

PRODUCT MONOGRAPH

PrNUVARING[®]

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

FOR VAGINAL USE ONLY

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Date of Preparation:
February 7, 2011

Date of Revision:

Submission Control No: 144642

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PrNUVARING®

etonogestrel/ethinyl estradiol slow release vaginal ring

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	Clinically Relevant Nonmedicinal 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 <i>For a complete listing see Dosage Forms, Composition and Packaging section</i>

INDICATIONS AND CLINICAL USE

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

- Conception control

CONTRAINDICATIONS

- Hypersensitivity to NuvaRing or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the Product Monograph.
- History of/or actual thrombophlebitis or thromboembolic disorders.
- History of/or actual cerebrovascular disorders.
- History of/or actual myocardial infarction or coronary arterial disease.
- Active liver disease or history of/or actual benign or malignant liver tumours.
- Known or suspected carcinoma of the breast.
- Known or suspected estrogen-dependent neoplasia.
- Undiagnosed abnormal vaginal bleeding.
- Any ocular lesion arising from ophthalmic vascular disease, such as partial or complete loss of vision or defect in visual fields.
- When pregnancy is suspected or diagnosed.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Women using NuvaRing (etonogestrel / ethinyl estradiol slow release vaginal ring) should be counselled that this product (as with other combined hormonal contraceptives) DOES NOT PROTECT against HIV infection (AIDS) and other sexually transmitted infections (STIs). For protection against STIs, it is advisable to use latex or polyurethane condoms IN COMBINATION WITH this product.

Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels. This risk increases with age and becomes significant in oral contraceptive-users over 35 years of age. Women who use combination hormonal contraceptives (including NuvaRing) should be counselled not to smoke

General

NuvaRing and other contraceptives that contain both an estrogen and a progestin are called combination hormonal contraceptives. Most of the warnings below are based on data obtained from the oral route of administration. There is no epidemiologic data available to determine whether the safety with the vaginal route of administration of combined hormonal contraceptives (such as NuvaRing) would be different than the oral route, and, in the absence of these comparable data, associated risks should be assumed to be similar for use through both routes.

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 combination hormonal contraceptives (including NuvaRing) and starters at early age. In a few women, the use of combination hormonal contraceptives (including NuvaRing) may accelerate the growth of an existing but undiagnosed breast cancer. Since any potential increased risk related to combination hormonal contraceptives (including NuvaRing) use is small, there is no reason to change prescribing habits at present.

Women receiving combination hormonal contraceptives (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 (COC's) 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.

Cardiovascular

Predisposing Factors for Coronary Artery Disease

Cigarette smoking increases the risk of serious cardiovascular side effects and mortality. Combination hormonal contraceptives (including NuvaRing), increase this risk, especially with increasing age.

Convincing data are available to support an upper age limit of 35 years for combination hormonal contraceptive 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 combination hormonal contraceptives, accentuate this risk is unclear.

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

Consequently, combination hormonal contraceptives 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 combination hormonal contraceptives (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 combination hormonal contraceptives (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 combination hormonal contraceptives. 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 combination hormonal contraceptives.

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.

Genitourinary

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. In some cases, vaginal (fibrous) tissue may grow over the ring, necessitating removal by a healthcare provider.

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 Ring

On rare occasions, NuvaRing has been reported to disconnect at the weld joint. Since the core of NuvaRing is solid, its contents will remain intact and release of hormone is unlikely to occur. In the event of a disconnected ring, expulsion (slipping out) is likely to occur (see “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 combination hormonal contraceptives (including NuvaRing).

Hematologic

Epidemiological studies have suggested an association between the use of combination oral contraceptives (COCs) and an increased risk of venous thrombotic and thromboembolic diseases.

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

- Venous thromboembolism (VTE), manifesting as deep vein thrombosis and/or pulmonary embolism, may occur during the use of all combined hormonal contraceptives, including NuvaRing. The approximate incidence of VTE in users of low estrogen dose (<0.05 mg EE) oral contraceptives is up to 4 per 10,000 women-years compared to 0.5 – 3 per 10,000 women-years in non-oral contraceptive users. The incidence of VTE associated with pregnancy is 6 per 10,000 women-years.

- 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 venous thromboembolism than certain second-generation oral contraceptives. These studies indicate an approximate 2-fold difference in risk, which corresponds to 1-2 cases of venous thromboembolism 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 venous thromboembolism in oral contraceptive users is rare.

Hepatic/Biliary/Pancreatic

Jaundice

Patients who have had jaundice including a history of cholestatic jaundice during pregnancy should be given combination hormonal contraceptives (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 combination hormonal contraceptives should not be resumed. In patients taking combination hormonal contraceptives, changes in the composition of the bile may occur and an increased incidence of gallstones has been reported.

Liver Disorders

Hepatic nodules (adenoma and focal nodular hyperplasia) have been reported, particularly in long-term users of combination hormonal contraceptives. 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.

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 combination hormonal contraceptives (including NuvaRing) and evaluation of the cause.

Ophthalmologic

Ocular Disease

Patients who are pregnant or are using combination hormonal contraceptives (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.

Peri-Operative Considerations

Thromboembolic Complications – Post-surgery

There is an increased risk of post-surgery thromboembolic complications in combination hormonal contraceptive (including NuvaRing) users, after major surgery. If feasible, combination hormonal contraceptives should be discontinued and an alternative method substituted at least one month prior to **MAJOR** elective surgery. Combination hormonal contraceptives should not be resumed until the first menstrual period after hospital discharge following surgery.

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 combination hormonal contraceptives (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 combination hormonal contraceptives, ranging from symptomatic improvement to worsening of the condition.

Sexual Function/Reproduction

Return to Fertility

After discontinuing combination hormonal contraceptive (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

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.

Special Populations

Pregnant Women: Combination hormonal contraceptives (including NuvaRing) should not be used by pregnant women. However, if conception accidentally occurs while using combination hormonal contraceptives, there is no conclusive evidence that the estrogen and progestin contained in combination hormonal contraceptives will damage the developing child.

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

Nursing Women: The effects of NuvaRing in nursing mothers have not been evaluated and are unknown. In breastfeeding women, the use of combination hormonal contraceptives results in the hormonal components being excreted in breast milk and may reduce its quantity and quality. If the use of combination hormonal contraceptives 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 combination hormonal contraceptives 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.

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.

Monitoring and Laboratory Tests

Physical Examination and Follow-up

Before combination hormonal contraceptives (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 combination hormonal contraceptives 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.

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.**

ADVERSE REACTIONS

Adverse Drug Reaction Overview

An increased risk of the following serious adverse reactions has been associated with the use of combination hormonal contraceptives (including NuvaRing):

- Thrombophlebitis
- Pulmonary embolism
- Mesenteric thrombosis
- Neuro-ocular lesions, e.g., retinal thrombosis
- Myocardial infarction
- Cerebral thrombosis
- Cerebral hemorrhage
- Hypertension
- Benign hepatic tumours
- Gallbladder disease
- Congenital anomalies

The following adverse reactions also have been reported in patients receiving combination hormonal contraceptives:

Nausea and vomiting, usually the most common adverse reaction, occurs in approximately 10% or less of patients during the first cycle. Other reactions, as a general rule, are seen less frequently or only occasionally, as follows:

- Gastrointestinal symptoms (such as abdominal cramps and bloating)
- Breakthrough bleeding
- Spotting
- Change in menstrual flow
- Dysmenorrhea
- Amenorrhea during and after treatment
- 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
- Migraine
- Increase in size of uterine leiomyomata
- Rash (allergic)
- Mental depression
- Reduced tolerance to carbohydrates
- Vaginal candidiasis
- Premenstrual-like syndrome
- Intolerance to contact lenses
- Change in corneal curvature (steepening)

- Cataracts
- Optic neuritis
- Retinal thrombosis
- Changes in libido
- Chorea
- Changes in appetite
- Cystitis-like syndrome
- Rhinitis
- Headache
- Nervousness
- Dizziness
- Hirsutism
- Loss of scalp hair
- Erythema multiforme
- Erythema nodosum
- Hemorrhagic eruption
- Vaginitis
- Porphyria
- Impaired renal function
- Raynaud's phenomenon
- Auditory disturbances
- Hemolytic uremic syndrome
- Pancreatitis

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The most common treatment-related AEs seen in all adequate and well-controlled pivotal clinical studies were headache, vaginitis, and leukorrhea (Table 1). These adverse events as well as the incidence of acne, breast tenderness, and nausea which are typical of contraceptives were low.

Table 1: Adverse events occurring in ≥1% of subjects in all adequate and well-controlled 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 (gynaecological)	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.

The incidence of adverse events was similar for the NuvaRing and COC groups (57.9% and 54.0%, respectively). The incidence of drug-related AEs was higher in the NuvaRing group than in the COC group (33.9% and 24.6%, respectively), partly due to the AEs 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 2).

Table 2: Adverse Events (at Least Possibly Related) Occurring in $\geq 2\%$ – Metabolic 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		

Less Common Clinical Trial Adverse Drug Reactions (<1% at least possibly related)

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

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

Musculo-skeletal system disorders – arthralgia, muscle weakness

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

Vision disorders – conjunctivitis, vision abnormal

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

Gastrointestinal system disorders – anus disorder, change in bowel habits, colitis ulcerative aggravated, constipation, diarrhoea, dyspepsia, flatulence, haemorrhoids, rectal disorder, tenesmus, vomiting

Liver and biliary system disorders – cholelithiasis, SGOT increased

Metabolic and nutritional disorders – dehydration, hypercholesterolaemia, hypertriglyceridaemia, oedema generalised, xerophthalmia

Endocrine disorders – estrogens increased, glucocorticoids increased, hypothyroidism

Cardiovascular disorders, general – hypertension, hypotension, oedema dependent

Heart rate and rhythm disorders – palpitation

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

Respiratory system disorders – asthma, dyspnoea, rhinitis

Red blood cell disorders – anaemia

Platelet, bleeding & clotting disorders – haematoma, purpura

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

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

Reproductive disorders, female – amenorrhoea, 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

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

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

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

Post-Market Adverse Drug 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%, see Warning and Precautions: Genitourinary).

DRUG INTERACTIONS

Overview

The concurrent administration of combination hormonal contraceptives (including NuvaRing) with other drugs may result in an altered response to either agent (Tables 3 and 4). Reduced effectiveness of combination hormonal contraceptives (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 combination hormonal contraceptives (including NuvaRing) are prescribed.

Table 3: Drugs Which May Decrease the Efficacy of Combination Hormonal Contraceptives (CHC)

Class of Compound	Drug	Proposed Mechanism	Suggested Management
Anticonvulsants	Carbamazepine Ethosuximide Phenobarbital Phenytoin Primidone	Induction of hepatic microsomal enzymes: Rapid metabolism of estrogen and increased binding of progestin and ethinyl estradiol to SHBG.	Use higher dose CHC (50 mcg ethinyl estradiol) another drug or another method.
Antibiotics	Ampicillin Cotrimoxazole Penicillin	Enterohepatic circulation disturbance, intestinal hurry.	For short course, use additional method or use another drug. For long course, use another method.
	Rifampicin	Increased metabolism of progestins. Suspected acceleration of estrogen metabolism.	Use another method.
	Chloramphenicol Metronidazole Neomycin Nitrofurantoin Sulfonamides Tetracyclines	Induction of hepatic microsomal enzymes. Also disturbance of enterohepatic circulation.	For short course, use additional method or use another drug. For long course, use another method.
	Troleandomycin	May retard metabolism of CHC increasing the risk of cholestatic jaundice.	
Antifungal	Griseofulvin	Stimulation of hepatic metabolism of contraceptive steroids may occur.	Use another method.
Sedatives and Hypnotics	Benzodiazepines Barbiturates Chloral hydrate Glutethimide Meprobamate	Induction of hepatic microsomal enzymes.	For short course, use additional method or another drug. For long course use another method or higher dose oral contraceptive.
Antacids		Decreased intestinal absorption of progestins.	
Other Drugs	Phenylbutazone Antihistamines Analgesics Antimigraine Preparations Vitamin E	Reduced contraceptive efficacy has been reported. Remains to be confirmed.	

Table 4: Modification of Other Drug Action by Oral 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	Fluid retention may increase risk of 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 renal clearance.	Dose of drug may have to be increased.
	Antipyridine	Impaired metabolism.	Decrease dose of drug.
	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.

Class of Compound	Drug	Modification of Other Drug Action	Suggested Management
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.	
Meperidine		Possible increased analgesia and CNS 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 .	

Several of the anti-HIV protease inhibitors have been studied with co-administration of oral combination hormonal contraceptives; significant changes (increase and decrease) in the mean AUC of the estrogen and progestin have been noted in some cases. 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 protease inhibitors for further drug-drug interaction information.

Drug-Drug Interactions

Interactions between contraceptive steroids and other drugs have been reported in the literature (see Overview).

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 pharmacokinetics of NuvaRing were evaluated in one cycle in 24 healthy female subjects randomized to a single-dose vaginal administration on Day 8 of 100 mg of a nonoxynol-9 spermicide gel or a 1,200 mg miconazole nitrate antimycotic capsule.

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.

In a separate trial, the pharmacokinetics of NuvaRing were evaluated in one cycle in 12 healthy female subjects randomized to 3 doses of an oil-based 200 mg miconazole nitrate antimycotic suppository or a water-based 200 mg miconazole nitrate antimycotic vaginal cream on Days 8, 9, and 10 of the NuvaRing cycle. Following multiple doses, the mean serum concentrations of etonogestrel and ethinyl estradiol remained elevated compared to the concentrations on the first day of interaction treatment, and were elevated by 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.

Drug-Food Interactions

Interactions with food have not been established.

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. 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.

Drug-Laboratory Interactions

Results of laboratory tests should be interpreted in the light that the patient is on combination hormonal contraceptives (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 combination hormonal contraceptive (including NuvaRing) therapy when specimens obtained from surgical procedures and Pap smears are submitted for examination.

Drug-Lifestyle Interactions

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 a diaphragm or cervical cap. A diaphragm or cervical cap is therefore not recommended as a back-up method with NuvaRing use.

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.

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)¹². 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 DOSAGE AND ADMINISTRATION – Missed Dose and INFORMATION FOR THE PATIENT – 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 condoms 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.

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.

Non-Contraceptive Benefits of Combination Hormonal Contraceptives (including NuvaRing)

Several health advantages other than contraception have been reported.

1. Combination hormonal contraceptives (including NuvaRing) reduce the incidence of cancer of the endometrium and ovaries.
2. Combination hormonal contraceptives (including NuvaRing) reduce the likelihood of developing benign breast disease and as a result decrease the incidence of breast biopsies.
3. Combination hormonal contraceptives (including NuvaRing) reduce the likelihood of development of functional ovarian cysts.
4. Combination hormonal contraceptive (including NuvaRing) users have less menstrual blood loss and have more regular cycles, thereby reducing the chance of developing iron-deficiency anemia.
5. The use of combination hormonal contraceptives (including NuvaRing) may decrease the severity of dysmenorrhea and premenstrual syndrome and may improve acne vulgaris, hirsutism and other androgen-mediated disorders.
6. Combination hormonal contraceptives (including NuvaRing) decrease the incidence of acute pelvic inflammatory disease and thereby reduce as well the incidence of ectopic pregnancy.
7. Combination hormonal contraceptives (including NuvaRing) have potential beneficial effects on endometriosis.

DOSAGE AND ADMINISTRATION

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 a good habit for the woman to regularly verify the presence of NuvaRing. 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.

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 condoms 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 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 condoms 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.

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 combination hormonal contraceptive

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 condoms 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 CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS – Hematologic concerning thromboembolic disease. Also see WARNINGS AND PRECAUTIONS for – Special Populations: Nursing Women regarding breastfeeding.) 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.

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 $1,272 \pm 311$ pg/mL compared to a mean concentration range of $1,578 \pm 408$ to $1,374 \pm 328$ 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 condoms 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 be used as a standard dosing regimen, as there are no long-term safety data available on the continuous use of NuvaRing.

OVERDOSAGE

Overdosage of combination hormonal contraceptives 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.

ACTION AND 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.

Mechanism of Action

Combination hormonal contraceptives (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).

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.

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 5.

Table 5: Summary of NuvaRing's Pharmacokinetic Parameters in 16 healthy female subjects

	C_{max} mean (SD) pg/mL	t_{1/2} (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 6.

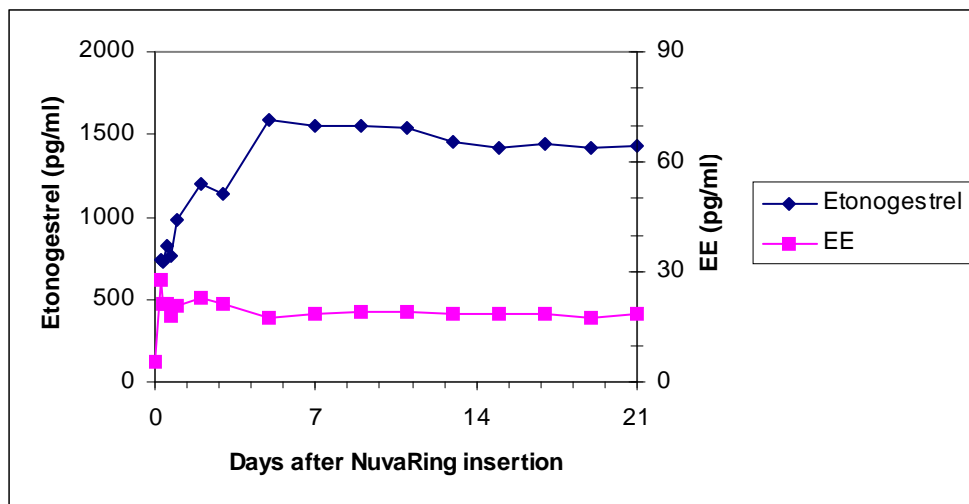
Ethinyl estradiol: Ethinyl estradiol released by NuvaRing is rapidly absorbed. The bioavailability of ethinyl estradiol after vaginal administration is approximately 55.6%, which is comparable to that with oral administration of ethinyl estradiol. However, the overall systemic exposure to ethinyl estradiol 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 6.

Table 6: 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 (AUC 0-4 \ddagger) 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. Ethinyl estradiol is primarily metabolized by aromatic hydroxylation, but a wide variety of hydroxylated and methylated metabolites are formed. These are present as free metabolites and as sulfate and glucuronide conjugates. The hydroxylated ethinyl estradiol metabolites have weak estrogenic activity. The biological activity of etonogestrel metabolites is unknown.

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

Special Populations and Conditions

Race: 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 (see 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.

STORAGE AND STABILITY

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 in direct sunlight or at temperatures above 30°C.

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.

SPECIAL HANDLING INSTRUCTIONS

NuvaRing does not contain any latex.

DOSAGE FORMS, COMPOSITION AND PACKAGING

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. The ring should be replaced in this reclosable sachet after use for convenient disposal.

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 also contains ethylene vinylacetate copolymers (28% and 9% vinylacetate) and magnesium stearate.

NuvaRing is available in: Boxes of 3 sachets
 Boxes of 1 sachet

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

I. Progestogen

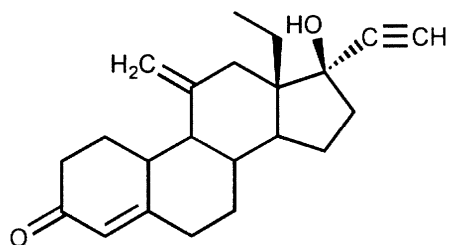
Proper Name: Etonogestrel

Chemical Name: 1) 18,19-Dinor-17 ∇ -pregn-4-en-20-yn-3-one,13-ethyl-17-hydroxy-11-methylene-;
2) 13-Ethyl-17-hydroxy-11-methylene-18,19-dinor-17 ∇ -pregn-4-en-20yn-3-one.
3) (17 ∇)13-ethyl-17-hydroxy-11-methylene-18,19- dinorpregn-4-en-20-yn-3-one.

Molecular Formula: C₂₂H₂₈O₂

Molecular Weight: 324.46

Structural Formula:



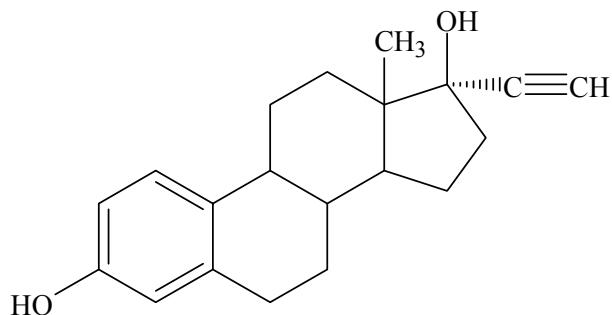
Physical Form: White to practically white crystalline powder which may have a slight odour.

Solubility: At 22EC: n-Hexane - 2 mg/mL
Ethanol (96%) - 60 mg/mL
Ethyl acetate - 60 mg/mL
Water - practically insoluble

Melting Point: 197.6EC

II. Estrogen

Proper Name: Ethinyl Estradiol Ph.Eur.
Chemical Name: 19-Nor-17 β -pregna-1,3,5(10)-trien-20-yne-3,17-diol
Molecular Formula: C₂₀H₂₄O₂
Molecular Weight: 296.4
Structural Formula:



Physical Form: White, crystalline powder
Solubility: Soluble in ethanol, ether, acetone, chloroform.
Practically insoluble in water.
Melting Point: 182-184EC

CLINICAL TRIALS

Study demographics and trial design

Table 7: Summary of patient demographics for clinical trials in specific indication

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender	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 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.	Cycle control – The statistical analysis of the cycles focused on the following parameters: <ul style="list-style-type: none"> • occurrence of breakthrough bleeding/spotting • absence of withdrawal bleeding/spotting • occurrence of breakthrough bleeding • occurrence of 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
34219			1,145	28.2 (18-41)			

Study Results – Pivotal Trials

a) Contraceptive Efficacy – Pearl Index

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

In 2 large 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.

Table 8: Percentage of women experiencing an unintended pregnancy during the first year of typical use and the first year of perfect use of contraception and the percentage continuing use at the end of the first year, in the United States

Method (1)	% of women experiencing an unintended pregnancy within the first year of use		% of women continuing use at 1 year ^c (4)
	Typical use ^a (2)	Perfect use ^b (3)	
No method ^d	85	85	
Spermicides ^e	29	18	42
Withdrawal	27	4	43
Periodic abstinence	25		51
Calendar		9	
Ovulation method		3	
Symptothermal ^f		2	
Postovulation		1	
Cap ^g			
Parous women	32	26	46
Nulliparous women	16	9	57
Sponge			
Parous women	32	20	46
Nulliparous women	16	9	57
Diaphragm ^h	16	6	57
Condom ^h			
Female (Reality)	21	5	49
Male	15	2	53
Combined pill and minipill	8	0.3	68
Ortho-Evra patch	8	0.3	68
NuvaRing	8	0.3	68
Depo-Provera	3	0.3	56
Lunelle	3	0.05	56
IUD			
ParaGard (copper T)	0.8	0.6	78
Mirena (levonorgestrel containing intrauterine system)	0.1	0.1	81
Norplant and Norplant-2	0.05	0.05	84
Female sterilization	0.5	0.5	100
Male sterilization	0.15	0.10	100

Emergency contraceptive pills: Treatment initiated within 72 h after unprotected intercourse reduces risk of pregnancy by at least 75%.ⁱ

Lactational amenorrhea method: A highly effective, temporary method of contraception.^j

Source: Trussell J. Contraceptive efficacy. In: Hatcher RA, Trussell J, Stewart F, et al., editors *Contraceptive technology eighteenth revised edition*. New York: Ardent Media, 2004.

^a Among typical couples who initiate use of a method (not necessarily for the first time), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason. Estimates of the probability of pregnancy during the first year of typical use for spermicides, withdrawal, periodic abstinence, the diaphragm, the male condom, the pill and Depo-Provera are taken from the 1995 NFSG corrected for underreporting of abortion; see text for the derivation of estimates for the other methods.

^b Among couples who initiate use of a method (not necessarily for the first time) and who use it perfectly (both consistently and correctly), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason. See text for the derivation of estimate for each method.

^c Among couples attempting to avoid pregnancy, the percentage who continue to use a method for 1 year.

^d The percentages becoming pregnant in columns (2) and (3) are based on data from populations where contraception is not used and from women who cease using contraception in order to become pregnant. Among such populations, about 89% become pregnant within 1 year. This estimate was lowered slightly (to 85%) to represent the percentage who would become pregnant within 1 year among women now relying on reversible methods of contraception if they abandoned contraception altogether.

^e Foams, creams, gels, vaginal suppositories and vaginal film.

^f Cervical mucus (ovulation) method supplemented by calendar in the preovulatory and basal body temperature in the postovulatory phases.

^g With spermicidal cream or jelly.

^h Without spermicides.

ⁱ The treatment schedule is one dose within 120 h after unprotected intercourse, and a second dose 12 h after the first dose. Both doses of Plan B can be taken at the same time. Plan B (1 dose is 1 white pill) is the only dedicated product specifically marketed for emergency contraception. The US Food and Drug Administration has in addition declared the following 18 brands of oral contraceptives to be safe and effective for emergency contraception: Ogestrel or Ovral (1 dose is 2 white pills), Alesse, Lessina, or Levlite, (1 dose is 5 pink pills), Levlen or Nordette (1 dose is 4 light-orange pills), Cryselle, Levora, Low-Ogestrel, or Lo/Ovral (1 dose is 4 white pills), Tri-Levlen or Triphasil (1 dose is 4 yellow pills), Portia, Seasonale, or Trivora (1 dose is 4 pink pills), Aviane (one dose is 5 orange pills), and Emprise (one dose is 4 orange pills).

^j However, to maintain effective protection against pregnancy, another method of contraception must be used as soon as menstruation resumes, the frequency or duration of breastfeeds is reduced, bottle feeds are introduced or the baby reaches 6 months of age.

b) Cycle Control

Relative frequencies of bleeding/spotting and bleeding days showed a consistent pattern throughout all 13 cycles for the controlled 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.

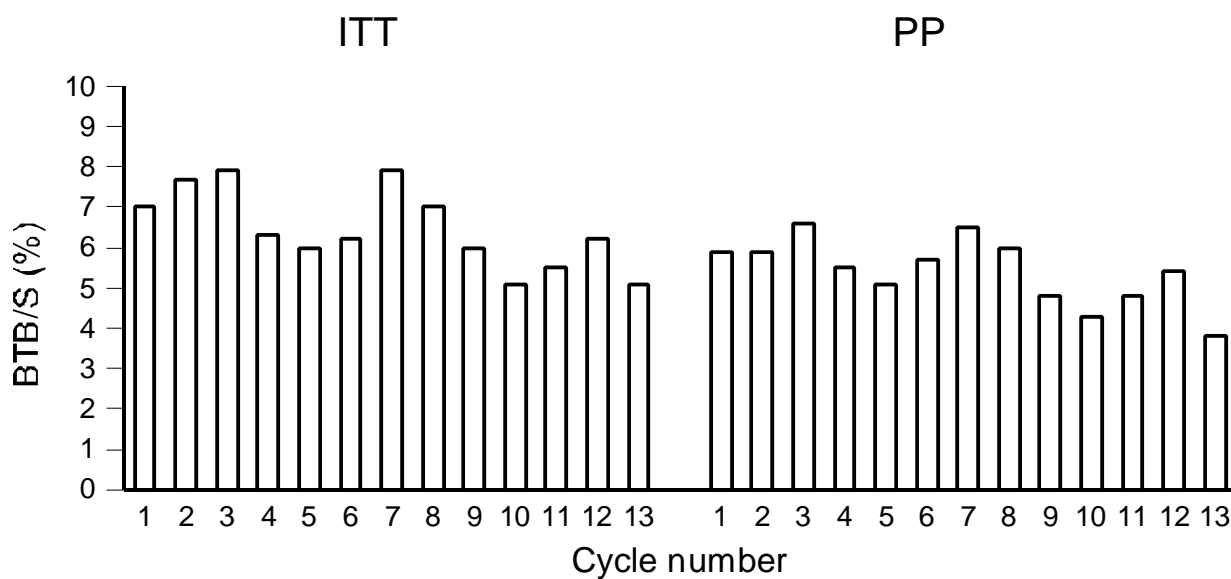
For the combined controlled studies, incidences of bleeding variables over Cycles 1-13 were acceptable and comparable to that of other combined hormonal contraceptives (Table 9). The incidence of breakthrough bleeding/spotting ranged from 5.1% - 7.9% and the incidence of absence of withdrawal bleeding 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 (absence of breakthrough bleeding/spotting, absence of withdrawal bleeding, as well as absence of early and continued 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 9: Parameters of Bleeding Pattern During the First Year of use – Combined Controlled 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 Controlled Studies



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

c) Tolerance

Acceptability of NuvaRing was evaluated in the controlled 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 Table 10. 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 10: Responses from Acceptability Questionnaire at Last Assessment – Combined Controlled Studies

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

The proportion of women reporting that they were satisfied or very satisfied with the ring was 96% for completers. Eighty-five percent (85%) of all women were satisfied with the use of NuvaRing and 90% would recommend this method to others.

d) Safety

In the combined controlled open-label studies 351/2322 (15.1%) treated subjects discontinued due to AEs; most were drug-related AEs. The most common AEs 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 11).

Table 11: Mean Change (\pm standard deviation) in Blood Pressure and Body Weight from Baseline – Combined Controlled Studies (ITT)

	Cycle			
	3	6	9	13
Diastolic (mmHg)	-0.1 \pm 8.4	-0.3 \pm 8.9	0.0 \pm 8.7	0.5 \pm 8.9
Systolic (mmHg)	-0.2 \pm 10.3	-0.1 \pm 11.0	-0.2 \pm 11.0	0.6 \pm 11.2
Body weight (kg)	0.02 \pm 2.29	0.05 \pm 3.12	0.47 \pm 3.40	0.84 \pm 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 μ g levonorgestrel/30 μ g 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 12). 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 12). 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 12: Cycle control in combined metabolic studies (NuvaRing n=121; COC n=126) (ITT)

Cycle	Incidence of Breakthrough Bleeding/Spotting (%)		Incidence of Intended Bleeding Pattern (%)	
	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.

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-AEs, device-related problems and vaginal discomfort. The most commonly reported AEs (5%) were vaginitis, headache, upper respiratory tract infection, leukorrhea, sinusitis, and nausea. There did not appear to be an

increased incidence of these AEs with long-term NuvaRing treatment, and there were no clinically meaningful differences in the incidence of these common AEs 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.

DETAILED PHARMACOLOGY

Animal and in vitro pharmacology

Animal pharmacology and in vitro receptor binding studies indicate that etonogestrel is a highly selective progestational agent (Table 13) with no estrogenic effects, and only residual androgenicity.

Table 13: 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°C using the reference standard 16 α -ethyl-21-hydroxy-9-nor-pregn-4-ene-3,20-dione.

The binding affinity of etonogestrel is approximately 1/10 of 5 α -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.

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 tumour and mammary tumour 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.

Reproductive Toxicity Studies

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.

Mutagenicity Studies

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.

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IMPORTANT: PLEASE READ

PART III: CONSUMER INFORMATION

Pr **NUVARING**[®]

etonogestrel/ethinyl estradiol slow release vaginal ring

CONTRACEPTIVE VAGINAL RING

This leaflet is part III of a three-part "Product Monograph" published when NuvaRing was approved for sale in Canada, and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about NuvaRing. Contact your doctor or pharmacist if you have any questions about the use of this product.

**READ THIS PAMPHLET CAREFULLY
BEFORE YOU START USING NUVARING.**

ABOUT THIS MEDICATION

What the medication is used for:

NuvaRing (NEW-vah-ring) is a flexible contraceptive vaginal ring used to prevent pregnancy.

What it does:

Since NuvaRing releases two different types of hormones, an estrogen and a progestin, it is called a combination hormonal contraceptive (CHC). NuvaRing delivers 120 mcg of the progestin etonogestrel and 15 mcg/day of the estrogen, ethinyl estradiol. NuvaRing works by releasing a steady dose of progestin and estrogen into the body. The ring is inserted into the vagina and left in place for 3 weeks in a row.

Like other combination hormonal contraceptives, NuvaRing works in two ways:

1. By inhibiting the monthly release of an egg by the ovaries.
2. By changing the mucus produced by the cervix. This slows the movement of the sperm through the mucus into the uterus further reducing the chance of fertilization.

NuvaRing has been shown to be highly effective in preventing pregnancy when used as prescribed.

When used according to directions, 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 getting pregnant increases if NuvaRing is not used exactly according to the directions.

Other ways to prevent pregnancy

Other methods of birth control are available to you.

The following table gives reported pregnancy rates for various forms of birth control, including no birth control. The reported rates represent the number of women out of 100 who would become pregnant in one year.

Reported Pregnancies per 100 Women per Year

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

Pregnancy rates vary widely because people differ in how consistently and/or correctly they use each method. (This does not apply to IUDs since they are implanted in the uterus). When used as directed, users may achieve pregnancy rates in the lower ranges. Others may expect pregnancy rates more in the middle ranges.

Hormonal contraceptives (such as NuvaRing) have important advantages over other methods of birth control. They also have certain risks that other methods do not. Your doctor is the best person to explain the consequences of any possible risks.

IMPORTANT: PLEASE READ

Non-contraceptive benefits of hormonal contraceptives

Several health advantages have been linked to the use of hormonal contraceptives.

- Reduction in the incidence of cancer of the uterus and ovaries.
- Reduction in the likelihood of developing benign (non-cancerous) breast disease and ovarian cysts.
- Less menstrual blood loss and more regular cycles. The risk of developing iron-deficiency anemia is thus reduced.
- There may be a decrease in painful menstruation and premenstrual syndrome (PMS).
- Acne, excessive hair growth and male-hormone-related disorders also may be improved.
- Ectopic (tubal) pregnancy may occur less frequently.
- Acute pelvic inflammatory disease may occur less frequently.

When it should not be used:

Hormonal contraceptives are not suitable for every woman. You should not use combination hormonal contraceptives (including NuvaRing) if you have or have had any of the following conditions:

- unusual vaginal bleeding that has not yet been diagnosed
- blood clots in the legs, lungs, eyes, or elsewhere. For additional information, see section “RISKS OF USING HORMONAL CONTRACEPTIVES – Circulatory disorders”.
- a stroke, heart attack, chest pain (angina pectoris) or other blood circulatory disorders in the brain
- known or suspected cancer of the breast or sex organs
- liver tumour associated with the use of the pill or other estrogen-containing products
- jaundice (yellowing of the eyes or skin), liver disease or liver tumour
- cancers which are caused by or enhanced by estrogen
- eye diseases, eye lesions or defects or loss of vision
- allergic reactions or hypersensitivity to the hormones found in the contraceptives or to any of the other components found in the contraceptive
- if you are pregnant or think you might be pregnant

What the medicinal ingredient is:

NuvaRing contains two female hormones: etonogestrel (a progestin) and ethinyl estradiol (an estrogen).

What the important nonmedicinal ingredients are:

NuvaRing also contains ethylene vinylacetate copolymers and magnesium stearate. NuvaRing does not contain any latex.

What dosage forms it comes in:

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

NuvaRing is available in boxes of 1 sachet and 3 sachets.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels. This risk increases with age and becomes significant in birth control pill users over 35 years of age. Women should be counselled not to smoke.

Women who are obese are at particularly high risk of blood clots.

NuvaRing (as with other hormonal contraceptives) DOES NOT PROTECT against HIV infection (AIDS) and other Sexually Transmitted Infections (STIs). For protection against STIs, it is advisable to use latex or polyurethane condoms while using NuvaRing.

BEFORE you use NuvaRing talk to your doctor or pharmacist if:

- you are taking any other prescription or nonprescription drugs as these may interfere with the actions of NuvaRing
- you are or will be having major surgery
- you have breast conditions
- you have a family history of breast cancer
- you have breast disorders including pain, discharge from the nipples, thickenings, or lumps
- you have a family history of circulatory disorders including blood clots, heart attacks or strokes
- you have diabetes
- you have high blood pressure
- you have abnormal levels of fats in the bloodstream (high cholesterol or triglycerides)
- you are a cigarette smoker
- you have migraine headaches

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- you have heart or kidney disease
- you have a history of seizures or epilepsy
- you have a history of mental depression
- you have fibroid tumours of the uterus
- you have gallbladder or pancreatic disease
- you have plans for forthcoming surgery
- you have a history of jaundice or other liver disease

Your doctor can advise you if you have any conditions that would pose a risk to you. The use of combination hormonal contraceptives (including NuvaRing) should always be supervised by your doctor, with regular follow up to identify side effects associated with its use. Your visits may include a blood pressure check, a breast exam, an abdominal exam and a pelvic exam, including a Pap smear. Visit your doctor three months or sooner after the initial examination. Afterward, visit your doctor at least once a year. Use NuvaRing only on the advice of your doctor and carefully follow all directions given to you. Use NuvaRing exactly as prescribed or you could become pregnant.

If you see another doctor, inform him or her that you are using NuvaRing.

NuvaRing may not be suitable for women with conditions that make the vagina more susceptible to vaginal irritation or ulceration. In some cases, vaginal (fibrous) tissue may grow over the ring, necessitating removal by a doctor.

Pregnancy is almost always more risky than using combination hormonal contraceptives. However, this risk with hormonal contraceptives can be higher if you are over 35 and you smoke.

If you and your doctor decide that, for you, the benefits of NuvaRing outweigh the risks, you should be aware of the following:

RISKS OF USING HORMONAL CONTRACEPTIVES

Specific studies with vaginal administration of contraceptive hormones (as in NuvaRing) are limited. The information given below was obtained in studies with oral contraceptives (the Pill) and it may also apply to NuvaRing.

Circulatory disorders (including blood clot in legs, lungs, heart, eyes or brain)

Blood clots can develop whether or not you are using hormones for contraception. They can also happen if you are pregnant. The risk is higher in users of combined oral contraceptives than in non-users, but it is not as high as the risk during pregnancy.

Blood clots can also occur very rarely in the blood vessels of the heart (causing a heart attack) or the brain (causing a stroke). Extremely rarely blood clots can occur in the liver, gut, kidney or eye.

Following an episode of a blood clot recovery is not always complete. Very occasionally serious permanent disabilities may occur or a blood clot may even be fatal.

If you have to undergo an operation, are bedridden for some time, or you are not supposed to walk (for example, when you have your leg or legs in plaster, or a bandage is put on to treat varicose veins), the risk of having a blood clot may be temporarily higher. In women who use contraceptive hormones, the risk may be yet higher. In such a case, ask your doctor well in advance about what you should do. Your doctor may tell you to stop using your hormonal contraception several weeks before surgery or at the time of immobilization. Your doctor will also tell you when you can start using NuvaRing again after you are back on your feet.

If you notice possible signs of a blood clot, stop using NuvaRing and consult your doctor immediately (**see the symptoms in section 'Side Effects and What to do About Them'**).

Hormonal Contraceptives and Cancer

Breast cancer

Breast cancer has been found slightly more often in women that take the Pill than in women of the same age who do not take the Pill. It is not known whether the increased risk of breast cancer is caused by the use of a hormonal contraceptive. It may be that the women taking such a hormonal contraceptive were examined more often, so that the breast cancer is noticed earlier.

The most significant risk factors for breast cancer are increasing age and a strong history of breast cancer in the family (mother or sister). Other established risk factors include, onset of menstrual periods before age 12 years, never having children, having your first full-term pregnancy after the age of 30 years, never having breast fed a child, and daily alcohol consumption.

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You should notify your doctor if you notice any breast lumps. You should also discuss breast self-examination with your doctor. A yearly breast examination by a health care professional is recommended for all women. You should also tell your doctor if a close relative has or ever had breast cancer (see Warnings & Precautions).

Cervical cancer

Some studies have found an increase of cancer of the cervix in women who use hormonal contraceptives, although this finding may be related to factors other than the use of oral contraceptives. However, there is insufficient evidence to rule out the possibility that oral contraceptives may cause such cancers.

Chronic infection with the Human Papilloma Virus (HPV) is believed to be the most important risk factor for cervical cancer. In women who use combined oral contraceptives for a long time the chance of getting cervical cancer may be slightly higher. This finding may not be caused by the Pill itself but may be related to sexual behavior and other factors.

Liver tumours

In rare cases benign liver tumours and even more rarely, malignant liver tumours have been reported in users of the Pill. These tumours may lead to internal bleeding. Contact your doctor immediately if you experience severe pain or a lump in the abdomen.

Gallbladder disease

Users of hormonal contraceptives have a greater risk of developing gallbladder disease requiring surgery within the first year of use. The risk may double after four or five years of use.

Use in pregnancy

Hormonal contraceptives should not be taken by pregnant women. There is no evidence, however, that the Pill can damage a developing child. You should check with your doctor about risks to your unborn child from any medication taken during pregnancy.

Use while breast feeding

The hormones in contraceptives are known to appear in breast milk. These hormones may decrease the flow of breast milk if hormonal contraceptives are not resumed until nursing is established. Some of the medicine may pass through the milk to the baby and could cause yellowing of the skin (jaundice) and breast enlargement.

Pregnancy after stopping NuvaRing

A woman's menstrual period may be delayed after stopping hormonal contraceptives. There is no evidence that the use of the contraceptive vaginal ring leads to a

decrease in fertility. It is wise to delay starting a pregnancy for at least one menstrual period after stopping hormonal contraceptives, so that way the pregnancy can be more accurately dated. Your doctor can recommend a different (non-hormonal) method of contraception during this time.

Irregular Bleeding

During the use of NuvaRing, in some women, unexpected vaginal bleeding (spotting or breakthrough bleeding) between periods may occur. You may need to use sanitary protection, but continue to use the ring as normal. If the irregular bleeding continues, becomes heavy or starts again, tell your doctor.

Ring Disconnection

Very rarely NuvaRing may break. A broken ring is unlikely to cause an overdose because the ring will not release a higher amount of contraceptive hormones. If NuvaRing breaks, expulsion is more likely to occur (see 'What Should I do if NuvaRing disconnects?'). Therefore, if you notice that your NuvaRing has broken, discard that ring and replace it with a new ring as soon as possible.

Risk to the Partner

The effects of hormones released by NuvaRing on male partners during sexual intercourse have not been studied.

During market use, partner penis discomfort (e.g., pain, rash, bruises and abrasions), has been reported.

INTERACTIONS WITH THIS MEDICATION

Certain drugs may interact with hormonal contraceptives (including NuvaRing) and prevent NuvaRing from working properly. This can make hormonal contraceptives less effective in preventing pregnancy or cause unexpected bleeding (spotting or breakthrough bleeding). Hormonal contraceptives may also interfere with the working of other drugs.

Please inform your doctor or pharmacist if you are taking or have recently taken any other drugs or herbal products, even those without a prescription. Also, tell any other doctor or dentist who prescribes another drug (or the dispensing pharmacist) that you use NuvaRing. They can tell you if you need to use an additional method of contraception and if so, for how long.

Drugs that may interact with NuvaRing include:

- drugs used for the treatment of epilepsy (e.g. primidone, phenytoin, barbiturates, carbamazepine, oxcarbazepine, topiramate, felbamate); tuberculosis (e.g. rifampicin, rifabutin) and HIV infections (e.g. ritonavir)

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- antibiotics (e.g. penicillins, tetracyclines, metronidazole) for infectious diseases
- antifungals (e.g. griseofulvin)
- anti-coagulants (blood thinners)
- the herbal remedy, St. John's Wort
- antihypertensive drugs (for high blood pressure)
- antidiabetic drugs and insulin (for diabetes)
- prednisone
- sedatives and hypnotics (e.g. benzodiazepines, barbiturates, chloral hydrate, glutethimide, meprobamate)
- antacids
- other drugs such as phenylbutazone, antihistamines, analgesics, antimigraine preparations, or Vitamin E
- cyclosporine
- anti-epileptic drugs (lamotrigine)
- Vitamin B12

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 should occur, simply rinse the ring in cool to lukewarm (not hot) water and immediately reinsert it.

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.

PROPER USE OF THIS MEDICATION

If you decide to use hormonal contraceptives

If you and your doctor decide that, for you, the benefits of hormonal contraceptives outweigh the risks, you should be aware of the following:

1. Your doctor will advise you of the appropriate time to start the use of hormonal contraceptives after childbirth, miscarriage, or therapeutic abortion.
2. There is no need to stop taking hormonal contraceptives for a rest period.

If you want more information about contraceptive vaginal rings, ask your doctor or pharmacist.

Usual dose:

NuvaRing is designed to be a once-a-month contraceptive regimen. The ring has to be inserted in your vagina. You can verify the presence of NuvaRing yourself, whenever you wish. After the ring is inserted, it releases a continuous low dose of hormones into your body. The ring stays in place for 3 weeks and then is removed for a one week ring free period. It is not necessary or recommended to remove NuvaRing during intercourse.

READ THESE DIRECTIONS CAREFULLY

For the best protection from pregnancy, use NuvaRing exactly as directed. 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. Your healthcare provider should examine you at least once a year.

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 colour change in the ring or any visible signs of deterioration.

While using NuvaRing, you should not rely upon a diaphragm or cervical cap when you need a back-up method of birth control because NuvaRing may interfere with the correct placement and position of these devices.

IMPORTANT: PLEASE READ

When should I start NuvaRing?

Follow the instructions in one of the sections below to find out when to start using NuvaRing:

If you did not use a hormonal contraceptive in the preceding cycle

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 the first cycle.

If you are switching from a combined hormonal contraceptive containing both progestin and estrogen)

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

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

- 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 condoms and/or spermicide, for the first seven days after inserting NuvaRing.

“Use after pregnancy, miscarriage or abortion”

Talk to your doctor about using NuvaRing following an abortion, miscarriage or childbirth or under any other circumstances that are not listed in this Consumer Information.

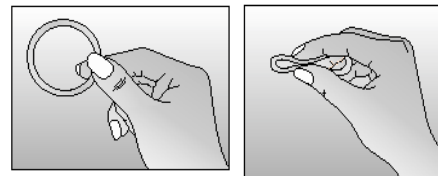
How do I insert NuvaRing?

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.



Figures 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, use your finger to gently push NuvaRing further into your vagina. **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.

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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).

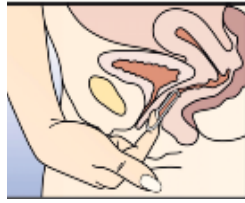


Figure 4

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 provider.

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 condoms 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. 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 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

Overdose:

Overdosage of combination hormonal contraceptives 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 NuvaRing is broken, it does not release a higher dose of hormones. There are no antidotes and further treatment should be symptomatic.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

IMPORTANT: PLEASE READ

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.

- If NuvaRing slips out of the vagina, **and it has been out 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.
- If NuvaRing has been out of the vagina **for more than three hours during the 1st or 2nd week**, you may not be adequately protected from pregnancy. 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**.

If NuvaRing slips out of the vagina for more than 3 hours during the 3rd week contraceptive efficacy may be reduced. 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 such as condoms and/or spermicides must be used until the new ring has been used continuously for seven days.

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

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. Contact your doctor immediately. The longer the ring-free interval, the higher the risk that you have become pregnant

How well tolerated is NuvaRing?

More than 2,100 women were questioned in a survey of their experiences using NuvaRing for several months.

Nearly all of the women found NuvaRing easy to insert (96%) and remove (98%). Most women did not feel NuvaRing once it was in place and 83% of women said they never or rarely felt NuvaRing during intercourse. Similarly, 68% of women said their partners never or rarely felt the ring during intercourse, and 91% reported that their partner did not mind them using the ring.

Of the women who completed the study (approximately 1,500), 96% reported they were satisfied or very satisfied with NuvaRing (85% of all women surveyed were satisfied), and 90% reported they would recommend NuvaRing to others.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Combination hormonal contraceptives (including NuvaRing) are not suitable for every woman.

In a small number of women, serious side effects may occur. The most serious side effects of combined hormonal contraceptives include:

- circulatory disorders (including blood clots in legs, lungs, heart, eyes, or brain)
- breast cancer
- gall bladder disease or liver tumours

Contact your doctor as soon as possible if you notice any changes in your own health, especially involving any of the items mentioned in this leaflet (see also Warnings and Precautions). Do not forget about the items related to your immediate family.

Be alert for the following symptoms and signs of serious adverse effects. Call your doctor immediately if they occur:

- sharp pain in the chest, coughing blood, or sudden shortness of breath. These symptoms could indicate a possible blood clot in the lung.
- pain and/or swelling in the calf. These symptoms could indicate a possible blood clot in the leg.
- crushing chest pain or heaviness. These symptoms could indicate a possible heart attack.
- sudden severe or worsening headache or vomiting, dizziness or fainting, disturbances of vision or speech, or weakness or numbness in an arm or leg. These symptoms could indicate a possible stroke.

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- sudden partial or complete loss of vision. This symptom could indicate a blood clot in the eye.
- severe pain or lump in the abdomen. These symptoms could indicate a possible tumour of the liver.
- severe depression
- yellowing of the skin (jaundice)
- unusual swelling of the extremities
- breast lumps.

With all hormonal contraceptives, for the first few months, you can have irregular vaginal bleeding (spotting or breakthrough bleeding) between your periods. You may need to use sanitary protection, but continue to use NuvaRing as normal. Irregular vaginal bleeding usually stops once your body has adjusted (usually after about 3 cycles). If it continues, becomes heavy or starts again, tell your doctor.

Users of NuvaRing have reported the following side effects:

- headache;
- vaginal discomfort (e.g. vaginal secretion, infection of the vagina);
- weight increase;
- nausea;
- breast pain;
- mood changes (e.g. depressive moods and emotional lability);
- painful menstruation;
- acne;
- decreased libido;
- abdominal pain;
- migraine;
- expulsion of the ring, problems during intercourse and feeling of the ring.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In rare cases the following undesirable effects were reported during use of NuvaRing: itching in the genital area, rash, inflammation of the cervix, urinary tract infection, bladder infection, dizziness, anxiety, diarrhea and vomiting, breast tumour formation, back pain, enlarged abdomen and fatigue.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom / effect	Talk with your doctor or pharmacist		Remove the ring and call your doctor or pharmacist
	Only if severe	In all cases	
Uncommon			
sharp pain in chest, coughing blood, or sudden shortness of breath/blood clot in the lung			√
pain in the calf/blood clot in the leg			√
crushing chest pain or heaviness/ heart attack			√
sudden severe or worsening headache or vomiting, dizziness or fainting, disturbance of vision or speech, or weakness or numbness in an arm or leg/stroke			√
sudden partial or complete loss of vision or double vision/ blood clot in the eye			√
severe pain or lump in the abdomen/ liver tumour			√
severe depression			√
yellowing of the skin/ jaundice			√
unusual swelling of the extremities			√
breast lumps/ breast cancer		√	√
urinary urgency, frequency, burning and/or painful urination, and can not locate the ring in the vagina/ inadvertent insertion of NuvaRing into the urinary bladder		√	√

This is not a complete list of side effects. For any unexpected effects while taking NuvaRing, contact your doctor or pharmacist.

IMPORTANT: PLEASE READ

HOW TO STORE IT

Store NuvaRing at room temperature (2-30°C) and avoid direct sunlight.

Keep out of reach of children and pets.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701D
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Merck Canada Inc. at: 1-800-463-5442

This leaflet was prepared by Merck Canada Inc.
Last revised: February 7, 2011

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