SCHEDULING STATUS

S3

1. NAME OF MEDICINAL PRODUCT

NuvaRing® Vaginal Ring

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

NuvaRing contains 11,7 mg etonogestrel and 2,7 mg ethinylestradiol. When placed in the vagina, each ring releases on average 0,120 mg of etonogestrel and 0,015 mg of ethinyl estradiol per day over a 3 week period of use.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

NuvaRing is a smooth, transparent ring without major visible damages, with one transparent to less transparent region. The ring has an outer diameter of 54 mm and a cross-sectional diameter of 4 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

NuvaRing is indicated for contraception.

4.2 Posology and method of administration

Posology

To achieve contraceptive efficacy of NuvaRing. NuvaRing must be used as directed (see "**How to use NuvaRing**" and "**How to start NuvaRing**".

Paediatric population

The safety and efficacy of NuvaRing in adolescents under the age of 18 have not been studied.

Method of administration

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 to 4).

Once NuvaRing has been inserted (see "How to start NuvaRing'") it is left in the vagina continuously for 3 weeks.

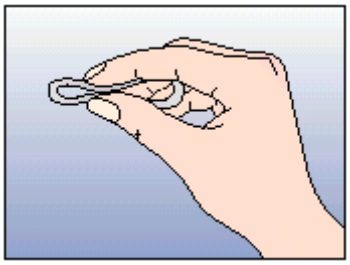
Advise women to regularly check for the presence of NuvaRing in the vagina (for example, before and after intercourse). If NuvaRing is accidentally expelled, the woman should follow the instructions given in Section "**What to do if the ring was temporarily outside the vagina**" (for more information, see also Section "**Expulsion**").

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 under section 6.6. The withdrawal bleed usually starts 2 to 3 days after removal of NuvaRing and may not have finished completely before the next ring insertion is due.

Use with other vaginal products

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

Figure 1
Take NuvaRing out of the sachet



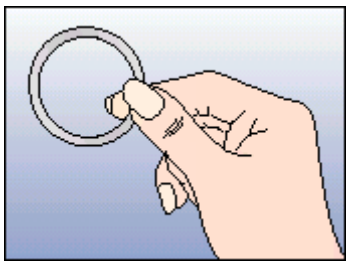


Figure 2
Compress the ring

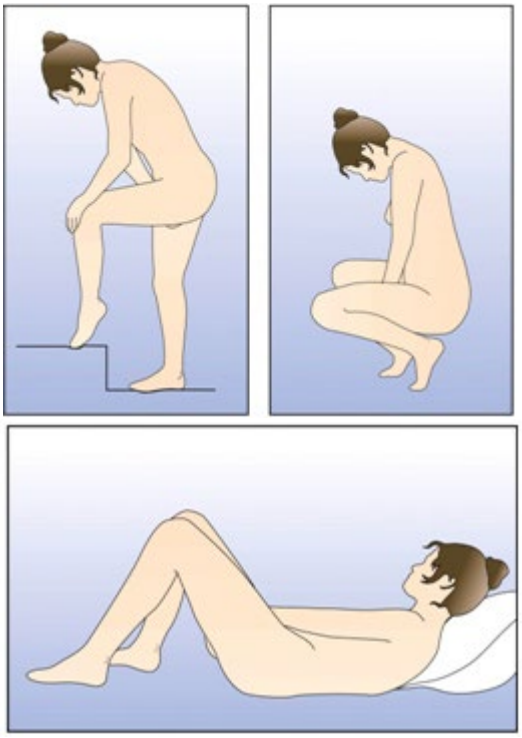
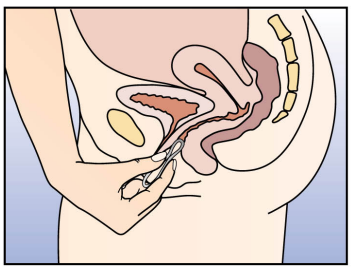
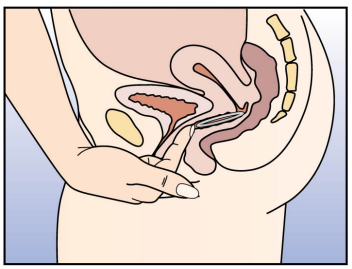


Figure 3
Choose a comfortable position to insert the ring





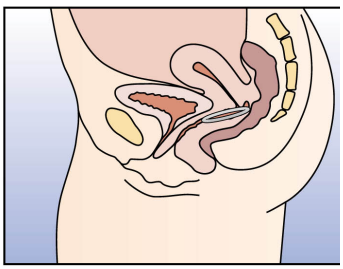


Figure 4A Figure 4B Figure 4C

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).

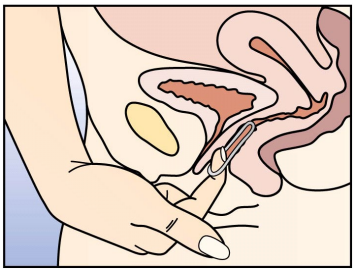


Figure 5:

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.

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 oral contraceptive

The woman should insert NuvaRing at the latest on the day following the usual tablet-free or placebo tablet interval of her previous combined oral 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 progestogen-only method (minipill, implant or injection) or from a progestogen-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 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 need not take additional contraceptive measures. If an immediate switch is considered undesirable, the woman should follow the advice given above 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 breastfeeding women see section 4.6.

Women should be advised to start during the 4th 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. The increased risk of VTE (venous thromboembolism) during the postpartum period should be considered when restarting NuvaRing (see section 4.4).

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 male 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 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 male condom should be 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 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 bleed 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.

If NuvaRing was out of the vagina for an unknown amount of time, the possibility of pregnancy should be considered. A pregnancy test should be performed prior to inserting a new ring.

- **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.

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.

4.3 Contraindications

NuvaRing is contraindicated 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 ischaemic 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).
- Major surgery with prolonged immobilisation (see section 4.4).
- 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 (e.g., hypertension, a family history of thromboembolic events, prolonged immobilisation – see further risk factors for thromboembolism under "**Special warnings and precautions for use, Circulatory Disorders**" below).
- Pancreatitis or a history thereof if associated with severe hypertriglyceridemia.
- Presence or history of hepatic disease as long as liver function values have not returned to normal.
- Presence or history of liver tumours (benign or malignant).
- Known or suspected malignant condition of the genital organs or breast, if sex-steroid influenced.
- Undiagnosed vaginal bleeding.
- Known or suspected pregnancy.
- Hypersensitivity, including anaphylaxis and angioedema, to the active substance or to any of the excipients listed in section 6.1 of NuvaRing.

NuvaRing is contraindicated for use with the Hepatitis C virus (HCV) combination medicine regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir (see section 4.4).

4.4 Special warnings and precautions for use

Warnings

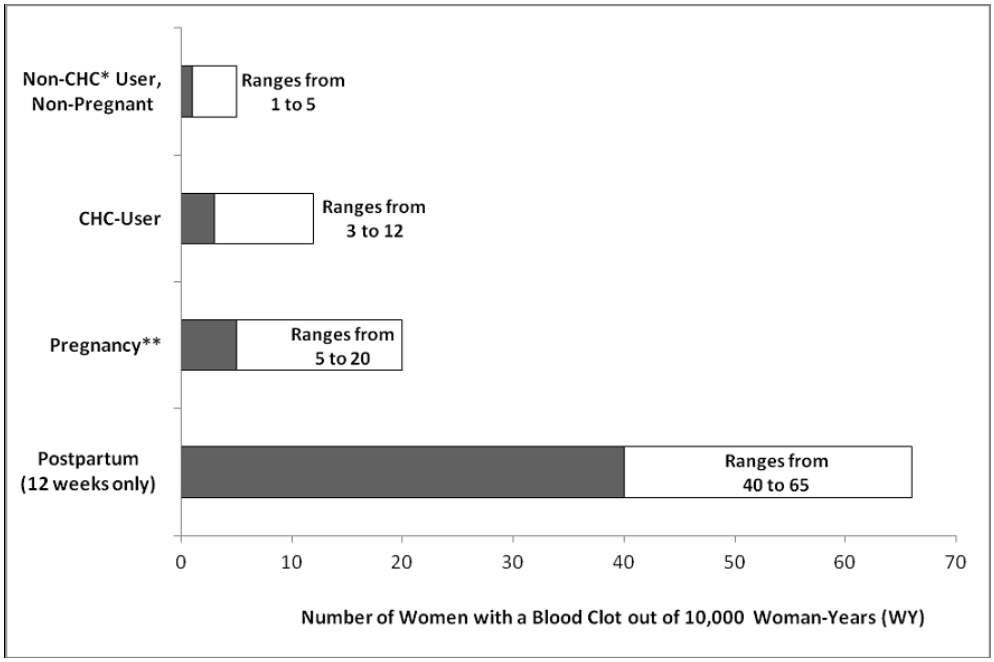
If any of the conditions/risk factors mentioned below is present, the benefits of the use of NuvaRing should be weighed against the possible risks for each individual woman and discussed with the woman before she decides to start using it. In the event of aggravation, exacerbation or first appearance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

Depressed mood and depression are well-known undesirable effects of hormonal contraceptive use (see section 4.8). Depression can be serious and is a well-known risk factor for suicidal behaviour and suicide. Women should be advised to contact their physician in case of mood changes and depressive symptoms, including shortly after initiating the treatment.

1. Circulatory Disorders

- The use of combined hormonal contraceptives (CHCs) has been associated with the occurrence of venous thrombosis (deep vein thrombosis and pulmonary embolism) and arterial thrombosis and associated complications, sometimes with fatal consequences.
- Use of oral or non-oral combined hormonal contraceptives carries an increased risk of venous thromboembolism (VTE) compared with no use. The excess risk of venous thromboembolism is highest during the first year a woman ever uses a combined hormonal contraceptive. Data from a large, prospective cohort safety study of various combined hormonal contraceptives suggest that this increased risk, as compared to that in non-combined oral contraceptive users, is greatest during the first 6 months of combined hormonal contraceptive use and is present after initially starting a combined hormonal contraceptive or restarting (following a 4 week or greater pill-free interval) the same or a different combined hormonal contraceptive. This increased risk is less than the risk of VTE associated with pregnancy which is estimated as 5 to 20 cases per 10 000 women-years (WY). VTE is fatal in 1 to 2 % of cases.
- The figure below shows the risk of developing a VTE for women who are not pregnant and do not use oral contraceptives, for women who use oral contraceptives, for pregnant women, and for women in the postpartum period. To put the risk of developing a VTE into perspective: If 10 000 women who are not pregnant and do not use oral contraceptives are followed for one year, between 1 and 5 of these women will develop a VTE.

  Likelihood of Developing a VTE



*CHC=combined hormonal contraception

**Pregnancy data based on actual duration of pregnancy in the reference studies. Based on a model assumption that pregnancy duration is nine months, the rate is 7 to 27 per 10 000 WY.

- In studies required or sponsored by regulatory agencies, NuvaRing users had a risk of VTE similar to combined oral contraceptive users (see table below for adjusted hazard ratios). A large prospective, observational study, the Transatlantic Active Surveillance on Cardiovascular Safety of NuvaRing (TASC), investigated the risk of VTE for new users, switchers, and restarters of NuvaRing and combined oral contraceptives in a population that is representative of routine clinical users. The women were followed for 24 to 48 months. The results showed a similar risk of VTE among NuvaRing users (VTE incidence 8,3 per 10 000 WY) and women using combined oral contraceptives (VTE incidence 9,2 per 10 000 WY). For women using combined oral contraceptives, excluding desogestrel (DSG), gestodene (GSD) and drospirenone (DRSP), VTE incidence was 8,5 per 10 000 WY.
- A retrospective cohort study using data from 4 health plans in the US ("FDA-funded study") showed a VTE incidence for new users of NuvaRing of 11,4 events per 10 000 WY and for new users of a levonorgestrel (LNG)-containing COC of 9,2 events per 10 000 WY.

Estimates (Hazard Ratios) of Venous Thromboembolism Risk in Users of NuvaRing Compared to Users of Combined Oral Contraceptives (COCs)

Epidemiologic Study (Author, Year of Publication) Population Studied	**Comparator Product(s)**	**Hazard Ratios (HR) (95 % CI)**
TASC (Dinger, 2012) Initiators, including new users, switchers and restarters	All COCs available during the course of the study* COCs available excluding DSG-, GSD-, DRSP-containing OCs	HR†: 0,8 (0,5-1,5) HR†: 0,9 (0,4-2,0)
"FDA-funded study" (Sidney, 2011) First use of a combined hormonal contraceptive (CHC) during the study period	COCs available during the course of the study§ LNG/0.03 mg ethinyl estradiol	HR¶: 1,09 (0,55-2,16) HR¶: 0,96 (0,47-1,95)

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

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

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

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

- Extremely rarely, thrombosis has been reported to occur in other blood vessels e.g., hepatic, mesenteric, renal, cerebral or retinal veins and arteries, in combination oral contraceptive users. There is no consensus as to whether the occurrence of these events is associated with the use of combination oral contraceptive.
- Symptoms of venous or arterial thrombosis can include: Unusual 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.
    - prolonged immobilisation, 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 4 weeks in advance) and not to resume until 2 weeks after complete remobilisation. See also section 4.3 "**Contraindications**".
    - obesity (body mass index over 30 kg/m^2)
    - and possibly also with superficial thrombophlebitis and varicose veins. There is no consensus about the possible role of these conditions in the aetiology of venous thrombosis.
- The risk of arterial thromboembolic complications increases with:
    - older age, especially older than 35 years
    - smoking (with both heavier smoking and older age the risk further increases, especially in women over 35 years of age)

- dyslipoproteinemia
- obesity (body mass index over 30 kg/m^2)
- 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, chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis) and sickle cell disease.
- The increased risk of thromboembolism in the puerperium must be considered (for information on "**Fertility, pregnancy and lactation**" see Section 4.6).
- An increase in the 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.
- Women using combined hormonal contraceptives (CHCs) should be advised to contact their medical practitioner in case of possible symptoms of thrombosis. In case of suspected or confirmed thrombosis, combined hormonal contraceptive use should be discontinued. Adequate contraception should be initiated because of the teratogenicity of anti-coagulant therapy (coumarins).

2. Tumours

- The most important risk factor for cervical cancer is persistent human papilloma virus (HPV) infection. Epidemiological studies have indicated that long-term use of COC's contributes to this increased risk, but there continues to be uncertainty about the extent to which this finding is attributable to confounding effects, like increased cervical screening and difference in sexual behaviour including use of barrier contraceptives, or a causal association. 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 combination oral contraceptives. The excess risk gradually disappears during the course of the 10 years after cessation of combination oral contraceptive use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent combination oral contraceptive 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.
- In another epidemiological study of 1,8 million Danish women followed an average of 10,9 years, the reported RR of breast cancer among COC users increased with longer duration of use compared with women who never used COCs (overall RR = 1,19; RR ranged from 1,17 for 1 to less than 5 years of use to 1,46 after more than 10 years of use). The reported absolute risk difference (number of breast cancer cases between never users compared with current and recent COC users) was small: 13 per 100 000 woman-years.
- 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 tumours, and even more rarely, malignant liver tumours have been reported in users of combination oral contraceptives. In isolated cases, these tumours have led to life-threatening intra-abdominal haemorrhages. Therefore, a hepatic tumour should be

considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal haemorrhage occur in women using NuvaRing.

3. Hypersensitivity reactions

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

4. Hepatitis C

During clinical trials with the HCV combination medicine regimen ombitasvir/paritaprevir/ritonavir with and without dasabuvir, ALT elevations greater than 5 times the upper limit of normal (ULN) were significantly more frequent in women using ethinylestradiol-containing medications such as CHCs. NuvaRing must be discontinued prior to starting therapy with the combination medicine regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir (see section 4.3 and 4.5). NuvaRing can be restarted approximately 2 weeks following completion of treatment with the combination medicine regimen.

5. 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. However, if a sustained clinically significant hypertension develops during the use of NuvaRing then it is 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 uremic 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 progestogens 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 contraceptives. However, diabetic women should be carefully monitored while using NuvaRing especially in the first months of use.
- Crohn's disease and ulcerative colitis have been associated 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 while 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, or that the use of NuvaRing affects the treatment of vaginitis (see section 4.5 "**Interaction with other medicinal products and other forms of interaction**".

- Very rarely, it has been reported that the ring adhered to vaginal tissue, necessitating removal by a healthcare provider. In some cases when the tissue had grown over the ring, removal was achieved by cutting the ring without incising the overlaying vaginal tissue.

Medical Examination/Consultation

Prior to the initiation or reinstitution 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 "**Special warnings and precautions for use**" **(**section 4.4). The frequency and nature of these assessments should be based on established practice guidelines and be adapted to the individual woman.

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

Reduced Efficacy

The efficacy of NuvaRing may be reduced in the event of non-compliance (section 4.2, "**Deviations from the recommended regimen**"), or when concomitant medications that decrease the plasma concentrations are used (section 4.8).

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.

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.

Broken rings

On rare occasions NuvaRing has been reported to get disconnected during use (see section 4.5). Since NuvaRing's core is solid, its contents will remain intact and release of hormones will not be significantly affected. Vaginal injury associated with ring breakage has been reported. In the event of disconnection of the ring, expulsion is likely to occur (see section 4.4, "**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.

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 (for example, before and after intercourse). If NuvaRing is accidentally expelled, the woman should follow the instructions given in section 4.2 ("**What to do if the ring is temporarily outside the vagina**").

4.5 Interaction with other medicines and other forms of interaction

Interaction with other medicinal products

Note: the prescribing information of concomitant medications should be consulted to identify potential 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 or herbal products that induce microsomal enzymes, specifically cytochrome P450 enzymes (CYP), which can result in increased clearance reducing plasma concentrations of sex hormones and may decrease the effectiveness of combined hormonal contraceptives, including NuvaRing. These products include phenytoin, phenobarbital, primidone, bosentan, carbamazepine, rifampicin, and possibly also oxcarbamazepine, topiramate, felbamate, griseofulvin, some HIV protease inhibitors (e.g., ritonavir) and non-nucleoside reverse transcriptase inhibitors (e.g., efavirenz), and products containing the herbal remedy *St. John's wort*.

Enzyme induction can occur after a few days of treatment. Maximal enzyme induction is generally observed within a few weeks. After medicine therapy is discontinued, enzyme induction can last for about 28 days.

When co-administered with hormonal contraceptives, many combinations of HIV protease inhibitors (e.g., nelfinavir) and non-nucleoside reverse transcriptase inhibitors (e.g., nevirapine), and/or combinations with Hepatitis C virus (HCV) medicinal products (e.g., boceprevir, telaprevir), can increase or decrease plasma concentrations of progestins, including etonogestrel, or estrogen. The net effect of these changes may be clinically relevant in some cases.

Women receiving any of the above-mentioned hepatic enzyme-inducing medicinal or herbal products should be advised that the efficacy of NuvaRing may be reduced. A barrier

contraceptive method should be used in addition to NuvaRing administration of the hepatic enzyme-inducing medicinal product, and for 28 days after discontinuation of the hepatic enzyme-inducing medicinal product. Note: NuvaRing should not be used with a diaphragm, cervical cap or female condom.

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

For women on long-term therapy with enzyme-inducing medicinal products, an alternative method of contraception unaffected by enzyme-inducing medicinal products should be considered.

In a pharmacokinetic interaction study, oral administration of amoxicillin (875 mg, two times daily) or doxycycline (200 mg on day 1, followed by 100 mg per day) for 10 days during the use of NuvaRing, did not significantly affect the pharmacokinetics of etonogestrel and ethinylestradiol (EE). The effects of other antibiotics on etonogestrel or ethinylestradiol concentrations have not been evaluated.

Concomitant administration of strong (e.g., ketoconazole, itraconazole, clarithromycin) or moderate (e.g., fluconazole, diltiazem, erythromycin) CYP3A4 inhibitors may increase the serum concentrations of estrogens or progestins, including etonogestrel.

There have been reports of ring breakage during concomitant use of intravaginal preparations, including antimycotic, antibiotic and lubricant products (see section 4.4 “**Broken Rings**”). Based on pharmacokinetic data, vaginally administered antimycotics and spermicides are unlikely to affect the contraceptive efficacy and safety of NuvaRing.

Hormonal contraceptives may interfere with the metabolism of other medicines. Accordingly,

plasma and tissue concentrations may either increase (e.g., cyclosporin) or decrease (e.g., lamotrigine).

During clinical trials with the HCV combination medicine regimen ombitasvir/paritaprevir/ritonavir with and without dasabuvir, ALT elevations greater than 5 times the upper limit of normal (ULN) were significantly more frequent in women using ethinylestradiol-containing medications such as CHCs. NuvaRing must be discontinued prior to starting therapy with the combination medicine regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir (see section 4.3 and 4.5). NuvaRing can be restarted approximately 2 weeks following completion of treatment with the combination medicine regimen.

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.

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).

4.6 Fertility, pregnancy and lactation

Fertility

NuvaRing is indicated for the prevention of pregnancy. If the woman wants to stop using NuvaRing because she wants to get pregnant, she is advised to wait until she has a natural period before trying to conceive as this will help her calculate when the baby is due.

Pregnancy

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 combined oral contraceptives prior to pregnancy, nor a teratogenic effect when combined oral contraceptives were used inadvertently during early pregnancy. Although this probably applies to all combined oral contraceptives 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 the contraceptive steroids in NuvaRing are likely to be higher than in combined oral contraceptive users. Clinical experience of the outcomes of pregnancies exposed to NuvaRing has not been reported.

Lactation

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.

Adverse medicine reactions that have been reported in users of NuvaRing are listed in the Table below. The most appropriate MedDRA term (version 11.0) to describe a certain adverse event is listed.

All adverse reactions are listed by system organ class and frequency: common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), and not known (cannot be estimated from the available data).

System Organ Class	**Common**	**Uncommon**	**Rare**	**Not Known[1]**
Infections and infestations	Vaginal infection	Cervicitis, cystitis, urinary tract infection		
Immune system disorders				Hypersensitivity reactions, including angioedema and anaphylaxis
Metabolism and nutrition disorders		Increased appetite		
Psychiatric	Depression,	Mood altered		

System Organ Class	Common	Uncommon	Rare	Not Known[1]
disorders	decreased libido			
Nervous system disorders	Headache, migraine	Dizziness, hypoesthesia		
Eye disorders		Visual disturbance		
Vascular disorders		Hot flushes	Venous thrombo-embolism[3], arterial thrombo-embolism[3]	
Gastrointestinal disorders	Abdominal pain, nausea	Diarrhoea, vomiting, abdominal distension, constipation		
Skin and subcutaneous tissue disorders	Acne	Alopecia, eczema, pruritus, rash		Urticaria
Musculoskeletal and connective tissue disorders		Back pain, muscle spasms, pain in extremity		
Renal and urinary disorders		Dysuria, micturition		

System Organ Class	Common	Uncommon	Rare	Not Known[1]
		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, menorrhagia, metrorrhagia, pelvic discomfort, premenstrual syndrome, uterine spasm, vaginal burning sensation, vaginal odour, vaginal pain, vulvovaginal		Penis disorders[2], galactorrhoea

System Organ Class	Common	Uncommon	Rare	Not Known[1]
		discomfort, vulvovaginal dryness		
General disorders and administration site conditions		Fatigue, irritability, malaise, oedema, sensation of foreign body		
Investigations	Weight increased	Blood pressure increased		
Injury, poisoning and procedural complications	Medical device discomfort, Vaginal contraceptive device expelled	Contraceptive device complication, Device breakage		Vaginal injury associated with ring breakage

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

[2] 'Penis disorders' includes reports of 'local reaction on penis'.

[3] Incidence in observational cohort studies of: ≥ 1/10 000 to < 1/1 000 women-years

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.

Mechanism of action

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

5.2 Pharmacokinetic Properties

Etonogestrel

Absorption

Etonogestrel released by NuvaRing is absorbed rapidly by the vaginal mucosa. Maximum serum concentrations of etonogestrel of approximately 1 700 pg/mL are reached at about 1 week after insertion. Serum concentrations show small fluctuations and slowly decrease to approximately 1 600 pg/mL after 1 week, 1 500 pg/mL after 2 weeks and 1 400 pg/mL after 3 weeks of use. Absolute bioavailability is approximately 100 %, which is higher than after oral administration.

Distribution

Etonogestrel is bound to serum albumin and to sex hormone binding globulin (SHBG). The apparent volume of distribution of etonogestrel is 2,3 litre/kg.

Metabolism

Etonogestrel is metabolised by the known pathways of steroid metabolism. The apparent clearance from serum is about 3,5 litre/h. No direct interaction was found with the co-administered ethinylestradiol.

Elimination

Etonogestrel serum levels decrease in 2 phases. The terminal elimination phase is characterised 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.

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 19 pg/mL after 1 week, 18 pg/mL after 2 weeks and 18 pg/mL after 3 weeks if use. Absolute bioavailability is approximately 56 %, which is comparable with oral administration of ethinylestradiol.

Distribution

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

Metabolism

Ethinylestradiol is primarily metabolised by aromatic hydroxylation but a wide variety of hydroxylated and methylated metabolites are formed. These are present as free metabolites and as sulphate and glucuronide conjugates. The apparent clearance is about 35 litre/h.

Elimination

Ethinylestradiol serum levels decrease in 2 phases. The terminal elimination phase is characterised 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.

SPECIAL POPULATIONS

Paediatric population

The pharmacokinetics of NuvaRing in healthy postmenarcheal female adolescents under the age of 18 have not been studied.

Effect of renal impairment

No studies were performed to evaluate the effect of renal disease on the pharmacokinetics of NuvaRing.

Effect of hepatic impairment

No studies were performed to evaluate the effect of hepatic disease on the pharmacokinetics of NuvaRing. However, steroid hormones may be poorly metabolized in women with impaired liver function.

Ethnic groups

No formal studies were performed to assess pharmacokinetics in ethnic groups.

5.3 Preclinical Safety Data

Preclinical 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. However, it should be borne in mind that sex steroids can promote the growth of certain hormone-dependent tissues and tumours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethylene vinyl acetate copolymer, 28 % vinyl acetate;

ethylene vinyl acetate copolymer, 9 % vinyl acetate

magnesium stearate.

6.2 Incompatibilities

Not Applicable

6.3 Shelf-life

Not Applicable

6.4 Special precautions for storage

Store NuvaRing in the original package.

Prior to dispensing: Refrigerate at 2 to 8 °C for up to 36 months.

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

After dispensing: Store at room temperature below 30 °C for up to 4 months.

Keep out of reach of children.

6.5 Nature and contents of container

NuvaRing contraceptive vaginal ring is ready-for-use, packed in a sealed reclosable sachet of laminated aluminium foil with a low-density polyethylene heat seal coating on the inside in contact with the vaginal ring, and a non-sealable polyethyleneterephthalate layer on the outside. The

sachet incorporates a low-density polyethylene reclosable feature (zipper) so that after use the ring can be put back into it, for hygienic disposal. The sachet is placed into a flat carton box. Each box contains 1 ring.

NuvaRing is a smooth, transparent ring without major visible damages, with one transparent to less transparent region. The ring has an outer diameter of 54 mm and a cross-sectional diameter of 4 mm.

6.6 Special precautions for disposal and other handling

See section 4.2. The dispenser has to indicate on the box the date of dispensing and the date before which NuvaRing has to be used. After removal, NuvaRing should be stored in the reclosable sachet. NuvaRing should be disposed of with the normal household waste in a manner that avoids accidental contact with other people. NuvaRing should not be flushed down the toilet.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Organon South Africa (Pty) Ltd

Spaces, 1st Floor, 22 Magwa Crescent, Gateway West

Waterfall City, Midrand, 2090

South Africa

8. REGISTRATION NUMBER

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