to 13.0% in the NUVARING group, and 1.8% to 10.3% in the COC group). Continued withdrawal bleedings (over Cycles 1-5) ranged from 17.4% to 28.0% in the NUVARING group and from 45.9% to 57.1% in the LNG/EE OC group. This difference was statistically significant. In both groups early withdrawal bleeding and continued bleeding consisted mostly of spotting days only.

Incidences of breakthrough bleeding/spotting episodes for the NUVARING group over Cycles

1-6 ranged from 1.1% - 5.0% (Table 14). In the COC group, these incidences over Cycles 2 6 ranged from 5.4% - 11.0%, whereas in Cycle 1 the incidence was 38.8%. This observed difference for Cycle 1 was statistically significant. Note that, for Cycle 1, the NUVARING group inserted the ring on Day 5 of the

menstrual period, whereas the LNG/EE group started pill intake on Day 1. To allow for this difference, a correction was made during data analysis by excluding the first seven days of Cycle 1.

The incidence of intended bleeding pattern for the NUVARING group was significantly higher over Cycles 1-5 (ranging from 65.3% - 68.4%) than the COC group (ranging from 28.4% - 46.8%) (Table 14). The high incidences of intended bleeding pattern during Cycle 6 (93.8% in the NUVARING group and 91.4% in the COC group) were due to continued withdrawal bleedings not being reported, since it would have required post-treatment bleeding data.

Table 14 – Cycle control in combined metabolic studies (NUVARING n=121; COC n=126) (ITT)

	Incidence of Breakthrough Bleeding/Spotting (%)		Incidence of Intended Bleeding Pattern (%)	
Cycle	**NUVARING**	**COC**	**NUVARING**	**COC**
1	1.9	38.8	65.4	28.4
2	4	10.7	68.3	35.7
3	3.1	10.1	65.3	44
4	1.1	6.3	68.4	46.8
5	4.3	11	66.3	45.9
6	5	5.4	93.8	91.4

A subsequent large comparative study with 150/30µg LNG/EE OC (n=512 vs n=518) evaluating vaginal bleeding characteristics over 13 cycles showed the incidence of breakthrough bleeding/ spotting for NUVARING ranged from 2.0 - 6.4%. The incidence of intended bleeding pattern for NUVARING ranged from 58.8 - 72.8%.

Overall, the cycle control achieved during NUVARING use was excellent and better than that in women who used an oral contraceptive for many of the parameters that were examined.

Metabolic Studies

Lipid Metabolism Study

A causal relationship between ischemic heart disease and unfavorable plasma lipid/lipoprotein profiles, specifically, a high LDL/HDL ratio, is now widely accepted on the basis of epidemiologic, biochemical and other evidence. It has also been demonstrated that androgens influence the lipid/lipoprotein ratio unfavourably, while estrogens have a beneficial effect, largely by increasing HDL2 and, to a lesser extent, by reducing LDL levels.

NUVARING had generally favorable effects on lipids. In a clinical study involving 40 NUVARING-treated subjects, the following effects on lipid metabolism parameters were observed: total cholesterol (Total-C) was unchanged, high-density lipoprotein cholesterol (HDL-C) was unchanged, HDL2 increased 26.3%, HDL3 decreased 4.6%, low-density lipoprotein cholesterol (LDL-C) was unchanged, triglycerides increased 23.8%, apolipoprotein A-1 (apo A-1) increased 10.3%, apolipoprotein B (apo B) increased 6.2%,

and lipoprotein (a) decreased 12.9%.

In the same clinical study NUVARING was also compared to a levonorgestrel/ethinyl estradiol oral contraceptive group (LNG/EE OC). Total cholesterol levels remained more or less unchanged in both groups. However, HDL-, HDL2-, and HDL3- cholesterol levels were significantly higher in NUVARING group than in the LNG/EE OC group. Levels of HDL-, HDL2-, and HDL3- cholesterol were decreased from baseline in the LNG/EE OC group and unchanged (HDL), increased (HDL2) and slightly decreased (HDL3) in NUVARING group. LDL-cholesterol levels were significantly lower in NUVARING group, due to an increase in the LNG/EE OC group and no change or decrease in NUVARING group. Triglyceride levels were increased in both groups. No significant difference between the two groups was noted. Group comparisons indicated significantly higher apolipoprotein A-I levels for the NUVARING group. No treatment differences for apolipoprotein B levels were observed. Compared to baseline, levels increased in the two groups, except for apolipoprotein A-I that decreased in the LNG/EE OC group. Lipoprotein (a) levels were decreased in both groups. No significant difference between the two groups was noted.

The magnitude of the effect of a combined hormonal contraceptive on plasma SHBG depends on both the estrogen dose and the dose and hormonal profile of the progestogenic component. A progestogen with low androgenic activity, such as etonogestrel, is expected to induce higher SHBG concentrations as compared to the ones with higher androgenic activity. Comparison between two treatment groups showed a significantly higher increase of adjusted SHBG levels for the NUVARING group (62% at Cycle 6) than the LNG/EE OC group. At Cycle 6, relative increases from baseline were 170% for the NUVARING group and 56% for the LNG/EE OC group.

Hemostasis Study

A specific hemostasis study (n=44) was performed with NUVARING. In addition to conventional parameters such as fibrinogen, plasminogen, tissue plasminogen activator and plasminogen activator inhibitor-I antigen, a number of new assays have been introduced. These assays detect markers that are generated in the proteolytic process of the thrombin-generating or fibrinolytic cascade and, in contrast to the more conventional parameters mentioned before, are considered to reflect the 'in vivo' hemostasis activity. Therefore they may be more predictive of a pre-thrombotic state (Winkler et al., 1995) than the conventional parameters. This concerns the procoagulation parameters prothrombin fragment 1 and 2 and the thrombin-antithrombin III complex, which are indicative of thrombin generation, and the profibrinolysis parameter plasmin-antiplasmin complex and fibrin turnover parameters such as D-dimer and fibrinogen degradation products as markers of the fibrinolytic cascade. Of further importance are Factor VII because it reflects ongoing coagulatory activity and the anticoagulation parameters antithrombin III, protein C and protein S, because women with a deficiency in any of these factors may not be able to adjust sufficiently to changes induced by external factors.

The effects of NUVARING on the above mentioned hemostasis parameters were investigated in an open-label, group-comparative study with a 0.150 mg LNG and 0.030 mg EE containing OC. The effects on the coagulation and fibrinolysis parameters seen in the NUVARING group were not statistically different from the effects seen in the LNG/EE OC group, except for the relatively higher increase of the procoagulation parameter Factor VII and the anticoagulation parameter Protein C, and the relative less decrease of the profibrinolysis parameter t-PA in the NUVARING group. No difference between the two treatment groups was observed for fibrin turnover. Both in NUVARING and in the LNG/EE OC group most of the hemostatic parameters that were investigated showed (small) changes from baseline. The clinical relevance of all these changes is not clear. The hemostatic system is very complex and intricately balanced; to a certain extent, the intrinsic balancing system can overcome the activation/inhibition of one or more of the hemostatic parameters. Furthermore, it is very difficult to correct for a possible natural rhythm, which hampers interpretation of changes from baseline. Nevertheless, both NUVARING and the LNG/EE OC had

no effect on the end products of the fibrinolytic cascade, namely the fibrin degradation products.

In view of the knowledge that individual women might have increased susceptibility for thrombosis, the data obtained with NUVARING and the LNG/EE OC were also compared on an individual basis, with emphasis on women having one or more hemostasis parameters outside the reference ranges. During the study most of the subjects in both treatment groups had one or more in-treatment values outside the reference range. However, none were clinically significant nor considered clinically relevant by the investigator.

In conclusion, although for some parameters differences were observed between NUVARING and the LNG/EE OC, there was no evidence of a pronounced disturbance of the hemostatic balance with either product. Furthermore, both NUVARING and the LNG/EE OC had no effect on the end products of the fibrinolytic cascade, namely the fibrin degradation products.

Carbohydrate Metabolism Study

In another metabolic study (n=37) there was less of an effect on the adrenal function parameter total cortisol with NUVARING than with LNG/EE OC. The thyroid function parameter TSH showed a significantly higher relative increase in the NUVARING group at Cycle 3, but not at the Cycle 6 assessment. Free thyroxin levels were unchanged compared to baseline in both groups. The effects on carbohydrate metabolism parameters seen in the NUVARING group were similar to the effects seen in the LNG/EE OC group.

Bone Mineral Density

A controlled open-label, multicenter trial was conducted to evaluate the effects of NUVARING on bone mineral density (BMD) in healthy young women (n=105; 76 completers) over a 2 year period (26 cycles). The control group (n=39; 31 completers) consisted of women who did not use a hormonal method of contraception, and an IUD was offered as trial medication. The mean age of subjects was 27 years in the NUVARING group and 29 years in the control group.

For the NUVARING group, the BMD for lumbar spine and femoral neck were not statistically different from baseline after two years of follow-up (change in z-score was –0.093 and –0.048, respectively). In the control group, a slight increase of BMD for both the lumbar spine and femoral neck was observed (change in z-score of 0.257 and 0.223, respectively). At the end of 2 years, there was a statistically significant difference in the change of BMD from baseline, between the NUVARING group and the control group.

No adverse effects on bone mass have been observed.

Other Studies

Microbiological changes were investigated in a specific safety study (n=58, 13 cycles). The majority of these findings, based on Nugent scores, were Grade I (normal) at screening, at Cycle 6 and at last assessment, and more subjects showed improvement than worsening. No subjects showed a shift from Grade I at screening to Grade III (bacterial vaginosis) at Cycle 6. The majority of vaginal colposcopy observations were normal at screening, at Cycle 6 and at last assessment. The frequency of normal to abnormal changes was low and an equal number of subjects showed abnormal to normal changes. No adverse effects on the cervix and the vagina were found.

Overall Safety

Data from all clinical studies (n=2,501) with NUVARING showed that it is generally safe and well tolerated. Approximately 15% of NUVARING-treated subjects in all clinical studies with NUVARING discontinued

due to an adverse event, primarily due to the ring-specific-adverse events, device-related problems and vaginal discomfort. The most commonly reported adverse events (≥5%) were vaginitis, headache, upper respiratory tract infection, leukorrhea, sinusitis, and nausea. There did not appear to be an increased incidence of these adverse events with long-term NUVARING treatment, and there were no clinically meaningful differences in the incidence of these common adverse events that could be attributed to differences in demographic characteristics age, body mass index, race, and starter/switcher status. There were no clinically relevant changes from baseline in blood chemistry, hematology, or heart rate measurement.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Acute Toxicity Studies

Acute toxicity studies were conducted in rats and in mice using the oral and intraperitoneal route. Etonogestrel (ENG) was dosed orally by gavage (2,000 mg/kg) or intraperitoneally by injection (500 mg/kg). No mortalities occurred at the dose levels used. This is in agreement with published data indicating that natural and synthetic sex steroids, in general, exert low toxic activity in animals.

Chronic Toxicity Studies

The chronic toxicity studies comprised of exposure to ENG by oral administration in rats (52 weeks) and dogs (26 weeks). In rats oral dosages of up to ~70 times and in dogs up to ~160 times the anticipated average human daily dose were administered. In general, ENG induced a pattern of endocrinological changes, in particular in the genital organs and the accessory glands in rats as well as in dogs. These changes were dose-related, generally reversible and they were to be expected on the basis of the hormonal activity of ENG. Studies in rats for up to 2 years and in dogs for up to 5.8 years using ENG-containing implants also revealed no systemic or local abnormalities considered to be related to ENG or the implant. These chronic toxicity studies showed that ENG lacks intrinsic toxic properties. This is consistent with the observation that ENG is the biologically active metabolite of desogestrel (DSG).

Special toxicity studies were performed in monkeys for up to 3 months using either suppositories, vaginal rings, or oral formulations containing ENG and ethinyl estradiol (EE). The results showed that treatment with ENG and EE at intravaginal dose levels up to about 25 times and oral dose levels up to 100 times the anticipated human vaginal dose did not induce overt signs of toxicity. Long-term exposure of monkeys to a placebo ethylene vinylacetate (EVA) copolymer-containing ring was also shown to be devoid of local or systemic effects. All effects could be ascribed to the pharmacological effects of the steroids released by the ring. These observations confirm the suitability of NUVARING for human vaginal use.

Additional studies were performed in which several components of the combined contraceptive vaginal ring were tested via a non-vaginal route. Extracts of EVA material caused neither sensitization nor irritation upon direct contact with tissues of mice and guinea pigs in vivo. Implantation of the EVA material (with or without ENG) caused no toxic, irritation or sensitizing effects in rabbit, rat and dog. Potentially leachable components, when extracted in conformity with ISO guidelines were not cytotoxic under in vitro conditions.

The carcinogenic potential of ENG and the EVA copolymer was assessed in rats by using subdermal EVA-

containing implants continuously releasing ENG, up to 40 times the human vaginal dose, for a period of 2 years. Several assessments i.e., physical observations, body weight, food consumption, hematology, macroscopic post-mortem examinations and histopathological evaluation (55 tissues including the implant site) were performed. The data showed that EVA-containing implants continuously releasing ENG lack tumorigenic properties.

Since etonogestrel is the biologically active metabolite of desogestrel and since the metabolic profiles of the two compounds are very similar supportive evidence can be obtained from carcinogenicity studies previously performed with desogestrel. In these studies desogestrel was orally administered for 81 weeks either to mice at dose levels of 2x, 20x and 200x the human desogestrel dose or to rats for 104 weeks. In neither study were neoplastic changes observed. The conclusion that desogestrel and therefore etonogestrel was non-carcinogenic can also be derived from studies previously performed in rats, dogs and monkeys using oral administration of the combination of desogestrel and ethinyl estradiol. In these studies mice and rats were treated for 80 weeks and 104 weeks, respectively at dose levels 2x, 20x and 200x the human dose. Pituitary tumor and mammary tumor induction observed in mice and rats in those studies was fully ascribed to the estrogenic component. Dogs were treated for 3 years at dose levels 2x, 10x and 25x the anticipated human dose and monkeys for 3 years at dose levels 2x, 10x and 50x the human dose. In these species only the expected non-neoplastic changes were observed and no tumorigenic effects were seen. In conclusion, chronic toxicity and tumorigenicity studies demonstrated that there is no evidence of carcinogenicity of ENG, EE or the EVA copolymer.

Genotoxicity: Studies with etonogestrel also found no genotoxicity 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.

Reproductive and Developmental Toxicology: Reproductive toxicity studies were carried out in rats (Segment I and Segment II) and in rabbits (Segment II). Since pregnancy is a contraindication for the use of the vaginal ring no Segment III studies have been performed. The dose applied is approximately 500 times the anticipated average daily vaginal human dose. Treatment did not have any adverse effect on resulting litter parameters (after cessation of treatment), indicating no effect of ENG on the return of fertility after suppression with ENG. In rats and rabbits, at dosages up to ~250 times the anticipated human dose, ENG was neither embryotoxic nor teratogenic. Previous data reported using DSG support this conclusion. Thus, based on historical data on desogestrel and on recent data on ENG, it was concluded that ENG is devoid of reproductive toxicological hazards.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]NUVARING®

etonogestrel/ethinyl estradiol slow release vaginal ring

Read this carefully before you start taking NUVARING and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about NUVARING.

Serious Warnings and Precautions

- Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels. This risk increases with age, particularly in women over 35 years of age. The risk also increases with the number of cigarettes smoked. For this reason, women who smoke and are over 35 years of age should not use NUVARING.
- NUVARING DOES NOT PROTECT against sexually transmitted infections (STIs), including HIV/AIDS. For protection against STIs, it is advisable to use latex or polyurethane condoms while using NUVARING.

What is NUVARING used for?

NUVARING (NEW-vah-ring) is a flexible contraceptive vaginal ring used to prevent pregnancy in women who have had their first menstrual period (menarche).

How does NUVARING work?

NUVARING is considered to be a combination hormonal contraceptive (CHC). This is because it contains two female sex hormones, etonogestrel (a progestin) and ethinyl estradiol (an estrogen). NUVARING has been shown to be effective in preventing pregnancy when used as prescribed by your healthcare professional.

CHCs, like NUVARING works in two ways:

1. To stop the monthly release of an egg by the ovaries.
2. To change the mucus produced by your cervix. This slows the movement of the sperm through the mucus and through the uterus.

Effectiveness of NUVARING:
NUVARING is 98 to 99% effective at preventing pregnancy. This means that, for every 100 women who use NUVARING for a year, about one or two will become pregnant. Your chance of becoming pregnant increases if NUVARING is not used correctly.

Other ways to prevent pregnancy:
There are other methods of birth control available. These are usually less effective than contraceptive vaginal rings. If used properly, the other methods of birth control are effective enough for many women. The following table lists pregnancy rates for different types of birth control, including no birth control. A pregnancy rate is the number of women out of 100 who would become pregnant in one year.

Reported Pregnancies per 100 Women per Year

Subdermal implant	less than 1

Combination pill	less than 1 to 2
Contraceptive vaginal ring	between 1 and 2
Intrauterine device (IUD)	less than 1 to 6
Condom with spermicidal foam or gel	1 to 6
Mini-pill	3 to 6
Condom	2 to 12
Diaphragm with spermicidal foam or gel	3 to 18
Spermicide	3 to 21
Sponge with spermicide	3 to 28
Cervical cap with spermicide	5 to 18
Periodic abstinence (rhythm), all types	2 to 20
No birth control	60 to 85

There are differences in these pregnancy rates. This is because not all people use birth control as carefully or as regularly as they should. This does not apply to subdermal implants or IUDs since these are implanted under the skin or in the uterus, respectively. If you are careful and use your birth control regularly, pregnancy rates should be lower. Some types of birth control will require more effort that inserting a vaginal ring once a month. Hormonal birth control (such as NUVARING) has advantages over other methods of birth control. They also have certain risks that other methods do not. Talk to your healthcare professional about the advantages and risks.

What are the ingredients in NUVARING?

Medicinal ingredients: etonogestrel and ethinyl estradiol

Non-medicinal ingredients: ethylene vinylacetate copolymers and magnesium stearate. NUVARING is not made with natural rubber latex.

NUVARING comes in the following dosage forms:

Slow-release vaginal ring – 11.4 mg etonogestrel / 2.6 mg ethinyl estradiol to deliver 120 mcg etonogestrel / 15 mcg ethinyl estradiol per day.

Do not use NUVARING if:

- you are allergic to any ingredients in this drug.
- you have or have had a blood clot in the legs (deep vein thrombosis), lung (pulmonary embolism), eyes, or somewhere else in your body.
- you have the following risk factors for blood clots:
    - severe high blood pressure or high blood pressure that is not under control (hypertension)
    - blood clot disorders such as:
        - Abnormal Factor V Leiden mutation
        - Activated protein C (APC) resistance

        - Antithrombin-III-deficiency
        - Protein C deficiency
        - Protein S deficiency
        - hyperhomocysteinemia
        - Antiphospholipid-antibodies
    - you have an unusual amount of lipoproteins in your blood
    - you have diabetes with complications
    - you have too much body fat (you are obese)
    - you have a family history of blood clot disorders
    - you had or will have major surgery (including to the legs, pelvis or nervous system)
    - you cannot stand or move for longer periods of time, including prolonged bed rest
    - you are a woman over age 35 and smoke
- you have had a stroke or heart attack.
- you have or had coronary artery disease (including angina) or a condition that may be a first sign of stroke (such as mini stroke, small reversible stroke, chest pains).
- you have a disease of the heart valves with complications.
- you might have breast cancer.
- you have a cancer of the uterus, or a cancer that is sensitive to hormones.
- you have or had a history of liver tumors (cancerous or non-cancerous).
- you have or had jaundice. This is when the skin or whites of the eyes turn yellow. This may have been related to other medicines you were taking or may have happened during pregnancy.
- you have liver disease
- you have hepatitis C virus (HCV) and are taking the combination drug regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir, or some other Hepatitis C drug combinations (such as glecaprevir/ pibrentasvir).
- you have a blood vessel disease of the eye that has caused loss of vision.
- you are or think you might be pregnant.
- you have or have had migraine headaches with or without focal aura (flashes of light, blind spots and other vision changes).
- you have unusual vaginal bleeding without a known reason.
- you have or have had inflammation of the pancreas (pancreatitis) and high levels of fat in your blood (triglycerides).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take NUVARING. Talk about any health conditions or problems you may have, including if you:

- have had or will be having major surgery
- have a family history of blood clot disorders, heart attacks or strokes
- have or had a family history of diabetes
- are obese
- have high blood pressure
- have abnormal levels of fats in the bloodstream (high cholesterol or triglycerides)
- are a cigarette smoker
- have migraine headaches
- have a history of kidney problems
- have problems with the valves in your heart and/or irregular heartbeat
- have a history of seizures or have epilepsy

- have a history of depression
- have uterine fibroids. These are benign tumors of the uterus.
- have gallbladder or pancreatic disease
- have a history of liver problems
- have a condition called hereditary or acquired angioedema or if you have had episodes of swelling in body parts such as hands, feet, face, eyes or airway passages
- have inflammatory bowel disease including Crohn's disease or ulcerative colitis
- have sickle cell disease. This is a disease that affects hemoglobin, a molecule in red blood cells that delivers oxygen throughout the body.
- have hemolytic uremic syndrome. This is when there is an abnormal breakdown of blood cells, which clog the kidney.
- have systemic lupus erythematosus. This is a disease of the immune system that affects your joints, skin, kidneys, blood cells, brain, heart and lungs.
- have cholestasis. This is a condition where the bile flow from the liver is decreased.
- have porphyria. This is a disease of blood pigment that is passed down in families (inherited).
- have a skin condition called chloasma (hyperpigmentation)

Other warnings you should know about:

Growth of vaginal tissue over NUVARING

NUVARING may not be suitable for you if you have a condition that makes the vagina more susceptible to irritation or ulceration. Very rarely, vaginal tissue may grow over the ring. If this happens, it will need to be removed by your healthcare professional. In some cases where tissue had grown over the ring, NUVARING was removed by cutting the ring and not the overlying vaginal tissue.

Blood clot in legs, lungs, heart, eyes or brain

Women who use birth control that contains hormones are more likely to develop blood clots. Blood clots are the most common serious side effect of CHCs like NUVARING. The risk for blood clots is highest during the first year a woman uses hormonal birth control. The risk is also high if a woman restarts the same or new hormonal birth control. Clots can occur in many areas of the body and can lead to blindness or impaired vision as well as damage to or loss of a limb and death.

While you are using NUVARING, if you have any of the below symptoms, talk to your healthcare professional right away. These are signs of blood clots.

- sharp pain in your chest
- coughing up blood
- sudden shortness of breath
- crushing chest pain or chest heaviness
- irregular heartbeat
- sudden severe or worsening headache
- feeling full
- vomiting
- dizziness, trouble walking
- fainting, seizures
- anxiety, confusion
- changes in vision
- changes in speech

- pain and / or swelling in your calf
- weakness or numbness in your face, arm or leg
- sudden pain, swelling and slight blue or red discolouration of an arm or leg
- discomfort radiating to your back, jaw, throat or stomach

Blood clots can develop whether or not you are using hormones for birth control. They can also happen if you are pregnant. The risk is higher in users of CHCs, including NUVARING than in non-users, but it is not as high as the risk during pregnancy. You should talk to your healthcare professional about the available options.

Cancer

Using hormonal birth control may increase the risk of certain cancers including cancer of the breast, cervix and liver.

Breast cancer: The risk of breast cancer in women increases as you get older. It also increases if there is family history of breast cancer, meaning if your mother or sister have or had breast cancer. Other factors that increase your risk for breast cancer are being obese, never having children, or having your first full-term pregnancy at a late age.

If you have breast cancer now, or had it in the past do not use NUVARING. The hormones in NUVARING can affect some cancers.

Some women who use CHCs may have a higher risk of developing breast cancer before menopause. These women may have used hormonal birth control for a long time (more than eight years), or may have started using hormonal birth control at an early age.

In a few women, using hormonal birth control can speed up the growth of a breast cancer that has not yet been found. Finding breast cancer early can reduce the effect of the cancer on a woman's life expectancy. The risks for breast cancer related to using hormonal birth control seems to be small. You should, however, have a healthcare professional check your breasts at least once per year.

While you are using NUVARING, check your breasts often. See your healthcare professional if you notice any changes, such as:

- dimpling or sinking of the skin
- changes in the nipple
- any lumps you can see or feel

Cervical cancer: Women who use hormonal birth control may have a higher chance of getting cervical cancer. However, this may be due to other reasons including infection with the Human Papilloma Virus (HPV). HPV is an important risk factor for cervical cancer. However, it is possible that hormonal birth control may also cause such cancers.

Liver cancer: Liver cancer (hepatocellular carcinomoa) and liver tumors may be linked to hormonal birth control. The risk for liver cancer increases the longer you use hormonal birth control. However liver tumours are extremely rare. If you feel severe abdominal pain or find a lump in your abdomen, talk to your healthcare professional right away.

Do not use NUVARING if you have a history of liver tumours (cancerous or non-cancerous).

Gallbladder disease

The risk for gallbladder disease that needs surgery is higher in women using hormonal birth control. The risk is highest in the first year of use and increases the longer the hormonal birth control is used.

Vaginal bleeding

Breakthrough bleeding or spotting sometimes happens in women using CHCs including NUVARING. This is blood coming from the vagina between periods. It is most likely to happen in the first months of starting NUVARING. If the bleeding is heavy or does not stop, talk to your healthcare professional.

While you are using NUVARING you may not get your period each month. If you were not using NUVARING as directed by your healthcare professional, you should have a pregnancy test. This will rule out if the missed period is because you are pregnant.

Pregnancy, Breastfeeding, Miscarriage and Abortions

Use in pregnancy: Hormonal birth control should not be used by pregnant women. Stop using NUVARING if you get pregnant. You should check with your healthcare professional about risks to your unborn child from any medication taken during pregnancy.

Use after pregnancy, miscarriage or an abortion: Your healthcare professional will tell you when to start using NUVARING after childbirth, miscarriage or an abortion.

Use while breastfeeding: if you are breastfeeding, talk to your healthcare professional before staring to use NUVARING. Other types of birth control that do not contain hormones are recommended until your baby has stopped breastfeeding. The hormones in NUVARING may lower the amount and quality of your breast milk. This may not happen however, if you wait until after breastfeeding is established.

Pregnancy after stopping NUVARING: You will have a menstrual period when you stop using NUVARING. Wait until after your next period before getting pregnant. This will help to better date the pregnancy. Talk to your healthcare professional about other forms of birth control you can use during this time.

NUVARING Disconnection/Breakage

Very rarely, NUVARING may break. A broken ring is unlikely to cause an overdose because the ring will not release a higher amount of hormones. There have been reports that the broken ring has caused vaginal injury. If NUVARING breaks, it is more likely to be expelled (fall out) of your vagina (see '**What should I do if NUVARING disconnects?**'). If you notice that your NUVARING has broken, remove that ring and discard it. Replace it with a new ring as soon as possible.

Risk to your Partner

The effects of hormones released by NUVARING on male partners during sexual intercourse have not been studied. There have been reports of male partners experiencing penis discomfort such as pain, rash, bruising, rubbing or scraping. Talk to your healthcare professional if you or your male partner have any concerns.

Skin conditions

Chloasma may develop while you are using NUVARING. This appears as yellowish-brown patches on the skin, particularly of the face. It is more likely to happen if you have previously had chloasma gravidarum. This is when these patches appear on the skin of the face during pregnancy. This is commonly known as "the mask of pregnancy". If you have or had chloasma, avoid too much exposure to the sun while using NUVARING.

Surgery

Tell your healthcare professional if you are scheduled for surgery. You may need to stop using NUVARING one month before surgery and during prolonged bedrest. You may need to wait until you get your first menstrual period after surgery before restarting NUVARING.

Check-ups and tests

Before you start using NUVARING, you will need to have examinations and tests. Your healthcare professional will conduct a physical exam. They will examine your breasts, liver, arms and legs. They will conduct a pelvic exam which includes a PAP smear. Your healthcare professional will also ask you some questions about your personal health history and that of your close relatives. They will also measure your blood pressure and do blood tests.

While you are using NUVARING, you will need to have regular check-ups with your healthcare professional. Your first check up should be about three months after you start using NUVARING. Afterward, you will see your healthcare professional about once per year. At these visits, your healthcare professional will conduct physical and internal exams. They will also measure your blood pressure and do blood tests.

If you are scheduled for any laboratory tests, be sure to tell your healthcare professional that you are using NUVARING. This is because hormonal birth control can affect some blood tests.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Certain drugs may interact with hormonal birth control (including NUVARING) and prevent NUVARING from working properly. This can make them less effective in preventing pregnancy or cause unexpected bleeding (spotting or breakthrough bleeding). Hormonal birth control may also interfere with how other drugs work.

The following may interact with NUVARING:

- drugs used to treat epilepsy including lamotrigine, primidone, phenytoin, barbiturates, phenobarbital, carbamazepine, oxcarbazepine, topiramate, felbamate;
- drugs used to treat tuberculosis including rifampicin, rifabutin;
- drugs used to treat of HIV infections or AIDS including ritonavir, nelfinavir, nevirapine, efavirenz;
- drugs for Hepatitis C Virus infections including ombitasvir, paritaprevir, ritonavir, with or without dasabuvir, boceprevir, telaprevir, and some other Hepatitis C drug combinations (such as glecaprevir/ pibrentasvir);
- alpha-II adrenoreceptor agents including clonidine;
- drugs used to treat bacterial infections including nitrofurantoin, erythromycin, clarithromycin, chloramphenicol, neomycin, sulfonamides, troleandomycin;
- drugs used to treat fungal infections including griseofulvin, fluconazole, itraconazole, ketoconazole;
- drugs used to prevent blood clots (blood thinners);
- St. John's wort, an herbal product used to treat depression and other conditions;
- drugs used to treat high blood pressure including guanethidine, methyldopa, beta blockers, diltiazem;
- drugs used to treat high blood pressure in the blood vessels between the heart and lungs (pulmonary hypertension) including bosentan;
- drugs used to treat diabetes including insulin and oral drugs that lower blood sugar;
- drugs used to help you relax or sleep including barbiturates, glutethimide, meprobamate, lorazepam, oxazepam, diazepam, phenothiazines, reserpine;

- drugs used to treat depression including clomipramine;
- antacids used to treat indigestion;
- drugs used to treat fever, pain or inflammation including ASA, acetaminophen, meperidine, prednisone, phenylbutazone;
- drugs used to treat migraine headaches;
- drugs used to treat allergies;
- drugs used to lower cholesterol levels including clofibrate;
- drugs used to help prevent organ rejection including cyclosporine;
- folic acid, Vitamin E and Vitamin B12;
- a drug used to help treat bleeding called aminocaproic acid;
- drugs used to treat lung diseases such as asthma and COPD (bronchitis, emphysema) including betamimetic agents (e.g., isoproterenol), theophylline.

The effects of caffeine and alcohol may be increased. This is because hormonal birth control affects how they are metabolized.

If you are taking medicines or herbal products that might make NUVARING less effective, a barrier method of birth control should also be used. Since the effect of other medicines on NUVARING may last up to 28 days after stopping the medicine, you must use the additional barrier method of birth control for that long.

Do not use NUVARING if you have Hepatitis C and are being treated with ombitasvir / paritaprevir / ritonavir, with or without dasabuvir, or some other Hepatitis C drug combinations (such as glecaprevir/ pibrentasvir). Using these drugs at the same time as NUVARING can cause problems with your liver, such as an increase in the ALT liver enzyme. You can usually start using NUVARING about 2 weeks after finishing treatment with these combination drugs used for Hepatitis C, but talk to your healthcare professional before using NUVARING.

Can I use tampons when using NUVARING?

The blood levels of the hormones released by NUVARING were not changed when women used tampons along with NUVARING. It is unknown how this affects the safety and the pregnancy protection of NUVARING. Insert NUVARING before inserting a tampon. You should pay particular attention when removing a tampon to be sure that the ring is not accidentally pulled out. If this happens, simply rinse the ring in cool to lukewarm (not hot) water and immediately reinsert it.

Regularly check that NUVARING is in your vagina to ensure that you are protected from pregnancy.

Can I use vaginal medications?

The blood levels of the hormones released by NUVARING were not changed when women used vaginal, water-based spermicides (nonoxynol or N-9 products) along with NUVARING.

The blood levels of the hormones released by NUVARING were increased when women used either an oil-based or water-based vaginal medication (miconazole nitrate) for a yeast infection while NUVARING was in place. Therefore, this may also happen with other yeast infection medications. The clinical relevance of this increase is unknown. It is unknown how long-term use of spermicide or yeast infection medication with NUVARING affects the safety and the pregnancy protection of NUVARING.

Ring breakage has occurred when also using a vaginal product such as a lubricant or treatment for infection. If you notice that your NUVARING has broken, remove that ring and discard it. Replace it with a new ring as soon as possible.

How to use NUVARING:

- **Be sure to read these instructions:**
  - before you insert NUVARING for the first time, and
  - anytime you are not sure what to do.
- For the best protection from pregnancy, use NUVARING exactly as directed by your healthcare professional.
- Do not use NUVARING for a condition for which it was not prescribed. Do not give NUVARING to anyone else who may want to use it.
- You should not use a NUVARING if it was dispensed to you more than 4 months before or if the expiry date has passed. The dispensing date and expiry date are both shown on the carton and sachet.
- Do not use the ring if you notice a color change in the ring or any visible signs of deterioration.
- While using NUVARING, you should not use certain female barrier methods of birth control such as vaginal diaphragm, cervical cap or female condom as your back-up method of birth control. NUVARING may interfere with the correct placement and position of a diaphragm, cervical cap or female condom.

When should I start NUVARING?

Decide with your healthcare professional on the best day for you to start using NUVARING then follow the instructions in the section below:

<u>If you did not use a hormonal birth control in the preceding cycle</u>

Insert NUVARING within the first five days of your cycle (i.e., Day 1-5 of the menstrual bleeding). Make sure you also use an extra method of birth control (barrier method), such as male condoms or spermicides during the first seven days of NUVARING use in your first cycle.

<u>If you are switching from a combined hormonal contraceptive containing both progestin and estrogen</u>

Switch from your previous CHC by inserting NUVARING on any day, but at the latest on the day you would have started a new cycle. If you have been using your hormonal method of birth control consistently and correctly, no extra birth control method should be needed.

<u>If you are switching from a progestin-only contraceptive (mini-pill, implant, injection, or from a progestogen-releasing intra-uterine system {IUS})</u>

- When switching from a mini-pill, you can stop using the pill on any day of the month and switch to NUVARING. Insert NUVARING on the day immediately after your last pill.
- When switching from an implant, progestin-containing IUS or injectable contraceptive, start using NUVARING on the same day you have your implant or IUS removed or on the day your next injection is due.

When you are switching from a progestin-only contraceptive, use an extra method of birth control, such as a male condom and/or spermicide, for the first seven days after inserting NUVARING.

How do I insert NUVARING?

1. After washing and drying your hands, remove NUVARING from its foil pouch. Keep the foil pouch for proper disposal of the ring after use. Choose a position that is most comfortable for you (e.g., Figure 1).

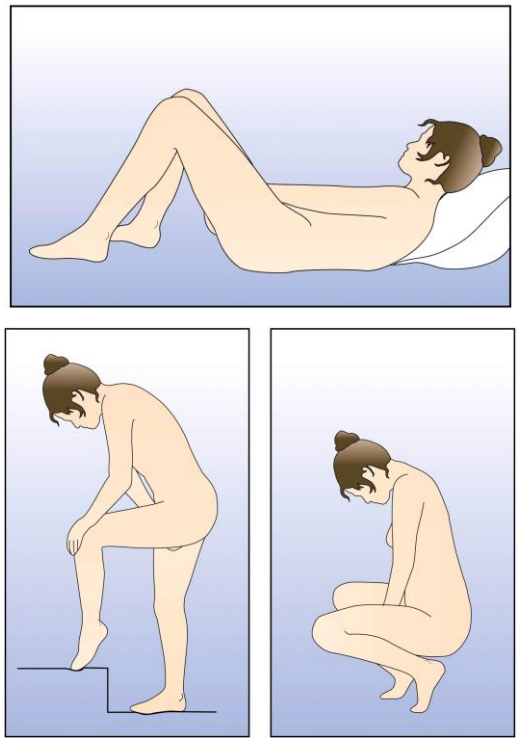


Figure 1: Positions for NUVARING insertion

2. Press the sides of NUVARING together between your thumb and index finger (Figure 2) and gently push the folded ring into your vagina (Figure 3). The exact position of NUVARING in the vagina is not important for it to work.

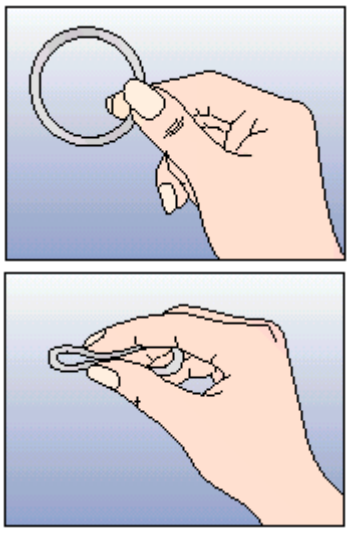


Figure 2: Holding NUVARING and pressing the sides together.

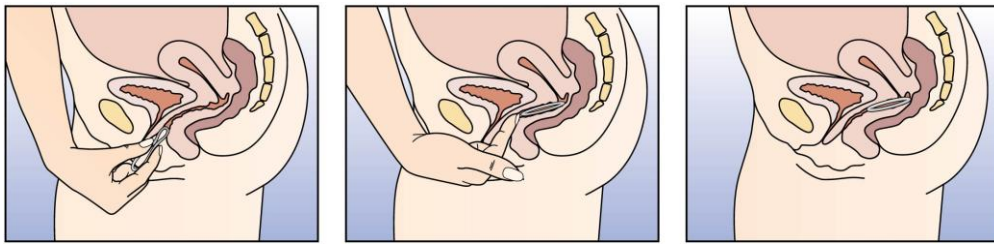


Figure 3: Inserting NUVARING.

Although some women may be aware of NUVARING in the vagina, most women do not feel it once it is in place. If you feel discomfort, change the position of the NUVARING (i.e., use your finger to gently push NUVARING further into your vagina) until it is comfortable. **There is no danger of NUVARING being pushed too far up in the vagina or getting lost.**

3. Once inserted, keep NUVARING in place for three weeks in a row.

How do I remove NUVARING?

1. Remove the ring three weeks after insertion on the same day of the week as it was inserted, at about the same time. For example, when NUVARING is inserted on a Sunday at about 10:00 PM, the ring should be removed on the Sunday three weeks later at about 10:00 PM.

   Remove NUVARING by hooking the index finger under the forward rim or by holding the rim between the index and middle finger and pulling it out (Figure 4).

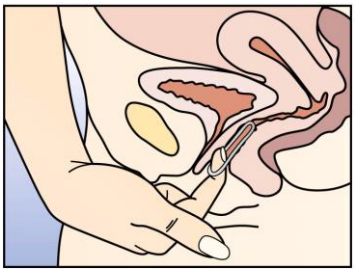


Figure 4

2. Place the used ring in the reclosable foil pouch and properly dispose of it in a waste receptacle, out of the reach of children and pets. Do not throw it in the toilet.

If you are unable to remove NUVARING, please contact your healthcare professional.

Your menstrual period will usually start two to three days after the ring is removed and may not have finished before the next ring is inserted. **To continue to have pregnancy protection, you must insert the new ring one week after the last one was removed, even if your menstrual period has not stopped.**

When do I insert a new ring?

After a one-week ring-free break, insert a new ring on the same day, at the same time of the week as it was removed in the last cycle. For example, if NUVARING was removed on a Sunday at about 10:00 PM, after the one-week break you should insert a new ring on a Sunday at about 10:00 PM.

If NUVARING is in your vagina too long:

If NUVARING has been left in your vagina for an extra week or less (up to four weeks total), you will

remain protected. Remove NUVARING and insert a new ring after a one-week ring-free break.

If NUVARING has been left in place for more than four weeks total, there is a possibility that you could become pregnant. You must rule out pregnancy before inserting a new NUVARING. You must use an extra method of birth control, such as male condom and/or spermicide, until the new NUVARING has been in place for seven days in a row.

What should I do if NUVARING disconnects?

On rare occasions, NUVARING may disconnect at the weld joint during use. Since the ring's core is solid its contents will remain intact and release of hormones will not be significantly affected. Vaginal injury associated with ring breakage has been reported. If NUVARING does disconnect, expulsion (slipping out) is likely to occur (see **If NUVARING slips out**). If you discover the ring has disconnected you should discard the ring and replace it with a new ring.

How to change the NUVARING start day to another day of the week:

If you wish to change the day on which you start a new NUVARING cycle to another day of the week, complete the current cycle, removing NUVARING on the same day of the week as the one on which you started. During the ring-free period, a new start day may be selected by inserting the new NUVARING on the first occurrence of the desired day. This will be your new Day 1. In no case should there be more than 7 consecutive ring-free days.

The shorter the ring-free interval, the higher the risk that you do not have a period from your previous cycle. However, spotting or bleeding may occur during the use of the next ring. This practice is for a one-time only change and should not to be used as a standard dosing regimen, as there are no long-term safety data available on the continuous use of NUVARING.

If you miss a menstrual period:

You must check to be sure that you are not pregnant if:

1. you miss a period and NUVARING was out of the vagina for more than three hours during the three weeks of ring use
2. you miss a period and you had waited longer than one week to insert a new ring
3. you have followed the instructions and you miss two periods in a row
4. you have left NUVARING in place for longer than four weeks

Usual dose:

Insert one NUVARING in the vagina and keep it in place for three weeks in a row. Remove it for a one-week break and then insert a new ring. During the one-week break, you will usually have your menstrual period.

Overdose:

Overdose of CHCs may cause nausea, vomiting, vaginal bleeding, or other menstrual irregularities. Given the nature and design of NUVARING it is unlikely that overdose will occur. If NUVARING is broken, it does not release a higher dose of hormones.

If you think you, or a person you are caring for, have taken too much NUVARING, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If NUVARING slips out:

NUVARING can slip out of the vagina if it has not been inserted properly, or while removing a tampon, during intercourse or straining during a bowel movement. Women with conditions affecting the vagina, such as a prolapsed uterus, may be more likely to have NUVARING slip out of the vagina. Therefore, it is a good habit to regularly check whether the ring is still in your vagina (for example, before and after intercourse).

If NUVARING was out of the vagina for:

- **less than three hours**, you should still be protected from pregnancy. NUVARING can be rinsed with cool to lukewarm (not hot) water and should be re-inserted as soon as possible, and at the latest within three hours of expulsion (slipping out). If you have lost NUVARING, you must insert a new NUVARING and use it on the same schedule as you would have used the lost ring.
- **more than three hours during the 1st or 2nd week**, you may not be adequately protected from pregnancy. You should rinse the ring with cool to lukewarm (not hot) water. Re-insert the ring as soon as you remember and use an extra method of birth control, such as male condoms or spermicides, until the NUVARING has been in place continuously for seven days in a row.
- **more than 3 hours during the 3rd week**, you may not be adequately protected from pregnancy. Throw the ring away and choose one of the following two options:
  1. Insert a new ring immediately. Note: Inserting a new ring will start the next three-week use period. You may not experience a period from your previous cycle. However, breakthrough spotting or bleeding may occur.
  2. Have your period and insert a new ring no later than 7 days from the time the previous ring was removed or expelled. Note: This option should only be chosen if the ring was used continuously for the preceding 7 days.

In addition, a barrier method of birth control such as a male condom and/or spermicides must be used until the new ring has been used continuously for seven days.

If NUVARING was out of the vagina for:

- **unknown amount of time**, you may not be protected from pregnancy. Perform a pregnancy test and talk to your healthcare professional before inserting a new ring.

If the ring-free period is extended:

If the ring-free interval has been extended beyond one week, the possibility of pregnancy should be considered and an extra method of birth control, such as male condoms or spermicide MUST be used until NUVARING has been used continuously for seven days.

Talk to your healthcare professional immediately. The longer the ring-free interval, the higher the risk that you have become pregnant.

What are possible side effects from using NUVARING?

These are not all the possible side effects you may have when using NUVARING. If you experience any side effects not listed here, tell your healthcare professional.

The following side effects may occur:

- headache
- vaginal discomfort (e.g., vaginal secretion)
- weight increase

- nausea
- breast pain
- painful menstruation
- acne
- decreased libido
- abdominal pain
- migraine
- expulsion of the ring
- problems during intercourse and feeling of the ring
- itching in the genital area
- rash
- inflammation of the cervix
- urinary tract infection
- dizziness
- anxiety
- diarrhea and vomiting
- breast discharge
- back pain
- enlarged abdomen
- fatigue
- vaginal injury associated with broken rings

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Remove the ring and get immediate medical help**
	Only if severe	**In all cases**	
UNCOMMON			
Arterial thromboembolism, Myocardial infarction (blood clot in the artery, heart attack): sudden pain, discomfort, pressure, heaviness, sensation of squeezing or fullness in the shoulder, chest, arm, or below the breastbone; discomfort radiating to the back, jaw, throat, arm, stomach, feeling of being full, having indigestion or choking; sweating, nausea, vomiting or dizziness; extreme weakness, anxiety, or shortness of breath; rapid or irregular heartbeats			√
Blood clot in the eye: sudden partial or complete loss of vision			√

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Remove the ring and get immediate medical help**
	Only if severe	**In all cases**	
Breast lumps, breast tumors, breast cancer			√
Deep vein thrombosis (blood clot in the leg): swelling of one leg or one foot, pain or tenderness in the leg, difficulty standing or walking, feeling of warmth in the leg, red or discolored skin on the leg, sudden pain, swelling and slight blue discolouration of an extremity			√
Depression: persistent sad mood accompanied by difficulty sleeping, weakness, lack of energy, fatigue			√
Edema: unusual swelling of the extremities			√
Gallbladder disease: pain on the upper right side of the abdomen, especially after meals, loss of appetite, nausea, vomiting, fever		√	
High blood pressure: chest pain, headaches, vision problems, nosebleeds, irregular heartbeat		√	
Inadvertent insertion of NUVARING into the urinary bladder: burning and/or painful urination, urinary urgency and/or frequency, and cannot locate the ring in the vagina		√	
Jaundice: yellowing of the skin or eyeballs, accompanied frequently by fever, fatigue, loss of appetite, dark-coloured urine or light-coloured bowel movements			√
Liver tumor: lump in the abdomen or severe pain			√
Pulmonary embolism (blood clot in the lung): coughing blood, sharp pain in chest, or sudden shortness of breath			√
Stroke: sudden severe headache or vomiting, dizziness or fainting, disturbances of vision of speech,			√

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Remove the ring and get immediate medical help**
	Only if severe	**In all cases**	
weakness or numbness in an arm or leg			
UNKNOWN			
Allergic reaction (hypersensitivity, angioedema): rash or hives, swelling of the face, lips, tongue and/or throat, difficulty swallowing or breathing, feeling sick to your stomach and throwing up			√
Vaginal bleeding changes: increased or decreased menstrual bleeding, spotting or bleeding between periods, infrequent periods or absence of bleeding	√		
Vaginal infection: itching or unusual or increased vaginal discharge	√		

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store NUVARING at room temperature (2–30°C). Protect from light.

Do not use a NUVARING if it was dispensed to you more than 4 months ago. The dispensing date is shown on the box.

Do not use NUVARING after the expiry date which is shown on the box.

Do not use NUVARING if you notice a color change in the ring or any visible signs of deterioration.

Keep out of reach and sight of children and pets.

If you discover that a child has been exposed to the hormones from NUVARING, talk to your healthcare professional.

If you want more information about NUVARING:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.organon.ca, or by calling 1-844-820-5468.

This leaflet was prepared by Organon Canada Inc.

Last Revised: NOV 15, 2024