Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

NuvaRing 0.120 mg/0.015 mg per 24 hours, vaginal delivery system

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 per 24 hours, over a period of 3 weeks.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Vaginal delivery system.
NuvaRing is flexible, transparent, colourless 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.

NuvaRing is intended for women of fertile age. The safety and efficacy have been established in women aged 18 to 40 years.

The decision to prescribe NuvaRing should take into consideration the individual woman's current risk factors, particularly those for venous thromboembolism (VTE), and how the risk of VTE with NuvaRing compares with other combined hormonal contraceptives (CHCs) (see sections 4.3 and 4.4).

4.2 Posology and method of administration

Posology

To achieve contraceptive effectiveness, 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. An optional alternative is to insert the ring using the NuvaRing Applicator which is distributed separately or is included in the package. The NuvaRing Applicator may not be available in all countries. 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. 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 4.2, 'What to do if the ring is temporarily outside the vagina' (for more information, see also section 4.4, '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. w*hen 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.

Use with other female vaginal barrier methods

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

How to insert NuvaRing with fingers only:

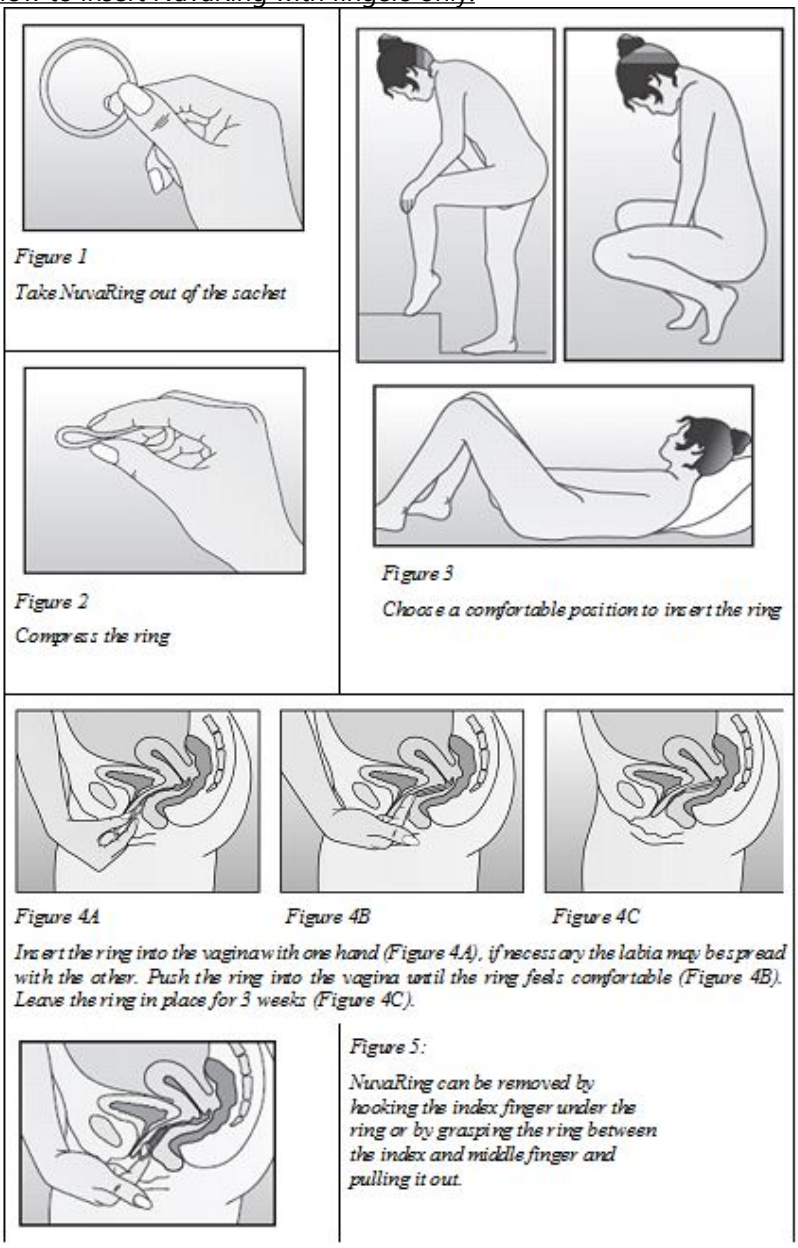


Figure 1

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*

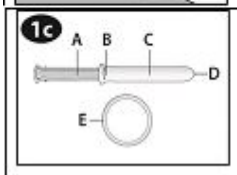
Insert the ring into the vagina with one hand (Figure 4A), if necessary the labia may be spread with the other. Push the ring into the vagina until the ring feels comfortable (Figure 4B). Leave the ring in place for 3 weeks (Figure 4C).

Figure 5:

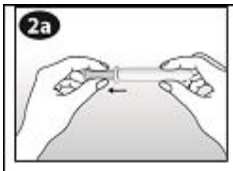
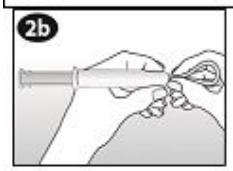
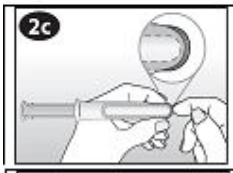
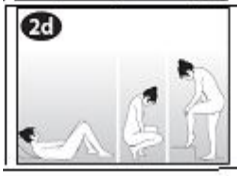
NuvaRing can be removed by hooking the index finger under the ring or by grasping the ring between the index and middle finger and pulling it out.

How to insert NuvaRing with the applicator:

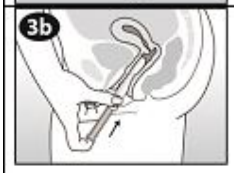
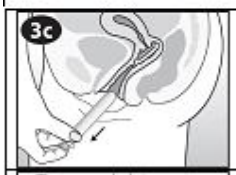
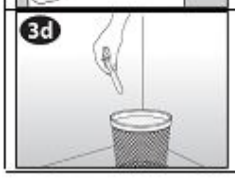
1: Prepare

	Wash your hands before opening the package. Open ONLY immediately before use. DO NOT use if the contents or packaging are visibly damaged.
	The applicator is for use with the NuvaRing ring ONLY, not with other products.
	Review the picture of the applicator to familiarise yourself with the parts of the applicator. A. Plunger B. Finger Grip C. Barrel D. Barrel Opening E. NuvaRing

2: Load & Position

	Pull the plunger back gently until it stops.
	Squeeze opposite sides of the ring together and insert the ring into the barrel opening.
	Gently push the ring into the barrel. The tip of the ring should stick out slightly from the barrel opening.
	Choose the position for inserting the ring that is most comfortable for you, like lying down, squatting, or standing with one leg up.

3: Insert & Dispose

	Place your thumb and middle finger on the finger grip.
	Gently insert the barrel into the vagina until your fingers (on the finger grip) touch your body. Then use your index finger to gently push the plunger entirely into the barrel. Some women have experienced a brief mild pinching sensation when using the applicator.
	The ring is pushed out of the applicator. Gently remove the applicator.
	Confirm that the ring is NOT in the applicator. Dispose of the used applicator with the normal household waste. DO NOT flush the applicator down the toilet. DO NOT reuse the applicator.

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 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 application 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.

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 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 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 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 (7×24 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

Although this is not the recommended regimen, 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

If in exceptional cases a period needs to be **delayed**, 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

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

- Presence or risk of venous thromboembolism (VTE)
    - Venous thromboembolism - current VTE (on anticoagulants) or history of (e.g. deep venous thrombosis [DVT] or pulmonary embolism [PE]).
    - Known hereditary or acquired predisposition for venous thromboembolism, such as APC-resistance (including Factor V Leiden), antithrombin-III-deficiency, protein C deficiency, protein S deficiency.
    - Major surgery with prolonged immobilisation (see section 4.4).
    - A high risk of venous thromboembolism due to the presence of multiple risk factors (see section 4.4).
- Presence or risk of arterial thromboembolism (ATE)
    - Arterial thromboembolism - current arterial thromboembolism, history of arterial thromboembolism (e.g. myocardial infarction) or prodromal condition (e.g. angina pectoris).
    - Cerebrovascular disease – current stroke, history of stroke or prodromal condition (e.g.transient ischaemic attack, TIA).
    - Known hereditary or acquired predisposition for arterial thromboembolism, such as hyperhomocysteinaemia and antiphospholipid-antibodies (anticardiolipin-antibodies, lupus anticoagulant).
    - History of migraine with focal neurological symptoms.
    - A high risk of arterial thromboembolism due to multiple risk factors (see section 4.4) or to the presence of one serious risk factor such as:
        - diabetes mellitus with vascular symptoms
        - severe hypertension
        - severe dyslipoproteinaemia.
- 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 tumours (benign or malignant).
- Known or suspected malignant conditions of the genital organs or the breasts, if sex steroid-influenced.
- Undiagnosed vaginal bleeding.
- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1 of NuvaRing

NuvaRing is contraindicated for concomitant use with medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir, medicinal products containing glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir (see section 4.5).

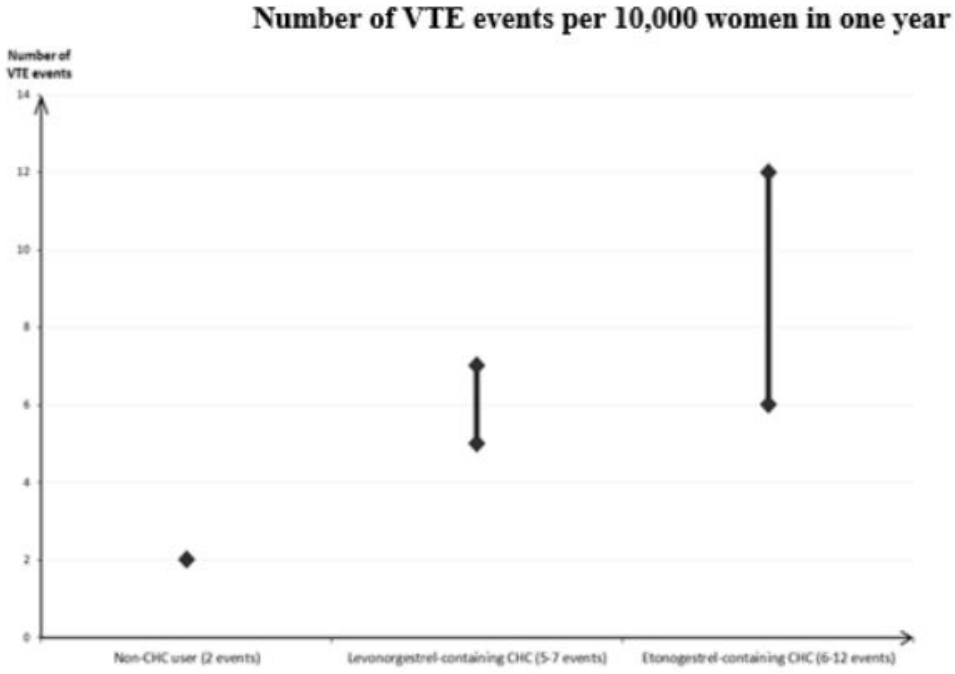
4.4 Special warnings and precautions for use

Warnings
If any of the conditions or risk factors mentioned below is present, the suitability of NuvaRing should be discussed with the woman.

In the event of aggravation, or first appearance of any of these conditions or risk factors, the woman should be advised to contact her doctor to determine whether the use of NuvaRing should be discontinued.

1. Circulatory Disorders
Risk of venous thromboembolism (VTE)
The use of any combined hormonal contraceptive (CHC) increases the risk of venous thromboembolism (VTE) compared with no use. Products that contain levonorgestrel, norgestimate or norethisterone are associated with the lowest risk of VTE. Other products such as NuvaRing may have up to twice this level of risk. The decision to use any product other than one with the

lowest VTE risk should be taken only after a discussion with the woman to ensure she understands the risk of VTE with NuvaRing, how her current risk factors influence this risk, and that her VTE risk is highest in the first ever year of use. There is also some evidence that the risk is increased when a CHC is re-started after a break in use of 4 weeks or more.
In women who do not use a CHC and are not pregnant about 2 out of 10,000 will develop a VTE over the period of one year. However, in any individual woman, the risk may be far higher, depending on her underlying risk factors (see below).
It is estimated that out of 10,000 women who use a low dose CHC that contains levonorgestrel, about 6[1] will develop a VTE in one year. Inconsistent results on the risk of VTE with NuvaRing compared with CHCs that contain levonorgestrel have been found (with relative risk estimates ranging from no increase, RR=0.96, to an almost 2-fold increase, RR=1.90). This corresponds to between about 6 and 12 VTEs in a year out of 10,000 women who use NuvaRing.
In both cases, the number of VTEs per year is fewer than the number expected in women during pregnancy or in the postpartum period.
VTE may be fatal in 1-2 % of the cases.



[1]Mid-point range of 5-7 per 10,000 WY, based on a relative risk for CHCs containing levonorgestrel versus non-use of approximately 2.3 to 3.6

Number of VTE events per 10,000 women in one year
• Extremely rarely, thrombosis has been reported to occur in CHC users in other blood vessels, e.g. hepatic, mesenteric, renal, or retinal veins and arteries.

Risk factors for VTE
The risk for venous thromboembolic complications in CHC users may increase substantially in a woman with additional risk factors, particularly if there are multiple risk factors (see table).
NuvaRing is contraindicated if a woman has multiple risk factors that put her at high risk of venous thrombosis (see section4.3).
If a woman has more than one risk factor, it is possible that the increase in risk is greater than the sum of the individual factors – in this case her total risk of VTE should be considered. If the balance of benefits and risks is considered to be negative, a CHC should not be prescribed (see section4.3).

Table: Risk factors for VTE

Risk factor	Comment
Obesity (body mass index over 30kg/m^2)	Risk increases substantially as BMI rises. Particularly important to consider if other risk factors also present.
Prolonged immobilisation, major surgery, any surgery to the legs or pelvis, neurosurgery, or major trauma Note: Temporary immobilisation including air travel > 4 hours can	In these situations it is advisable to discontinue use of the patch/pill/ring (in the case of elective surgery at least four weeks in advance) and not resume until two weeks after complete remobilisation. Another method

Risk factor	Comment
also be a risk factor for VTE, particularly in women with other risk factors.	of contraception should be used to avoid unintentional pregnancy. Antithrombotic treatment should be considered if NuvaRing has not been discontinued in advance.
Positive family history (venous thromboembolism ever in a sibling or parent especially at a relatively early age, e.g. before 50)	If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any CHC use.
Other medical conditions associated with VTE	Cancer, systemic lupus erythematosus, haemolytic uraemic syndrome, chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis) and sickle cell disease
Increasing age	Particularly above 35 years

• There is no consensus about the possible role of varicose veins and superficial thrombophlebitis in the onset or progression of venous thrombosis.
• The increased risk of thromboembolism in pregnancy, and particularly the 6-week period of the puerperium, must be considered (for information on Pregnancy and lactation see section 4.6).

Symptoms of VTE (deep vein thrombosis and pulmonary embolism)
In the event of symptoms women should be advised to seek urgent medical attention and to inform the healthcare professional that she is taking a CHC.

Symptoms of deep vein thrombosis (DVT) can include:
- unilateral swelling of the leg and/or foot or along a vein in the leg;
- pain or tenderness in the leg which may be felt only when standing or walking;
- increased warmth in the affected leg; red or discoloured skin on the leg.

Symptoms of pulmonary embolism (PE) can include:
- sudden onset of unexplained shortness of breath or rapid breathing;
- sudden coughing which may be associated with haemoptysis;
- sharp chest pain;
- severe light headedness or dizziness;
- rapid or irregular heartbeat.

Some of these symptoms (e.g. "shortness of breath", "coughing") are non-specific and might be misinterpreted as more common or less severe events (e.g. respiratory tract infections).

Other signs of vascular occlusion can include: sudden pain, swelling and slight blue discolouration of an extremity.

If the occlusion occurs in the eye symptoms can range from painless blurring of vision which can progress to loss of vision. Sometimes loss of vision can occur almost immediately.

Risk of arterial thromboembolism (ATE)
Epidemiological studies have associated the use of CHCs with an increased risk for arterial thromboembolism (myocardial infarction) or for cerebrovascular accident (e.g. transient ischaemic attack, stroke). Arterial thromboembolic events may be fatal.

Risk factors for ATE
The risk of arterial thromboembolic complications or of a cerebrovascular accident in CHC users increases in women with risk factors (see table). NuvaRing is contraindicated if a woman has one serious or multiple risk factors for ATE that puts her at high risk of arterial thrombosis (see section4.3). If a woman has more than one risk factor, it is possible that the increase in risk is greater than the sum of the individual factors – in this case her total risk should be considered. If the balance of benefits and risks is considered to be negative a CHC should not be prescribed (see section4.3).

Table: Risk factors for ATE

Risk factor	Comment
Increasing age	Particularly above 35 years

Smoking	Women should be advised not to smoke if they wish to use a CHC. Women over 35 who continue to smoke should be strongly advised to use a different method of contraception.
Hypertension	
Obesity (body mass index over 30kg/m^2)	Risk increases substantially as BMI increases. Particularly important in women with additional risk factors
Positive family history (arterial thromboembolism ever in a sibling or parent especially at relatively early age, e.g. below 50)	If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any CHC use.
Migraine	An increase in frequency or severity of migraine during CHC use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation.
Other medical conditions associated with adverse vascular events	Diabetes mellitus, hyperhomocysteinaemia, valvular heart disease and atrial fibrillation, dyslipoproteinaemia and systemic lupus erythematosus.

Symptoms of ATE

In the event of symptoms women should be advised to seek urgent medical attention and to inform the healthcare professional that she is taking a CHC.

Symptoms of a cerebrovascular accident can include:
- sudden numbness or weakness of the face, arm or leg, especially on one side of the body;
- sudden trouble walking, dizziness, loss of balance or coordination;
- sudden confusion, trouble speaking or understanding;
- sudden trouble seeing in one or both eyes;
- sudden, severe or prolonged headache with no known cause;
- loss of consciousness or fainting with or without seizure.

Temporary symptoms suggest the event is a transient ischaemic attack (TIA).

Symptoms of a myocardial infarction (MI) can include:
- pain, discomfort, pressure, heaviness, sensation of squeezing or fullness in the chest, arm, or below the breastbone;
- discomfort radiating to the back, jaw, throat, arm, stomach;
- feeling of being full, having indigestion or choking;
- sweating, nausea, vomiting or dizziness;
- extreme weakness, anxiety, or shortness of breath;
- rapid or irregular heartbeats.

- In case of suspected or confirmed VTE or ATE, CHC use should be discontinued. Adequate contraception should be initiated because of the teratogenicity of anti-coagulant therapy (coumarins).

2. Tumours

- Epidemiological studies indicate that the long-term use of oral contraceptives displays a risk factor for the development of cervical cancer in women infected with human papillomavirus (HPV). However, there is still uncertainty about the extent to which this finding is influenced by confounding effects (e.g. differences in number of sexual partners or in use of barrier contraceptives). No epidemiological data on the risk of cervical cancer in users of NuvaRing are available (see 'medical examination/consultation').
- 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 tumours, and even more rarely, malignant liver tumours have been reported in users of COCs. 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. 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 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; haemolytic uraemic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss.
- Exogenous oestrogens may induce or exacerbate symptoms of hereditary and acquired 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 oestrogens 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.

- New onset or deterioration of Crohn's disease and ulcerative colitis has been reported to occur with the use of hormonal contraceptives, but the evidence of an association with its use is inconclusive.
- 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, or that the use of NuvaRing affects the treatment of vaginitis (see section 4.5).
- 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 overlying vaginal tissue.
- 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.

Medical examination/consultation

Prior to the initiation or reinstitution of NuvaRing use a complete medical history (including family history) should be taken and pregnancy must be ruled out. Blood pressure should be measured and a physical examination should be performed, guided by the contraindications (see section 4.3) and warnings (see section 4.4). It is important to draw a woman’s attention to the information on venous and arterial thrombosis, including the risk of NuvaRing compared with other CHCs, the symptoms of VTE and ATE, the known risk factors and what to do in the event of a suspected thrombosis.

The woman should also be instructed to carefully read the user leaflet and to adhere to the advice given. The frequency and nature of examinations should be based upon established practice guidelines and be adapted to the individual woman.

Women should be advised that hormonal contraceptives do 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), or when concomitant medications that decrease the plasma concentration of ethinylestradiol and/or etonogestrel are used (section 4.5).

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 very rare occasions NuvaRing has been reported to get disconnected during use (see section 4.5). Vaginal injury associated with ring breakage has been reported. The woman is advised to remove the broken ring and reinsert a new ring as soon as possible and use a barrier method such as a male condom in addition for the next 7 days. The possibility of a pregnancy should be considered and the woman should contact her physician.

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. Prolonged expulsion may lead to contraceptive failure and/or breakthrough bleeding. Therefore, to ensure efficacy the woman should be advised to regularly verify the presence of NuvaRing (for example, before and after intercourse).

If NuvaRing is accidentally expelled and is left outside of the vagina for **less than 3 hours** contraceptive efficacy is not reduced. The woman should rinse the ring with cool to lukewarm (not hot) water and reinsert it 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** contraceptive efficacy may be reduced. In that case, the applicable advice given in section 4.2 'What to do if the ring was temporarily outside the vagina' should be followed.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions WITH OTHER MEDICINAL PRODUCTS

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

Effects of other medicinal products on NuvaRing
Interactions can occur with drugs or herbal products that induce microsomal enzymes which can result in increased clearance of sex hormones and which may lead to breakthrough bleeding and/or contraceptive failure.

Management
Enzyme induction can already be observed after a few days of treatment. Maximum enzyme induction is generally seen within a few weeks. After the cessation of drug therapy, enzyme induction may be sustained for about 4 weeks.

Short-term treatment

Women on treatment with enzyme-inducing drugs or herbal products should temporarily use a barrier method or another method of contraception in addition to NuvaRing. Note: NuvaRing should not be used with a diaphragm, cervical cap, or female condom. The barrier method must be used during the whole time of the concomitant drug therapy and for 28 days after its 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.

Long-term treatment
In women on long-term treatment with hepatic enzyme-inducing active substances, another reliable, non-hormonal method of contraception is recommended.

The following interactions have been reported in the literature.

Substances increasing the clearance of combined hormonal contraceptives
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 oxcarbazepine, 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.

Substances with variable effects on the clearance of combined hormonal contraceptives
When co-administered with hormonal contraceptives, many combinations of HIV protease inhibitors (e.g. nelfinavir) and non-nucleoside reverse transcriptase inhibitors (e.g. nevirapine), and/or combinations with HCV medicinal products (e.g. boceprevir, telaprevir), can increase or decrease plasma concentrations of progestagens, including etonogestrel, or oestrogen. The net effect of these changes may be clinically relevant in some cases.

Substances decreasing the clearance of combined hormonal contraceptives
The clinical relevance of potential interactions with enzyme inhibitors remains unknown.
Concomitant administration of strong (e.g. ketoconazole, itraconazole, clarithromycin) or moderate (e.g. fluconazole, diltiazem, erythromycin) CYP3A4 inhibitors may increase the serum concentrations of oestrogens or progestogens, 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 drugs. Accordingly, plasma and tissue concentrations may either increase (e.g. ciclosporin) or decrease (e.g. lamotrigine).

Pharmacodynamic interactions
During clinical trials with patients treated for hepatitis C virus infections (HCV) with medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, transaminase (ALT) elevations higher than 5 times the upper limit of normal (ULN) occurred significantly more frequently in women using ethinylestradiol-containing medications such as combined hormonal contraceptives (CHCs). Additionally, also in patients treated with glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir, ALT elevations were observed in women using ethinylestradiol-containing medications such as CHCs (see section 4.3). Therefore, NuvaRing users must switch to an alternative method of contraception (e.g., progestagen-only contraception or non-hormonal methods) prior to starting therapy with these combination drug regimens. NuvaRing can be restarted 2 weeks following completion of treatment with these combination drug regimens.

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').

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 COCs prior to pregnancy, nor a teratogenic effect when COCs were used inadvertently during early pregnancy.

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

The increased risk of VTE during the postpartum period should be considered when re-starting NuvaRing (see sections 4.2 and 4.4).

Breastfeeding
Lactation may be influenced by oestrogens, 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 has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The most frequently reported undesirable effects in the clinical trials with NuvaRing were headache and vaginal infections and vaginal discharge, each reported by 5-6% of the women.

Description of selected adverse reactions
An increased risk of arterial and venous thrombotic and thromboembolic events, including myocardial infarction, stroke, transient ischaemic attacks, venous thrombosis and pulmonary embolism has been observed in women using CHCs, which are discussed in more detail in section 4.4.

Also other undesirable effects have been reported in women using CHCs: these are discussed in more detail in section 4.4.

Adverse drug reactions that have been reported in clinical trials, observational studies, or during postmarketing use with NuvaRing are listed in the Table below. The most appropriate MedDRA term 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		

System Organ Class	Common	Uncommon	Rare	Not known[1]
		infection		
Immune system disorders				Hypersensitivityreactions, including anaphylaxis and exacerbation of symptoms of hereditary andacquired angioedema
Metabolism and nutrition disorders		Increased appetite		
Psychiatric disorders	Depression, Libido decreased	Affect lability, Mood altered, Mood swings		
Nervous system disorders	Headache, Migraine	Dizziness, Hypoaesthesia		
Eye disorders		Visual disturbance		
Vascular disorders		Hot flush	Venous thromboembolism Arterial thromboembolism	
Gastrointestinal disorders	Abdominal pain, Nausea	Abdominal distension, Diarrhoea, Vomiting, Constipation		
Skin and subcutaneous tissue disorders	Acne	Alopecia, Eczema, Pruritus, Rash, Urticaria		Chloasma
Musculoskeletal and connective tissue disorders		Back pain, Muscle spasms, Pain in extremity		
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, Menorrhagia, Metrorrhagia, Pelvic discomfort, Premenstrual syndrome, Uterine spasm, Vaginal	Galactorrhoea	Penis disorders

System Organ Class	Common	Uncommon	Rare	Not known[1]
		burning sensation, Vaginal odour, Vaginal pain, Vulvovaginal discomfort, Vulvovaginal dryness		
General disorders and administration site conditions		Fatigue, Irritability, Malaise, Oedema, Sensation of foreign body		Vaginal ring site tissue overgrowth
Investigations	Weight increased	Blood pressure increased		
Injury, poisoning and procedural complications	Vaginal ring discomfort, Vaginal ring expelled	Vaginal ring complication		Vaginal injury associated with ring breakage

[1] Listing of adverse events based on spontaneous reporting.

Hormone-dependent tumours (e.g. liver tumours, breast cancer) have been reported in association with CHC use. For further information see section 4.4.

On very rare occasions NuvaRing has been reported to get disconnected during use (see sections 4.4 and 4.5).

Interactions
Breakthrough bleeding and/or contraceptive failure may result from interactions of other drugs (enzyme inducers) with hormonal contraceptives (see section 4.5).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie

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: Other gynecologicals, Intravaginal contraceptives, vaginal ring with progestagen and oestrogen, ATC code: G02BB01

Mechanism of action
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 oestrogen 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.

Clinical efficacy and safety

Clinical studies were performed worldwide (US, EU, and Brazil) in women between the ages of 18 and 40 years. The contraceptive efficacy appeared to be at least comparable with that known for combined oral contraceptives. The following table shows the Pearl Indices (number of pregnancies per 100 woman years of use) found in the clinical studies with NuvaRing.

Analysis Method	**Pearl Index**	**95 % CI**	**No of Cycles**
ITT (user + method failure)	0.96	0.64 – 1.39	37,977
PP (method failure)	0.64	0.35 – 1.07	28,723

With the use of higher-dosed COCs (0.05 mg ethinylestradiol) the risk of endometrial and ovarian cancer is reduced. Whether this also applies to a lower-dosed contraceptive like NuvaRing remains to be determined.

BLEEDING PATTERN

A large comparative study with 150/30 µg levonorgestrel/ethinylestradiol OC (n= 512 vs n= 518) evaluating vaginal bleeding characteristics over 13 cycles showed low incidences of breakthrough spotting or bleeding for NuvaRing (2.0-6.4%). Furthermore, vaginal bleeding was exclusively restricted to the ring-free interval for most subjects (58.8-72.8 %).

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.

Paediatric population

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

5.2 Pharmacokinetic properties

Etonogestrel

Absorption

Etonogestrel released by NuvaRing is rapidly absorbed 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. 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.

Biotransformation

Etonogestrel is metabolised 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 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 of use. The monthly systemic ethinylestradiol exposure ($AUC_{0-\infty}$) with NuvaRing is 10.9 ng.h/mL. 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.

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

Biotransformation
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 glucuronides conjugates. The apparent clearance is about 35 L/h.

Elimination
Ethinylestradiol serum levels decrease in two 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 conducted to evaluate the effect of hepatic disease on the pharmacokinetics of NuvaRing. However, steroid hormones may be poorly metabolised in women with impaired liver function.

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

5.3 Preclinical safety data

Non-clinical data with ethinylestradiol and etonogestrel 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.

Environmental Risk Assessment (ERA)
Environmental risk assessment studies have shown that 17α-ethinylestradiol and etonogestrel may pose a risk to surface water organisms (see section 6.6).

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:

3 years, store in a refrigerator (2 °C - 8 °C).

At the time of dispensing:

The dispenser places a date of dispensing on the packaging. The product should be inserted no later than 4 months from the date of dispensing, but in all cases prior to the expiry date, whichever comes first.

After dispensing:
4 months, store below 30 °C.

Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

NuvaRing
Sachet containing one NuvaRing. The sachet is made of aluminium foil with an inner layer of low-density polyethylene and an outer layer of polyethylene terephthalate (PET). It is reclosable and waterproof. The sachet is packed in a printed cardboard box together with the package leaflet.

NuvaRing Applicator
Distributed separately or included in the package. The NuvaRing Applicator may not be available in all countries. The applicator is a plastic, non-sterile device made from a polypropylene polymer, containing a friction reduction additive (comprising of less than 5%). It is intended for single use (i.e. disposable). Each applicator is individually packed. The applicator has a CE marking which is embossed on the device.

The product is supplied as:
- Pack of 1 ring
- Pack of 1 ring and 1 applicator
- Pack of 3 rings
- Pack of 3 rings and 3 applicators

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

NuvaRing
See section 4.2. 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 no later than 4 months from the date of dispensing, but in all cases prior to the expiry date, which ever comes first. 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. This medicinal product may pose a risk to the environment (see section 5.3). NuvaRing should not be flushed down the toilet. Any unused (expired) rings should be disposed of in accordance with local requirements.

NuvaRing Applicator
The NuvaRing Applicator must not be reused; it is designed for one time use. If the applicator is accidently dropped, it should be washed with cool to lukewarm (NOT hot) water. The applicator should be disposed of with the normal household waste immediately after use. It should not be flushed down the toilet.

7 MARKETING AUTHORISATION HOLDER

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