AUSTRALIAN PRODUCT INFORMATION

NUVARING®

(ethinylestradiol and etonogestrel) Vaginal ring

1 NAME OF THE MEDICINE

Etonogestrel and ethinylestradiol

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Controlled-release contraceptive ring for vaginal use. NuvaRing releases etonogestrel and ethinylestradiol at an average amount of 120 µg and 15 µg, respectively, per 24 hours, over a period of 3 weeks. The ring contains 11.7 mg etonogestrel and 2.7 mg ethinylestradiol.

For full list of excipients, see **Section 6.1 List of Excipients**.

3 PHARMACEUTICAL FORM

Vaginal drug delivery system.

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

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

For use for contraception.

4.2 DOSE AND METHOD OF ADMINISTRATION

DOSE

To achieve contraceptive effectiveness, NuvaRing must be used as directed (see 'HOW TO USE NUVARING' and 'HOW TO START NUVARING').

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 1-4*). However, it must be inserted correctly to minimize the chance of expulsion.

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 (e.g. while removing a tampon), it can be rinsed with cool to lukewarm (not hot) water and should be reinserted immediately. In the unusual case of women whose partners object to the presence of the ring during sexual intercourse, the ring should not be temporarily removed; rather it is preferable to switch to another method of contraception. In the two major clinical studies 2.7% of women experienced ring 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 10 pm the ring should be removed again on the Wednesday 3 weeks later at about 10 pm. 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 Special Precautions for Disposal.** 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 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.

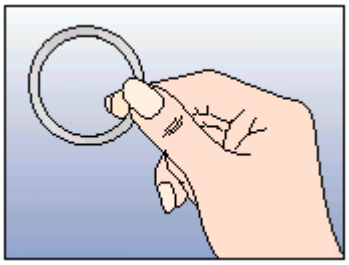


Figure 1
Take NuvaRing out of the sachet

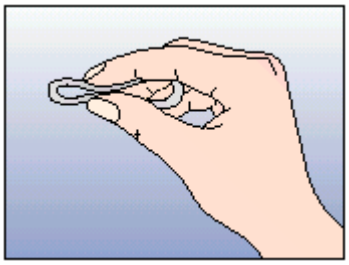
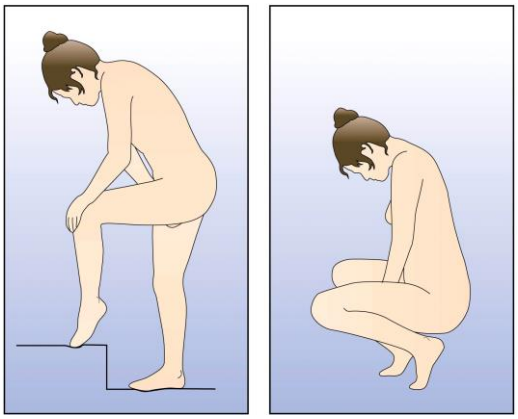


Figure 2
Compress the ring



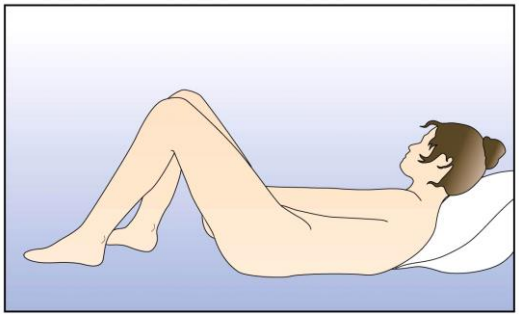


Figure 3
Choose a comfortable position to insert the ring

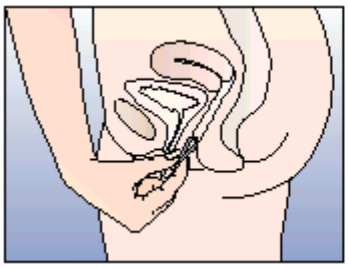
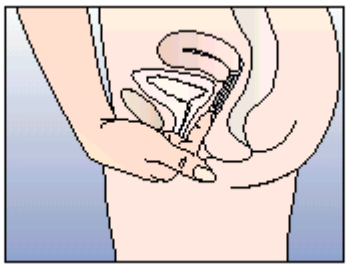
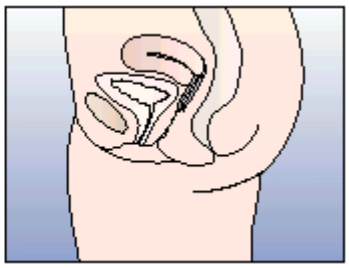




Figure 4A *Figure 4B* *Figure 4C*

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).

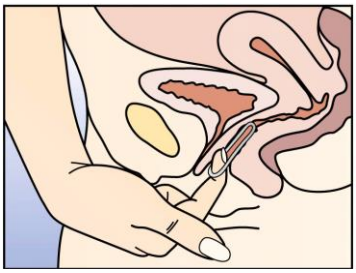


Figure 5
NuvaRing can be removed by hooking the index finger under the ring or by grasping the ring between the index and middle finger and pulling it out.

HOW TO START NUVARING

No hormonal contraceptive use in the preceding cycle

NuvaRing has to be inserted on the first day of the women'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 (such as male condoms or spermicide) should be used in addition for the first 7 days of NuvaRing use. See **Section 5.1 Pharmacodynamic Properties, Clinical trials**.

Changing from a combined hormonal contraceptive

The woman should insert NuvaRing at the latest on the day following the usual tablet-free or placebo tablet interval of her previous COC.

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

The woman may switch on any day from the minipill. She should switch from an implant or the IUS on the day of its removal and from an injectable on the day when the next injection would be due. In all of these cases, the woman should use an additional barrier method for the first 7 days.

Following first-trimester abortion

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

Following delivery or second-trimester abortion

For breast-feeding women, refer to **Section 4.6 Fertility, Pregnancy and Lactation, Use in lactation**.

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.

The increased risk of VTE during the postpartum period should be considered when restarting NuvaRing (see **Section 4.4 Special Warnings and Precautions for Use**).

Following amenorrhoea or oligomenorrhoea
Exclude the possibility of pregnancy and then start NuvaRing. The woman should be advised to additionally use a barrier contraceptive method for the first seven days of NuvaRing use. If unprotected intercourse has occurred consider the delay between conception and a positive pregnancy test.

DEVIATIONS FROM THE RECOMMENDED REGIME
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 if the patient forgets to insert a new NuvaRing after the 7 day ring free period.
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 NuvaRing is removed or expelled from the vagina during the 3 weeks of ring use.
NuvaRing should be left in the vagina for a continuous period of 3 weeks. If the ring is accidentally expelled and is left outside of the vagina for **less than 3 hours** contraceptive efficacy is not reduced. 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 for **more than 3 hours *during the 1st or 2nd week,*** 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 in addition to NuvaRing 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 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 (7 x 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 if NuvaRing is not removed after 3 weeks
The contraceptive efficacy of NuvaRing is adequate for up to 4 weeks. In circumstances where the ring has been in use for between 3 and 4 weeks, 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 should not be used in the presence of any of the conditions listed below. Should any of the conditions appear for the first time during the use of NuvaRing, it should be removed immediately.

- Presence or history of venous thrombosis, with or without pulmonary embolism.
- Presence or history of arterial thrombosis (e.g. cerebrovascular accident, myocardial infarction) or prodromi of a thrombosis (e.g. transient ischaemic attack or angina pectoris).
- Known hereditary or acquired predisposition for venous or arterial thromboembolism, such as Activated Protein C (APC) resistance (including Factor V Leiden), antithromboin-III deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinaemia and antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant).
- Major surgery with prolonged immobilization (see **Section 4.4 Special Warnings and Precautions for Use**).
- History of migraine with focal neurological symptoms.
- Diabetes mellitus with vascular involvement.
- The presence of a severe or multiple risk factor(s) for venous or arterial thrombosis may also constitute a contraindication (refer to **Section 4.4 Special Warnings and Precautions for Use**).
- Pancreatitis or a history thereof if associated with severe hypertriglyceridaemia.
- 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 sex steroid-influenced malignancies (e.g. of the genital organs or the breasts).
- Undiagnosed vaginal bleeding.
- Known or suspected pregnancy.
- Hypersensitivity to the active substances or to any of the excipients of NuvaRing.

NuvaRing is contraindicated for use with the Hepatitis C virus (HCV) combination drug regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir (see **Section 4.4 Special Warnings and Precautions for Use**).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

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 (such as myocardial infarction and stroke) and associated complications, sometimes with fatal consequences.

- An increased risk of thromboembolic and thrombotic disease associated with the use of CHCs is well-established. Although the absolute VTE rates are increased for users of CHCs compared to non-users, the rates associated with pregnancy are even greater, especially during the post-partum period (see Figure 6).

  The frequency of VTE in women using CHCs has been estimated to be 3 to 12 cases per 10,000 women-years.

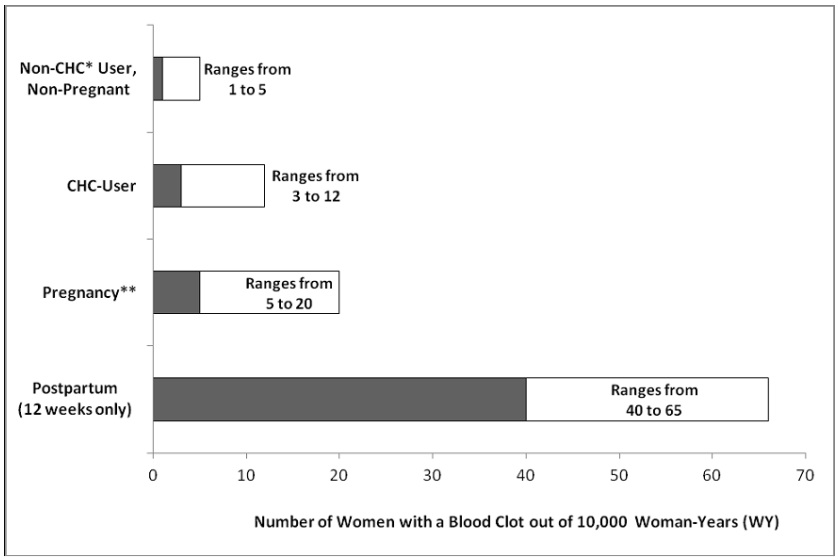
  The excess risk of VTE is highest during the first year of CHC use. The excess risk of VTE gradually disappears after use is discontinued. Data from a large, prospective cohort safety study of various COCs suggest that this increased risk, as compared to that in non-COC users, is greatest during the first 6 months of COC use and is present after initially starting a COC or restarting (following a 4 week or greater pill-free interval) the same or a different COC. This increased risk is less than the risk of VTE associated with pregnancy which is estimated as 5 to 20 cases per 10,000 women-year (WY). VTE is fatal in 1-2% of cases.

  Figure 6 shows the risk of developing a VTE for women who are not pregnant and do not use CHCs, for women who use CHCs, 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 CHCs are followed for one year, between 1 and 5 of these women will develop a VTE.

  Several epidemiology studies indicate that third generation oral contraceptives, including those containing desogestrel (etonogestrel, the progestin in NuvaRing, is the biologically active metabolite of desogestrel), are associated with a higher risk of venous thromboembolism than certain second generation oral contraceptives. In general, these studies indicate an approximate two-fold increased risk, which corresponds to an additional one to two cases of venous thromboembolism per 10,000 women-years of use.

However, data from additional studies have not shown this two-fold increase in risk.

Figure 6: 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 COC users (see Table below for adjusted hazard ratios). A large prospective, observational study, the Transatlantic Active Surveillance on Cardiovascular Safety of NuvaRing (TASC), investigated the risk of VTE for new users, switchers, and restarters of NuvaRing and COCs in a population that is representative of routine clinical users. The women were followed for 24 to 48 months. The results showed a similar risk of VTE among NuvaRing users (VTE incidence 8.3 per 10,000 WY; 95% CI: 5.0-12.9) and women using COCs (VTE incidence 9.2 per 10,000 WY; 95% CI: 6.0-13.5). For women using COCs, excluding desogestrel (DSG), gestodene (GSD) and drospirenone (DRSP), VTE incidence was 8.5 per 10,000 WY (95%CI: 4.5-14.6).
- 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.

Table 1: 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 *	HR†: 0.8 (0.5-1.5)
	COCs available excluding DSG-, GSD-, DRSP-containing OCs	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 ethinylestradiol	HR§: 1.1 (0.6-2.2) HR§: 1.0 (0.5-2.0)

*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 CHC users.
- 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 four weeks in advance) and not to resume until two 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 etiology of venous thrombosis.
- The risk of arterial thromboembolic complications increases with:
  - increasing age
  - smoking (with heavier smoking and increasing age the risk further increases, especially in women over 35 years of age)
  - dyslipoproteinaemia
  - 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 (including Factor V Leiden), hyperhomocysteinaemia, 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, haemolytic uraemic syndrome, chronic inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis), and sickle cell disease.
- The increased risk of thromboembolism in the puerperium must be considered (see **Section 4.6 Fertility, Pregnancy and Lactation, Use in pregnancy**).
- An increase in frequency or severity of migraine during hormonal contraceptive use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation of the use of hormonal contraceptives.
- When considering risk/benefit, the physician should take into account that adequate treatment of a condition may reduce the associated risk of thrombosis and that the risk associated with pregnancy is higher than that associated with hormonal contraceptive use.
- Women using combined hormonal contraceptives (CHCs) should be advised to contact their physician in case of possible symptoms of thrombosis. In case of suspected or confirmed thrombosis, CHC use should be discontinued. Adequate contraception should be initiated because of the teratogenicity of anti-coagulant therapy (coumarins).

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 COCs 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 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.
- 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.
- Epidemiological studies do not provide evidence for causation. 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. 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 drug 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 drug regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir (see **Section 4.3 Contraindications** and **Section 4.5 Interactions with Other Medicines and Other Forms of Interactions**). NuvaRing can be restarted approximately 2 weeks following completion of treatment with the combination drug regimen.

5. Other conditions

- Women with hypertriglyceridaemia, 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; haemolytic uraemic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss; (hereditary) angioedema.
- Acute or chronic disturbances of liver function may necessitate the discontinuation of the use of NuvaRing until markers of liver function return to normal. Recurrence of cholestatic jaundice and/or pruritus related to cholestasis, which occurred first during pregnancy or previous use of sex steroids necessitates the discontinuation of the ring.
- Although estrogens and progestagens may have an effect on peripheral insulin resistance and glucose tolerance, there is no evidence for a need to alter the therapeutic regimen in diabetics using low-dose hormonal contraceptives (containing < 50 µg ethinylestradiol). 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 reported in association with the use of hormonal contraceptives.
- Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation 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.
- As with other hormonal combination contraceptives there was a tendency in the clinical studies for some subjects to experience clinically significant weight changes. In US study 068003, 10.3% had a ≥ 7% weight loss while 18.1% experienced a ≥ 7% weight gain during therapy. In the European study 34219, 8.4% had a ≥ 7% weight loss while 10.2% experienced a ≥ 7% weight gain during therapy.
- During the use of NuvaRing, women may occasionally experience vaginitis. There are no indications that the efficacy of NuvaRing is affected by the treatment of vaginitis, nor that

the use of NuvaRing affects the treatment of vaginitis (see **Section 4.5 Interactions with Other Medicines and Other Forms of Interactions**).

- 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.
- Cases of toxic shock syndrome have been associated with tampons and certain barrier contraceptives. Very rare cases of TSS have been reported by NuvaRing users; in some cases the women were also using tampons. No causal relationship between the use of NuvaRing and TSS has been established. If a patient exhibits signs or symptoms of TSS, the possibility of this diagnosis should not be excluded and appropriate medical evaluation and treatment initiated.

Medical examination/consultation

A complete medical history and physical examination should be taken prior to the initiation or reinstitution of NuvaRing use, guided by **Section 4.3 Contraindications** and **Section 4.4 Special Warnings and Precautions for Use**, and should be repeated periodically. Periodic medical assessment is also of importance because contraindications (e.g. a transient ischaemic attack, etc.) or risk factors (e.g. a family history of venous or arterial thrombosis) may appear for the first time during the use of a hormonal contraceptive. The frequency and nature of these further periodic checks should be based upon established clinical practice guidelines and adapted to the individual woman but should generally include special reference to blood pressure, breasts, abdomen and pelvic organs, including routine cervical cytology.

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 (see **Section 4.2 Dose and Method of Administration, Deviations from the recommended regime**) or when concomitant medications that decrease the plasma concentration of etonogestrel are used (see **Section 4.5 Interactions with Other Medicines and Other Forms of Interactions**). Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

Reduced cycle control

Irregular bleeding (spotting or breakthrough bleeding) may occur during the use of NuvaRing, (refer to **Section 5.1 Pharmacodynamic Properties, Bleeding pattern).** 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 under **Section 4.2 Dose and Method of Administration**, 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 Interactions with Other Medicines and Other Forms of Interactions**). 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 4.2 Dose and Method of Administration, What to do if NuvaRing is removed or expelled from the vagina during the 3 weeks of ring use**). If NuvaRing is broken, the woman should discard the ring and replace 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 Dose and Method of Administration, What to do if NuvaRing is removed or expelled from the vagina during the 3 weeks of ring use**.

Use in the elderly

No data available

Paediatric use

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

Effects on laboratory tests

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

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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 oxcarbazepine, topiramate, felbamate, griseofulvin, chloramphenicol, neomycin, nitrofurantoin, tetracyclines, 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. Other enzyme inducers that may interact with hormonal contraceptives are: barbiturates.

Enzyme induction can occur after a few days of treatment. Maximal enzyme induction is generally observed within a few weeks. After drug 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 during 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 drug administration runs beyond the 3 weeks of a ring-cycle, the next ring should be inserted immediately, without having the usual ring-free period.

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 use of NuvaRing), did not significantly affect 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.

Other medicines that have been reported but not yet confirmed to reduce contraceptive efficacy are: phenylbutazone, sulfamethoxypyrizadine, hydantoins.

A single-dose vaginal administration of 100 mg water-based nonoxynol-9 spermicide gel did not affect the serum concentrations of etonogestrel or ethinylestradiol. A single-dose vaginal administration of an oil-based 1200 mg miconazole nitrate capsule increased the serum concentrations of etonogestrel and ethinylestradiol by approximately 17% and 16%, respectively. Following multiple doses of 200 mg miconazole nitrate by vaginal suppository or vaginal cream, the mean serum concentrations of etonogestrel and ethinylestradiol increased by up to 40%. There have been reports of ring breakage during concomitant use of intravaginal preparations, including antimycotic, antibiotic and lubricant products (see **Section 4.4 Special Warnings and Precautions for Use, Broken Rings**). However, 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 or pharmacodynamics of other drugs. Accordingly, plasma and tissue concentrations or clinical effects may be affected. Some of these drugs include: anticoagulants, some anti-diabetic drugs, ciclosporin, theophylline, imipramine and lamotrigine. Plasma and tissue concentrations may either increase (e.g. ciclosporin) or decrease (e.g. lamotrigine).

During clinical trials with the HCV combination drug regimen ombitasvir/paritaprevir/ritonavir with and without dasabuvir, ALT elevations greater than 5 times the upper limit of normal (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 drug regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir (see **Section 4.3 Contraindications** and **Section 4.4 Special Warnings and Precautions for Use**). NuvaRing can be restarted approximately 2 weeks following completion of treatment with the combination drug regimen.

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 **Section 4.2 Dose and Method of Administration, What to do if NuvaRing is removed or expelled from the vagina during the 3 weeks of ring use**).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on 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.

Use in pregnancy

Category B3.

NuvaRing is contraindicated in pregnancy. If pregnancy occurs with NuvaRing *'in situ'*, the ring should be removed.

In animal studies, maternal administration of high doses of estrogens has produced urogenital malformations in the offspring. Maternal administration of high doses of progestogens has also elicited masculinisation of the female fetus in animal studies. The clinical relevance of these animal findings is not certain. Epidemiological studies have revealed neither an increased risk of birth defects in children born to women who used COCs prior to pregnancy, nor a teratogenic effect when COCs were used inadvertently during early pregnancy. Although this probably applies to all COCs it is not clear whether this is also the case for NuvaRing.

Due to the intravaginal administration, intrauterine concentrations of the contraceptive steroids in NuvaRing are likely to be higher than in COC users. An effect on the fetus can therefore not be excluded. Clinical experience of the outcomes of pregnancies exposed to NuvaRing have not been reported.

Use in lactation

No postnatal toxicity data are currently available in animals or humans concerning the safety of the use of NuvaRing when breastfeeding. Contraceptive steroids and/or their metabolites are known to be excreted into the milk. 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.

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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The most serious undesirable effects associated with the use of hormonal contraceptives are listed under **Section 4.4 Special Warnings and Precautions for Use**.

Adverse effects 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 effect 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).

Table 2

System Organ Class	**Frequency of adverse effects**			
	Common	**Uncommon**	**Rare**	**Not known[1]**
Skin and subcutaneous tissue disorders	Acne	Pruritus, rash, alopecia, eczema		Urticaria
Nervous system disorders	Headache, migraine	Dizziness, hypoaesthesia		
Immune system disorders				Hypersensitivity reactions, including angioedema and anaphylaxis
Psychiatric disorders	Depression, emotional lability, libido decreased	Mood altered, Anxiety		
Gastrointestinal disorders	Abdominal pain, nausea, toothache, diarrhoea, vomiting	Abdominal distension, constipation		
Metabolism and nutrition disorders	Weight increased	Increased appetite		
Investigations	Weight increased	Blood pressure increased		
Renal and urinary disorders	n.a.	Cystitis, dysuria, micturition urgency, pollakiuria, urinary tract infection		
Injury, poisoning and procedural complications	Medical device discomfort, vaginal contraceptive device expelled	Contraceptive device complication, device breakage		Vaginal injury associated with ring breakage
Reproductive system and breast disorders	Abdominal pain (gynaecological), breast pain, breast tenderness, female device related problems (e.g. expulsion,	Amenorrhoea, breast discomfort, breast enlargement, breast mass, cervical polyp, cervicitis, coital bleeding, male device related		Penis disorders[2], galactorrhoea

System Organ Class	Frequency of adverse effects			
	Common	**Uncommon**	**Rare**	**Not known[1]**
	coital problems and foreign body feeling), dysmenorrhoea, leucorrhoea, pelvic pain, vaginal discharge, vaginitis, genital pruritus female	problems (e.g. coital discomfort), dyspareunia, ectropion of cervix, fibrocystic breast disease, menorrhagia, metrorrhagia, pelvic discomfort, premenstrual syndrome, uterine spasm, vaginal burning sensation, vaginal odour, vaginal pain, vulvovaginal discomfort, vulvovaginal dryness		
Neoplasm	n.a.	Breast fibroadenosis		
Infections and infestations	Vaginal infection	Cervicitis, cystitis, urinary tract infection		
Eye disorders		Visual disturbance		
Respiratory System	Bronchitis, coughing pharyngitis, rhinitis, sinusitis, URTI			
General disorders and administration site conditions	Back pain, fatigue, allergic reaction, fever, influenza-like symptoms	Abdomen enlarged, herpes simplex, irritability, malaise, oedema, sensation of foreign body		
Musculoskeletal and connective tissue disorders		Back pain, muscle spasms, pain in extremity		
Vascular disorders		Hot flush	Venous thromboembolism[3], arterial thromboembolism[3]	

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: ≥1/10000 to < 1/1000 women years.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

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.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

NuvaRing contains etonogestrel and ethinylestradiol. Etonogestrel is the biologically active metabolite of desogestrel, a progestagen widely used in oral contraceptives. It binds with high affinity to progesterone receptors in the target organs. Ethinylestradiol is an estrogen also widely used in contraceptive products. The contraceptive effect of NuvaRing is achieved primarily by inhibition of ovulation.

Clinical trials

Six efficacy and safety studies were performed in healthy, fertile and sexually active women aged 18-40 years. The endpoints included contraceptive efficacy, cycle control parameters, safety, laboratory variables and acceptability parameters. In these studies a total number of 2501 subjects using NuvaRing and 126 subjects using a comparator combined oral contraceptive (30 µg ethinylestradiol / 150 µg levonorgestrel) were studied. Total NuvaRing exposure was 24,519.9 treatment cycles (1879.34 women-years.

Table 3 Overview of main clinical efficacy and safety studies

Trial	Country	Study design	Duration of treatment	NuvaRing N	Comparator N	Efficacy, safety, vaginal bleeding	Specific safety
34219	Europe	Open-label,non-comparative	13 cycles	1145		X	
34220	Finland	Open-label, comparative	6 cycles	40	43	X	Lipid metabolism
34221	Iceland	Open-label, comparative	6 cycles	44	43	X	Coagulation & fibrinolysis
34222	UK & Netherlands	Open-label, comparative	6 cycles	37	40	X	Carbohydrate metabolism, adrenal & thyroid function
068003	USA & Canada	Open-label,non-comparative	13 cycles	1177		X	
068004	USA	Open-label,non-comparative	13 cycles	58		X	Local effects

CONTRACEPTIVE EFFICACY

The two large efficacy and safety trials had the objective to collect at least 10,000 cycles of treatment each. In these two trials, a total of 21 in-treatment pregnancies were reported: 11 subjects did not comply with the protocol in the cycle of conception or the preceding cycle. The in-treatment pregnancies of the remaining 10 subjects were considered to be Per Protocol pregnancies representing method-failure during “perfect use”. This results in a Pearl Index of 0.765 (95% confidence interval 0.367 - 1.407). The Pearl Index was higher in the US study (068003) than in the European study (34219). Compliance with the recommended ring/ring-

free regimen was lower, and the occurrence of temporary removals higher, in the US study than the European study, which may have contributed to the difference in Pearl Index. The difference in compliance between the US and Europe has previously been reported in literature for other contraceptives. These findings indicate that the instructions for use as described in the Product Information should be followed. Contraceptive efficacy is satisfactory and the data demonstrate that NuvaRing is an efficacious contraceptive product when used in accordance with the use instructions. There are insufficient evaluated data to make direct comparisons concerning the efficacy of NuvaRing relative to other methods. These two studies permitted the occasional use of condoms to prevent the transmission of sexually transmitted diseases.

Table 4 Contraceptive efficacy

Trial	**Country**	**Pearl Index**	
		Intent-to-Treat	**Per Protocol**
068003	USA	1.749	1.274
34219	Europe	0.646	0.396
Combined		1.176	0.765

BLEEDING PATTERN
Intended bleeding was defined as bleeding/spotting which occurs only during the ring-free period. The incidence of intended bleeding over cycles 1-12 ranged from 59.9% to 68.5% in the two large efficacy and safety studies. The incidence of other bleeding patterns was low and consistent over up to 13 cycles of NuvaRing use: breakthrough bleeding/spotting (5.1%-7.9%), absence of withdrawal bleeding (1.5-2.9%), early withdrawal bleeding (5.6-8.8%), withdrawal bleeding-spotting continuing beyond the ring-free period (mainly spotting days: 15.7-20.5%). The discontinuation rate due to bleeding irregularity was low (0.8%).

The bleeding characteristics of NuvaRing were compared to those of a 30 µg EE/150 µg LNG containing COC during 13 cycles in more than 1000 women. The results of this study show that the occurrence of breakthrough bleeding or spotting varied over the Cycles 2-13 from 2.0% to 6.4% in the NuvaRing group and from 3.5% to 12.6% in the LNG/EE OC group. Superiority for the NuvaRing group over the LNG/EE OC group was demonstrated, because a statistically significantly lower incidence was observed in cycles 2 and 9 of the 13 cycles. Cycle 1 was excluded from the analysis because the starting regimens were not comparable. Furthermore, the incidence of intended bleeding patterns was statistically significantly better in the NuvaRing group for each of the cycles 1-12; these occurred in 58.8% to 72.8% of the subjects in the NuvaRing group and in 43.3% to 57.9% of the subjects in the LNG/EE OC group.

OVULATION SUPPRESSION AND RETURN
In supportive studies the ovulation-inhibiting effect of NuvaRing appeared to be similar to that of a comparator combined oral contraceptive (30 µg ethinylestradiol / 150 µg desogestrel). Even though NuvaRing was inserted on day 5 and the COC was started on day 1 the study data support inhibition of ovulation in the first cycle with both products. Return of ovulation was assessed by ultrasound measurements and hormone assessments. Return of ovulation is likely to occur after 12 days after ring removal (median 19 days). Return of ovulation implies restoration of fertility. This conclusion is indirectly supported by the return of menses in 90% of women by the 4th week after last NuvaRing removal and the occurrence of 27 post-treatment pregnancies after last ring removal in the two large efficacy and safety trials.

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. The observed differences were not considered to be clinically relevant.

OTHER CONSIDERATIONS
Acceptability of NuvaRing was assessed in the two large efficacy and safety studies. The large majority of users felt that the ring could easily be inserted (97%) or removed (98%). In total, 35.4% of the subjects in these trials discontinued: 15.1% because of an adverse event/serious adverse event, 0.8% because of bleeding irregularity, 0.9% to become pregnant and 18.5% because of other reasons (mainly loss to follow-up, 2 women for unspecified reasons and 3 for "nonacceptance of NuvaRing concept"). Male discomfort during sexual intercourse was reported by 2% of clinical trial subjects.

Combined oral contraceptives (COCs) have, in addition to protection against pregnancy, several positive properties which, together with the negative properties (see **Section 4.4 Special Warnings and Precautions for Use**), can be useful in deciding on the method of birth control. The cycle is more regular and the menstruation is often less painful and bleeding is lighter. Apart from this, there is evidence of a reduced risk of endometrial cancer and ovarian cancer but it is not known whether these apply to NuvaRing. Furthermore, the higher-dosed COCs (50 µg ethinylestradiol), have been shown to reduce the incidence of ovarian cysts, pelvic inflammatory disease, benign breast disease and ectopic pregnancy. Confirmation is required as to whether these benefits also apply to lower dosed COCs or NuvaRing.

5.2 PHARMACOKINETIC PROPERTIES

NuvaRing releases relatively low doses of hormones continuously, which are rapidly absorbed by the vaginal mucosa. With the vaginal route of administration, lower doses are administered to achieve effective plasma concentrations than with many current combined oral contraceptives since a "hepatic first-pass" effect is avoided. The maximum serum values for etonogestrel and ethinylestradiol are approximately 40% and 30%, respectively, as compared to those of a comparator combined oral contraceptive (30 µg ethinylestradiol/150 µg desogestrel) and occur only once per cycle. The mean etonogestrel serum levels are in the same order of magnitude as those obtained for this comparator, whereas the ethinylestradiol serum levels are approximately 50%.

NuvaRing is used continuously for three weeks. Daily variations in hormonal levels that occur during oral contraceptive use are not a feature with NuvaRing. Vaginal administration avoids daily peak concentrations. NuvaRing is not subject to factors that may affect oral contraceptive tablets' efficacy such as vomiting, food interactions and diarrhoea.

Etonogestrel

Absorption

Etonogestrel released by NuvaRing is rapidly absorbed by the vaginal mucosa. Maximum serum concentrations of etonogestrel of approximately 1700 pg/mL are reached at about 1 week after insertion. Serum concentrations show small fluctuations and slowly decrease to approximately 1400 pg/mL after 3 weeks of use. Absolute bioavailability is approximately 100%, compared to approximately 80% for the DSG/EE COC.

Distribution

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

Metabolism

Etonogestrel is 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.

Excretion

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 18 pg/mL after 3 weeks of 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 L/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 glucuronides conjugates. The apparent clearance is about 35 L/h.

Excretion

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.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Etonogestrel was negative in assays for reverse gene mutation in bacteria, chromosomal aberrations in mammalian cells, and micronuclei formation in mice. Data on the genotoxic potential of ethinylestradiol are currently limited, but there is some evidence available in the literature suggesting that estrogens may be weakly genotoxic at high doses. The genotoxic potential of the ethylene vinylacetate polymers has not been investigated.

Carcinogenicity

No study has been conducted to investigate the carcinogenicity of NuvaRing. In a 24-month carcinogenicity study in rats with subdermal implants releasing 10 and 20 µg etonogestrel per day, (approximately 0.3 and 0.6 times the systemic steady state exposure of women using NuvaRing), no drug-related increase in tumour incidence was observed. Studies with a combination of ethinylestradiol and desogestrel in rats and mice elicited an increased incidence of pituitary and mammary gland tumours. Long-term animal studies of natural and synthetic estrogens have also shown an increased incidence of carcinomas in the breast, uterus, cervix, vagina, testis and liver.

An increased risk of tumours in estrogen-sensitive target organs, such as uterus, breast and ovary, is associated with prolonged estrogen therapy in women. In rare cases, benign liver adenomas, and even more rarely, malignant liver tumours have been reported in users of combined oral contraceptives. Although benign, hepatic adenomas may rupture and cause death through intra-abdominal haemorrhage.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Evatane® (28-25) ARTG No. 12054
Evatane® (1020 VN3) ARTG No. 12053
Magnesium stearate.

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

The shelf life of NuvaRing is 40 months, if stored in accordance with prescribed storage instructions.

The expiry date can be found on the packaging. In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG).

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Prior to dispensing:	36 months, store in a refrigerator (2°C - 8°C).
At the time of dispensing:	The dispenser places a date of dispensing on the box and the sachet(s). The product should not be inserted after the expiry date or 4 months from the date of dispensing, whichever comes first.
After dispensing:	4 months; do not store above 30°C.

Store NuvaRing in the original package.
Protect from light and freezing.

6.5 NATURE AND CONTENTS OF CONTAINER

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

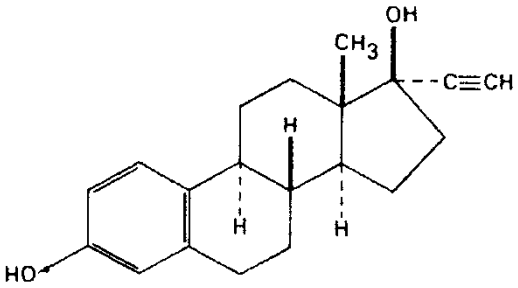
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Refer to **Section 4.2 Dose and Method of Administration**. The dispenser has to indicate the date of dispensing and the date before which NuvaRing has to be used on the box. After removal, NuvaRing should be replaced in the reclosable sachet and disposed of with the normal household waste in a manner that avoids accidental contact with others. NuvaRing should not be flushed down the toilet.

6.7 PHYSICOCHEMICAL PROPERTIES

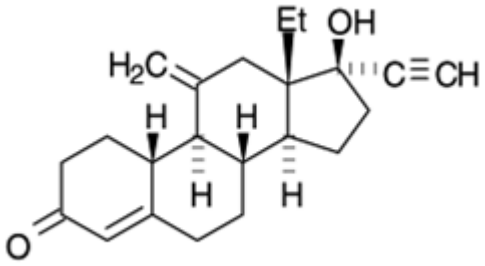
Chemical structure

Ethinylestradiol:



Chemical name: 19-nor-17α-pregna-1,3,5,(10)-trien-20-yne-3,17-diol
Molecular formula: $C_{20}H_{24}O_2$
Molecular mass: 296.4

Etonogestrel:



Chemical name: (17α)-13-ethyl-17-hydroxy-11-methylene-18,19 dinorpregn-4-en-20-yn-3-one
Molecular formula: $C_{22}H_{28}O_2$
Molecular mass: 324.44

CAS number

Ethinylestradiol: 57-63-6
Etonogestrel: 54048-10-1

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine (S4)

8 SPONSOR

Organon Pharma Pty Ltd
Building A, 26 Talavera Road
Macquarie Park NSW 2113

9 DATE OF FIRST APPROVAL

9 July 2008

10 DATE OF REVISION

22 December 2020

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
8	Amend sponsor details due to sponsorship transfer