

1. NAME OF THE MEDICINAL PRODUCT

NuvaRing®

0.120 mg/0.015 mg per 24 hours, vaginal ring

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

NuvaRing contains 11.7 mg etonogestrel and 2.7 mg ethinylestradiol.

The ring releases etonogestrel and ethinylestradiol at an average amount of 0.120 mg and 0.015 mg, respectively for 24 hours, over a period of 3 weeks.

For a full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Vaginal ring

NuvaRing is a flexible, transparent, and colorless to almost colorless ring, with an outer diameter of 54 mm and a cross-sectional diameter of 4 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Contraception

4.2 Posology and method of administration

4.2.1 How to use NuvaRing

The woman herself can insert NuvaRing in the vagina. The physician should advise the woman how to insert and remove NuvaRing. For insertion the woman should choose a position that is most comfortable for her, e.g. standing with one leg up, squatting, or lying down. NuvaRing should be compressed and inserted into the vagina until it feels comfortable. The exact position of NuvaRing in the vagina is not critical for the contraceptive effect of the ring (see *Figures 1-4*).

Once NuvaRing has been inserted (see 'How to start NuvaRing') it is left in the vagina continuously for 3 weeks. It is good habit for the woman to regularly verify the presence of NuvaRing. If NuvaRing is accidentally expelled, the woman should follow the instructions given in Section 4.2.3 'What to do if the ring is temporary outside the vagina' (for more information, see also Section 4.4.7 'Expulsion').

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NuvaRing must be removed after 3 weeks of use on the same day of the week as the ring was inserted. After a ring-free interval of one week a new ring is inserted (e.g. when NuvaRing is inserted on a Wednesday at about 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). NuvaRing can be removed by hooking the index finger under the ring or by grasping the ring between the index and middle finger and pulling it out (Figure 5). The used ring should be placed in the sachet (keep out of the reach of children and pets) and discarded as described in Section 6.6. The withdrawal bleed usually starts 2-3 days after removal of NuvaRing and may not have finished completely before the next ring insertion is due.

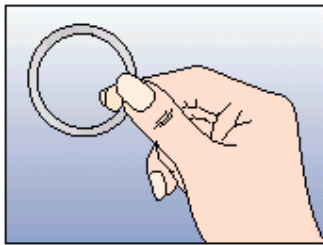


Figure 1
Take NuvaRing out of the sachet

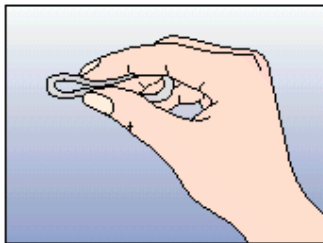


Figure 2
Compress the ring

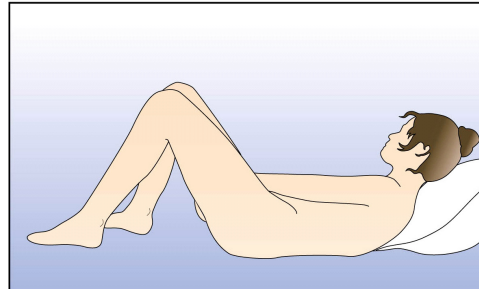
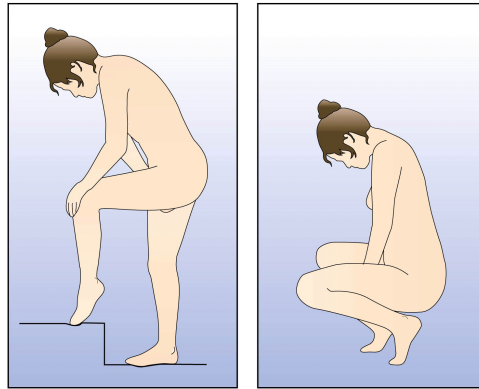


Figure 3
Choose a comfortable position to insert the ring

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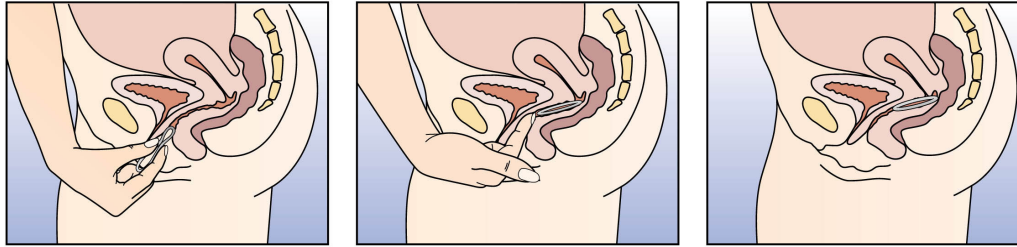


Figure 4A

Figure 4B

Figure 4C

Insert the ring into the vagina with one hand (Figure 4A), if necessary the labia may be spread with the other. Push the ring into the vagina until the ring feels comfortable (Figure 4B). Leave the ring in place for 3 weeks (Figure 4C).

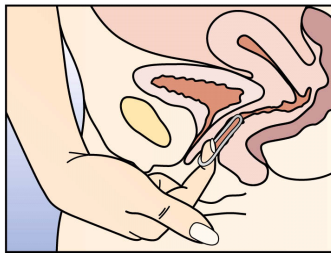


Figure 5:
NuvaRing can be removed by hooking the index finger under the ring or by grasping the ring between the index and middle finger and pulling it out.

4.2.2 How to start NuvaRing

No hormonal contraceptive use in the preceding cycle

NuvaRing has to be inserted on the first day of the woman's natural cycle (i.e. the first day of her menstrual bleeding). Starting on days 2-5 is allowed, but during the first cycle a barrier method is recommended in addition for the first 7 days of NuvaRing use.

Changing from a combined hormonal contraceptive

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.

If the woman has been using her previous method consistently and correctly and if it is reasonably certain that she is not pregnant she may also switch from her previous combined hormonal contraceptive on any day of the cycle.

The hormone-free interval of the previous method should never be extended beyond its recommended length.

Changing from a progestagen-only method (minipill, implant or injection) or from a progestagen-releasing intrauterine system (IUS).

The woman may switch on any day from the minipill (from an implant, or the IUS on the day of its removal, from an injectable when the next injection would

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be due) but should in all of these cases use an additional barrier method for the first 7 days of NuvaRing use.

Following first-trimester abortion

The woman may start immediately. When doing so, she needs not to take additional contraceptive measures. If an immediate switch is considered undesirable, the woman should follow the advice given for 'no hormonal contraceptive use in the preceding cycle'. In the meantime, she should be advised to use an alternative contraceptive method.

Following delivery or second-trimester abortion

For breast-feeding women, see Section 4.6.

Women should be advised to start during the fourth week after delivery or second-trimester abortion. When starting later, the woman should be advised to additionally use a barrier method for the first 7 days of NuvaRing use. However, if intercourse has already occurred, pregnancy should be excluded or the woman has to wait for her first menstrual period, before starting NuvaRing use.

4.2.3 Deviations from the recommended regimen

Contraceptive efficacy and cycle control may be compromised if the woman deviates from the recommended regimen. To avoid loss of contraceptive efficacy in case of a deviation, the following advice can be given:

- **What to do in case of a lengthened ring-free interval**

The woman should insert a new ring as soon as she remembers. A barrier method such as a condom should be used in addition for the next 7 days. If intercourse took place during the ring-free interval, the possibility of a pregnancy should be considered. The longer the ring-free interval, the higher the risk of a pregnancy.

- **What to do if the ring was temporarily outside the vagina**

NuvaRing should be left in the vagina for a continuous period of 3 weeks. If the ring is accidentally expelled it can be rinsed with cool to lukewarm (not hot) water and should be reinserted immediately.

If NuvaRing has been out of the vagina for **less than 3 hours** contraceptive efficacy is not reduced. The woman should reinsert the ring as soon as possible, but at the latest within 3 hours.

If NuvaRing has been out of the vagina, or is suspected to have been out of the vagina for **more than 3 hours during the 1st or 2nd week** of use, contraceptive efficacy may be reduced. The woman should reinsert the ring as soon as she remembers. A barrier method such as a condom should be

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used 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 a pregnancy.

If NuvaRing has been out of the vagina, or is suspected to have 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.

- **What to do in case of lengthened ring-use**

As long as NuvaRing has been used **for maximally 4 weeks**, contraceptive efficacy is still adequate. The woman may maintain her one-week ring-free interval and subsequently insert a new ring. If NuvaRing has been left in place for **more than 4 weeks**, contraceptive efficacy may be reduced and pregnancy should be ruled out before inserting a new NuvaRing.

If the woman has not adhered to the recommended regimen and subsequently has no withdrawal bleed in the following ring-free interval, pregnancy should be ruled out before inserting a new NuvaRing.

4.2.4 How to shift periods or how to delay a period

To **delay** a period the woman may insert a new ring without having a ring-free interval. The next ring can be used for up to 3 weeks again. The woman may experience bleeding or spotting. Regular use of NuvaRing is then resumed after the usual one-week ring-free interval.

To **shift** her period to another day of the week than the woman is used to with her current scheme, she can be advised to shorten her forthcoming ring-free interval by as many days as she likes. The shorter the ring-free interval, the higher the risk that she does not have a withdrawal bleed and will experience breakthrough bleeding and spotting during the use of the next ring.

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4.3 Contraindications

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

- Presence or history of venous thrombosis, with or without pulmonary embolism.
- Presence or history of arterial thrombosis (e.g. cerebrovascular accident, myocardial infarction) or prodromi of a thrombosis (e.g. angina pectoris or transient ischemic attack).
- Known predisposition for venous or arterial thrombosis, with or without hereditary involvement such as Activated Protein C (APC) resistance, antithrombin-III deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinemia and antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant).
- History of migraine with focal neurological symptoms.
- Diabetes mellitus with vascular involvement.
- The presence of a severe or multiple risk factor(s) for venous or arterial thrombosis may also constitute a contraindication (see under 'Special warnings and precautions for use').
- Pancreatitis or a history thereof if associated with severe hypertriglyceridemia.
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal.
- Presence or history of liver tumors (benign or malignant).
- Known or suspected malignant conditions of the genital organs or the breasts, if sex steroid-influenced.
- Undiagnosed vaginal bleeding.
- Known or suspected pregnancy.
- Hypersensitivity to the active substances or to any of the excipients of NuvaRing.

4.4 Special warnings and precautions for use

4.4.1 Warnings

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

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The physician should then decide on whether NuvaRing use should be discontinued. All data presented below are based upon epidemiological data obtained with combined oral contraceptives (COC). No epidemiological data are available on vaginal route of administration for the hormones but the warnings are also considered applicable to the use of NuvaRing.

1. *Circulatory Disorders*

- Epidemiological studies have suggested an association between the use of COCs and an increased risk of arterial and venous thrombotic and thromboembolic diseases such as myocardial infarction, stroke, deep venous thrombosis, and pulmonary embolism. These events occur rarely.
- Use of any combined oral contraceptive carries an increased risk of venous thromboembolism (VTE) compared with no use. The excess risk of VTE is highest during the first year a woman ever uses a combined oral contraceptive. This increased risk is less than the risk of VTE associated with pregnancy which is estimated as 6 cases per 10 000 pregnancies. VTE is fatal in 1-2% of cases.
- It is not known how NuvaRing influences the risk compared with other combined hormonal contraceptives.
- Extremely rarely, thrombosis has been reported to occur in other blood vessels, e.g. hepatic, mesenteric, renal, cerebral or retinal veins and arteries, in COC users. There is no consensus as to whether the occurrence of these events is associated with the use of COCs.
- Symptoms of venous or arterial thrombosis can include: unilateral leg pain and / or swelling; sudden severe pain in the chest, whether or not it radiates to the left arm; sudden breathlessness; sudden onset of coughing; any unusual, severe, prolonged headache; sudden partial or complete loss of vision; diplopia; slurred speech or aphasia; vertigo; collapse with or without focal seizure; weakness or very marked numbness suddenly affecting one side or one part of the body; motor disturbances; 'acute' abdomen.
- The risk of venous thromboembolism increases with:
 - increasing age;
 - a positive family history (i.e. venous thromboembolism ever in a sibling or parent at a relatively early age). If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any hormonal contraceptive use;

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- prolonged immobilization, major surgery, any surgery to the legs, or major trauma. In these situations it is advisable to discontinue use (in the case of elective surgery at least four weeks in advance) and not to resume until two weeks after complete remobilization;
 - obesity (body mass index over 30 kg/m²);
 - and possibly also with superficial thrombophlebitis and varicose veins. There is no consensus about the possible role of these conditions in the etiology of venous thrombosis.
- The risk of arterial thromboembolic complications increases with:
 - increasing age;
 - smoking (with heavier smoking and increasing age the risk further increases, especially in women over 35 years of age);
 - dyslipoproteinemia;
 - obesity (body mass index over 30 kg/m²);
 - hypertension;
 - migraine;
 - valvular heart disease;
 - atrial fibrillation;
 - a positive family history (arterial thrombosis ever in a sibling or parent at a relatively early age). If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any hormonal contraceptive use.
 - Biochemical factors that may be indicative of hereditary or acquired predisposition for venous or arterial thrombosis include Activated Protein C (APC) resistance, hyperhomocysteinemia, antithrombin-III deficiency, protein C deficiency, protein S deficiency, antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant).
 - Other medical conditions which have been associated with adverse circulatory events include diabetes mellitus, systemic lupus erythematosus, hemolytic uremic syndrome, and chronic inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis) and sickle cell disease.
 - The increased risk of thromboembolism in the puerperium must be considered (for information on "Pregnancy and lactation" see Section 4.6).
 - An increase in frequency or severity of migraine during hormonal contraceptive use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation of the use of hormonal contraceptives.

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- When considering risk/benefit, the physician should take into account that adequate treatment of a condition may reduce the associated risk of thrombosis and that the risk associated with pregnancy is higher than that associated with hormonal contraceptive use.

2. Tumors

- The most important risk factor for cervical cancer is persistent HPV infection. Some epidemiological studies have indicated that long-term use of COCs may further contribute to this increased risk but there continues to be controversy about the extent to which this finding is attributable to confounding effects, e.g. cervical screening and sexual behavior including use of barrier contraceptives. It is unknown how this effect relates to NuvaRing.
- A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently using COCs. The excess risk gradually disappears during the course of the 10 years after cessation of COC use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the overall risk of breast cancer. The breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users. The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in COC users, the biological effects of COCs or a combination of both.
- In rare cases, benign liver tumors, and even more rarely, malignant liver tumors have been reported in users of COCs. In isolated cases, these tumors have led to life-threatening intra-abdominal hemorrhages. Therefore, a hepatic tumor should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal hemorrhage occur in women using NuvaRing.

3. Other conditions

- Women with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis when using hormonal contraceptives.
- Although small increases in blood pressure have been reported in many women using hormonal contraceptives, clinically relevant increases are rare. A definitive relationship between hormonal contraceptive use and clinical hypertension has not been established. However, if a sustained clinically significant hypertension develops during the use of NuvaRing then it is

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prudent for the physician to suspend the use of the ring and treat the hypertension. Where considered appropriate, NuvaRing use may be resumed if normotensive values can be achieved with antihypertensive therapy.

- The following conditions have been reported to occur or deteriorate with both pregnancy and during the use of hormonal contraceptives, but the evidence of an association with its use is inconclusive: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; hemolytic uraemic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss; (hereditary) angioedema.
- Acute or chronic disturbances of liver function may necessitate the discontinuation of the use of NuvaRing until markers of liver function return to normal. Recurrence of cholestatic jaundice and/or pruritus related to cholestasis, which occurred first during pregnancy or previous use of sex steroids necessitates the discontinuation of the ring.
- Although estrogens and progestagens may have an effect on peripheral insulin resistance and glucose tolerance, there is no evidence for a need to alter the therapeutic regimen in diabetics using hormonal contraception. However, diabetic women should be carefully monitored while using NuvaRing especially in the first months of use.
- A deterioration of Crohn's disease and colitis ulcerosa has been reported in association with the use of hormonal contraceptives.
- Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation whilst using NuvaRing.

If a woman has any of the following conditions, she may not be able to insert NuvaRing correctly or may in fact lose the ring: prolapse of the uterine cervix, cystocele, and/or rectocele, severe or chronic constipation. Very rarely it has been reported that NuvaRing is inadvertently inserted in the urethra and possibly ending up in the bladder. Therefore, incorrect positioning should be considered in the differential diagnosis in case of symptoms of cystitis.

- During the use of NuvaRing, women may occasionally experience vaginitis. There are no indications that the efficacy of NuvaRing is affected by the treatment of vaginitis, nor that the use of NuvaRing affects the treatment of vaginitis (see Section 4.5.1 'Interactions').

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4.4.2 Medical examination/consultation

Prior to the initiation or reinstatement of NuvaRing use a complete medical history (including a family medical history) should be taken and pregnancy should be excluded. The blood pressure and a physical examination should be taken, guided by the contraindications (Section 4.3) and warnings (Section 4.4.1). The woman should be advised to carefully read the package leaflet and to follow the advice given. The frequency and nature of further periodic checks should be based upon established clinical practice and adapted to the individual woman.

Women should be advised that NuvaRing does not protect against HIV infections (AIDS) and other sexually transmitted diseases.

4.4.3 Reduced efficacy

The efficacy of NuvaRing may be reduced in the event of non-compliance (Section 4.2.3), or concomitant medication (Section 4.5.1).

4.4.4 Reduced cycle control

Irregular bleeding (spotting or breakthrough bleeding) may occur during the use of NuvaRing. If bleeding irregularities occur after previously regular cycles while NuvaRing has been used according to the recommended regimen, then non-hormonal causes should be considered, and adequate diagnostic measures are indicated to exclude malignancy or pregnancy. These may include curettage.

In some women, a withdrawal bleed may not occur during the ring-free interval. If NuvaRing has been used according to the instructions described in Section 4.2, it is unlikely that the woman is pregnant. However, if NuvaRing has not been used according to these instructions prior to the first missed withdrawal bleed or if two withdrawal bleeds are missed, pregnancy must be ruled out before use of NuvaRing is continued.

4.4.5 Male exposure to ethinylestradiol and etonogestrel

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

4.4.6 Broken rings

On rare occasions NuvaRing has been reported to get disconnected during use (see Section 4.5.1 'Interactions'). Since NuvaRing's core is solid, its

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contents will remain intact and release of hormones will not be significantly affected. In the event of disconnection of the ring, expulsion is likely to occur (see Section 4.2.3 'What to do if the ring was temporarily outside the vagina'). If NuvaRing is broken, the woman should discard the ring and replace it with a new ring.

4.4.7 Expulsion

NuvaRing has been reported to get expelled, for example if the ring has not been inserted properly, while removing a tampon, during sexual intercourse, or in case of severe or chronic constipation. Therefore, it is good habit for the woman to regularly verify the presence of NuvaRing. If NuvaRing is accidentally expelled, the woman should follow the instructions given in Section 4.2.3 'What to do if the ring is temporarily outside the vagina'.

4.5 Interaction with other medicinal products and other forms of interaction

4.5.1 Interactions

Interactions between hormonal contraceptives and other medicinal products may lead to breakthrough bleeding and/or contraceptive failure. The following interactions have been reported in the literature.

Hepatic metabolism: Interactions can occur with medicinal products that induce microsomal enzymes, which can result in increased clearance of sex hormones (e.g., phenytoin, phenobarbital, primidone, carbamazepine, rifampicin, and possibly also oxcarbazepine, topiramate, felbamate, ritonavir, griseofulvin and products containing St. John's wort).

Women on treatment with any of these medicinal products should temporarily use a barrier method in addition to NuvaRing or choose another method of contraception. With hepatic microsomal enzyme-inducing drugs, the barrier method should be used during the time of concomitant drug administration and for 28 days after their discontinuation.

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

Contraceptive failures have also been reported with antibiotics, such as penicillins and tetracyclines. The mechanism of this effect has not been elucidated. In a pharmacokinetic interaction study, oral administration of amoxicillin (875 mg, two times daily) or doxycycline (200 mg on day 1, followed by 100mg per day) for 10 days during use of NuvaRing, did not significantly affect pharmacokinetics of etonogestrel and ethinylestradiol (EE).

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Women on treatment with antibiotics (except amoxicillin and doxycycline) should use a barrier method until 7 days after discontinuation. If concomitant drug administration runs beyond the 3 weeks of a ring-cycle, the next ring should be inserted immediately, without having the usual ring-free interval.

Based on pharmacokinetic data, vaginally administered antimycotics and spermicides are unlikely to affect the contraceptive efficacy and safety of NuvaRing. During concomitant use of antimycotic ovules the chance of ring disconnection may be slightly higher (see Section 4.4.6 'Broken Rings')

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

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

4.5.2 Laboratory tests

The use of contraceptive steroids may influence the results of certain laboratory tests, including biochemical parameters of liver, thyroid, adrenal and renal function, plasma levels of carrier proteins, (e.g. corticosteroid binding globulin and sex hormone binding globulin), lipid / lipoprotein fractions, parameters of carbohydrate metabolism and parameters of coagulation and fibrinolysis. Changes generally remain within the normal laboratory range.

4.5.3 Interaction with tampons

Pharmacokinetic data show that the use of tampons has no effect on the systemic absorption of the hormones released by NuvaRing. On rare occasions NuvaRing might be expelled while removing a tampon (see advice for '*What to do if the ring was temporarily outside the vagina*' in section 4.2.3).

4.6 Pregnancy and lactation

NuvaRing is not indicated during pregnancy. If pregnancy occurs with NuvaRing in situ, the ring should be removed. Extensive epidemiological studies have revealed neither an increased risk of birth defects in children born to women who used COCs prior to pregnancy, nor a teratogenic effect when COCs were used inadvertently during early pregnancy. Although this probably applies to all COCs it is not clear whether this is also the case for NuvaRing.

A clinical study in a small number of women showed that despite the intravaginal administration, intrauterine concentrations of contraceptive steroids with NuvaRing are similar to the levels observed in COC users (see

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Section 5.2). Clinical experience of the outcomes of pregnancies exposed to NuvaRing has not been reported.

Lactation may be influenced by estrogens, as they may reduce the quantity and change the composition of breast milk. Therefore, the use of NuvaRing should generally not be recommended until the nursing mother has completely weaned her child. Small amounts of the contraceptive steroids and/or their metabolites may be excreted with the milk but there is no evidence that this adversely affects the infant's health.

4.7 Effects on ability to drive and use machines

On the basis of the pharmacodynamic profile, NuvaRing is expected to have no influence on the ability to drive and use machines.

4.8 Undesirable effects

The most serious undesirable effects associated with the use of hormonal contraceptives are listed in Section 4.4.1.

Adverse drug reactions that have been reported in users of NuvaRing are listed in the Table below. The most appropriate MedDRA term (version 9.1) to describe a certain adverse event is listed.

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System Organ Class	Common ≥ 1/100	Uncommon <1/100, ≥ 1/1000	Post Marketing¹
Eye disorders		Visual disturbance	
Gastrointestinal disorders	Abdominal pain, Nausea	Abdominal distension, Diarrhoea, Vomiting, Constipation	
General disorders and administration site conditions		Fatigue, Irritability, Malaise, Oedema, Sensation of foreign body	
Immune system disorders			Hypersensitivity
Infections and infestations	Vaginal Candidiasis, Vulvovaginal mycotic infection	Candidiasis, Cervicitis, Cystitis, Fungal infection, Urinary tract infection, Vaginal infection, Vaginitis bacterial	
Injury, poisoning and procedural complications	Medical device discomfort, Vaginal contraceptive device expelled	Contraceptive device complication, Device breakage	
Investigations	Weight increased	Blood pressure increased	
Metabolism and nutrition disorders		Increased appetite	
Musculoskeletal and connective tissue disorders		Back pain, Muscle spasms, Pain in extremity	
Nervous system disorders	Headache, Migraine	Dizziness, Hypoaesthesia	
Psychiatric disorders	Depression, Libido decreased	Affect lability, Mood altered, Mood swings	
Renal and urinary disorders		Dysuria, Micturition urgency, Pollakiuria	
Reproductive system and breast disorders	Breast tenderness, Genital pruritus female, Dysmenorrhoea, Pelvic pain, Vaginal discharge	Amenorrhoea, Breast discomfort, Breast enlargement, Breast mass, Cervical polyp, Coital bleeding, Dyspareunia, Ectropion of cervix, Fibrocystic breast disease, Genital discharge, Menorrhagia, Metrorrhagia, Pelvic discomfort, Premenstrual syndrome, Uterine spasm, Vaginal burning sensation, Vaginal odour, Vaginal pain, Vulvovaginal discomfort, Vulvovaginal dryness	Penis disorders ²
Skin and subcutaneous tissue disorders	Acne	Alopecia, Eczema, Pruritus, Rash	Urticaria
Vascular disorders		Hot flush	

1) Listing of adverse events based on spontaneous reporting. It is not possible to determine the exact frequency.

2) Penis disorders includes the following reported terms; rash on his penis, bruised penis, abrasions on penis, irritation on penis, cracks with bleeding on head of penis, penile irritation after sexual intercourse, painful penis after intercourse, dermatitis on his penis and scrotum.

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4.9 Overdose

There have been no reports of serious deleterious effects from an overdose of hormonal contraceptives. Symptoms that may occur in this case are nausea, vomiting and, in young girls, slight vaginal bleeding. There are no antidotes and further treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vaginal ring with progestagen and estrogen, ATC code: G02BB01

NuvaRing contains etonogestrel and ethinylestradiol. Etonogestrel is a 19-nortestosterone-derived progestagen and binds with high affinity to progesterone receptors in the target organs. Ethinylestradiol is an estrogen widely used in contraceptive products. The contraceptive effect of NuvaRing is based on various mechanisms, the most important of which is the inhibition of ovulation.

EFFICACY

Clinical studies were performed worldwide in women between the age of 18 and 40 years. In these studies the overall Pearl Index for NuvaRing amounts to 0.96 (95%CI: 0.64-1.39) and 0.64 (95% CI: 0.35 – 1.07) for the ITT and PP analysis, respectively. These values were similar to the Pearl Indexes obtained for the 0.150 / 0.030 mg LNG/EE COC and to the 3 / 0.030 mg DRSP/EE COC in the comparative studies.

Orally administered combined contraceptives have, next to protection against pregnancy, several positive properties which, together with the negative properties (see Warnings, Undesirable effects), can be useful in deciding on the method of birth control. The cycle is more regular and the menstruation is often less painful and bleeding is lighter. The latter may result in a decrease in the occurrence of iron deficiency. Apart from this, there is evidence of a reduced risk of endometrial cancer and ovarian cancer. Furthermore, the higher dosed COCs (0.05 mg EE) have been shown to reduce the incidence of ovarian cysts, pelvic inflammatory disease, benign breast disease, and ectopic pregnancy. Confirmation is required as to whether these benefits also apply to the lower dosed hormonal contraceptives.

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BLEEDING PATTERN

The bleeding characteristics of NuvaRing were compared to a 0.150 / 0.030 mg LNG/EE COC in more than 1000 women during one year. The results of this study show that the incidence of breakthrough spotting or bleeding was significantly lower in NuvaRing users as compared to the COC users. Furthermore, the incidence of bleeding being restricted exclusively to the hormone-free period was significantly higher in NuvaRing users.

EFFECTS ON BONE MINERAL DENSITY

The effects of NuvaRing (n=76) on bone mineral density (BMD) were studied in comparison to a non-hormonal intrauterine device (IUD) (n=31) in women over a period of two years. No adverse effects on bone mass have been observed.

5.2 Pharmacokinetic properties

Etonogestrel

ABSORPTION

Etonogestrel released by NuvaRing is rapidly absorbed by the vaginal mucosa. Maximum serum concentrations of etonogestrel of approximately 1700 pg/mL are reached at about 1 week after insertion. Serum concentrations show small fluctuations and slowly decrease to approximately 1400 pg/mL after 3 weeks. Absolute bioavailability is approximately 100%, which is higher than after oral administration. Cervical and intrauterine etonogestrel levels were measured in a small number of women using NuvaRing or an oral contraceptive containing 0.150 mg desogestrel and 0.020 mg ethinylestradiol. The observed levels were comparable.

DISTRIBUTION

Etonogestrel is bound to serum albumin and to sex hormone binding globulin (SHBG). The apparent volume of distribution of etonogestrel is 2.3 L/kg.

METABOLISM

Etonogestrel is metabolized by the known pathways of steroid metabolism. The apparent clearance from serum is about 3.5 L/h. No direct interaction was found with the co-administered ethinylestradiol.

ELIMINATION

Etonogestrel serum levels decrease in two phases. The terminal elimination phase is characterized by a half-life of approximately 29 hours. Etonogestrel and its metabolites are excreted at a urinary to biliary ratio of about 1.7:1. The half-life of metabolite excretion is about 6 days.

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Ethinylestradiol

ABSORPTION

Ethinylestradiol released by NuvaRing is rapidly absorbed by the vaginal mucosa. Maximum serum concentrations of about 35 pg/mL are reached 3 days after insertion and decrease to 18 pg/mL after 3 weeks. Absolute bioavailability is approximately 56%, which is comparable with oral administration of ethinylestradiol. Cervical and intrauterine ethinylestradiol levels were measured in a small number of women using NuvaRing or an oral contraceptive containing 0.150 mg desogestrel and 0.020 mg ethinylestradiol. The observed levels were comparable.

Serum ethinylestradiol levels were measured in a comparative randomized trial 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 ethinylestradiol exposure ($AUC_{0-\infty}$) of NuvaRing was statistically significantly lower than that of the patch and the COC, being 10.9, 37.4 and 22.5 ng.h/mL, respectively.

DISTRIBUTION

Ethinylestradiol is highly but non-specifically bound to serum albumin. An apparent volume of distribution of about 15 L/kg was determined.

METABOLISM

Ethinylestradiol 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 sulphate and glucuronides conjugates. The apparent clearance is about 35 L/h.

ELIMINATION

Ethinylestradiol serum levels decrease in two phases. The terminal elimination phase is characterized by a large individual variation in half-life, resulting in a median half-life of approximately 34 hours. Unchanged ethinylestradiol is not excreted; ethinylestradiol metabolites are excreted at a urinary to biliary ratio of 1.3:1. The half-life of metabolite excretion is about 1.5 days.

5.3 Preclinical safety data

Non-clinical data with etonogestrel and ethinylestradiol reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction, other than those already known for humans. However, it should

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be borne in mind that sex steroids can promote the growth of certain hormone-dependent tissues and tumors.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethylene vinylacetate copolymer, 28% vinylacetate;
ethylene vinylacetate copolymer, 9% vinylacetate;
magnesium stearate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

40 months

6.4 Special precautions for storage

Prior to dispensing: 36 months, store at 2 °C - 8 °C.

At the time of dispensing:

The dispenser places a date of dispensing on the packaging. The product should not be inserted after 4 months from the date of dispensing or the expiry date, whichever comes first.

After dispensing: 4 months, do not store above 30 °C

Store in the original package.

6.5 Nature and contents of container

Sachet containing one NuvaRing. The sachet is made of aluminum foil with an inner layer of low-density polyethylene and an outer layer of polyester. It is reclosable and waterproof. The sachet is packed in a printed cardboard box together with the package leaflet. Each box contains 1 or 3 rings.

6.6 Special precautions for disposal and other handling

See Section 4.2: 'Posology and method of administration'. The dispenser has to indicate the date of dispensing on the packaging. It is recommended for the 3-rings presentation to indicate this date on the ply carton as well as on the sachet. NuvaRing should be inserted not later than 4 months from the date of dispensing or the expiry date, which ever comes first.

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

7. MARKETING AUTHORISATION HOLDER

N.V. Organon, P.O. Box 20, 5340 BH Oss, The Netherlands.

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

August 2007

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