APPLICATION 2020

Etonogestrel/Ethynilestradiol Vaginal Ring

SUBMITTED TO

World Health Organization (WHO)

OBJETIVE

Application for inclusion of the Etonogestrel Ethynilestradiol Vaginal Ring in the WHO Model List of Essential Medicines

SUBMITTED BY

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General Items

1. **Summary statement of the proposal for inclusion, change or deletion.**

   Here within, please find the evidence to support the inclusion Ethinylestradiol/Etonogestrel Vaginal Ring in the World Health Organization's Essential Medicines List (EML).

   Unintended pregnancy is regarded as a serious public health issue both in developed and developing countries and has received growing research and policy attention during last few decades (1). It is a major global concern due to its association with adverse physical, mental, social and economic outcomes. Developing countries account for approximately 99% of the global maternal deaths in 2015, with sub-Saharan Africa alone accounting for roughly 66% (2). Even though the incidence of unintended pregnancy has declined globally in the past decade, the rate of unintended pregnancy remains high, particularly in developing regions. (3)

   Regarding the use of contraceptive vaginal rings, updated bibliography (4,5,6) states that contraceptive vaginal rings (CVR) offer an effective contraceptive option, expanding the available choices of hormonal contraception.

   Ethinylestradiol/Etonogestrel Vaginal Ring is a non-biodegradable, flexible, transparent with an outer diameter of 54 mm and a cross-sectional diameter of 4 mm. It contains 11.7 mg etonogestrel and 2.7 mg ethinyl estradiol. When placed in the vagina, each ring releases on average 0.120 mg/day of etonogestrel and 0.015 mg/day of ethinyl estradiol over a three-week period of use.

   Ethinylestradiol/Etonogestrel Vaginal Ring is intended for women of fertile age. The safety and efficacy have been established in women aged 18 to 40 years.

   The main advantages of CVRs are their effectiveness (similar or slightly better than the pill), ease of use without the need of remembering a daily routine, user ability to control initiation and discontinuation, nearly constant release rate allowing for lower doses, greater bioavailability and good cycle control with the combined ring, in comparison with oral contraceptives. (4)

2. **Relevant WHO technical department and focal point (if applicable).**

   N/A

3. **Name of organization(s) consulted and/or supporting the application.**

   N/A.

4. **International Nonproprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine.**

   International Nonproprietary Name (INN) 1: Ethinylestradiol

   International Nonproprietary Name (INN) 2: Etonogestrel

Anatomical Therapeutic Chemical (ATC): G02BB01 - vaginal ring with progestogen and estrogen.

5. **Dose forms(s) and strength(s) proposed for inclusion; including adult and age-appropriate paediatric dose forms/strengths (if appropriate).**

Ethinylestradiol/Etonogestrel Vaginal Ring is a non-biodegradable, flexible, transparent, colorless to almost colorless, combination contraceptive vaginal ring, with an outer diameter of 54 mm and a cross-sectional diameter of 4 mm. It is made of ethylene vinylacetate copolymers and magnesium stearate and contains 11.7 mg etonogestrel and 2.7 mg ethinyl estradiol. When placed in the vagina, each ring releases on average 0.120 mg/day of etonogestrel and 0.015 mg/day of ethinyl estradiol over a three-week period of use. It is not made with natural rubber latex.

It is intended for women of fertile age. The safety and efficacy have been established in women aged 18 to 40 years. The safety and efficacy of Ethinylestradiol/Etonogestrel Vaginal Ring in adolescents under the age of 18 have not been studied.

6. **Whether listing is requested as an individual medicine or as representative of a pharmacological class.**

The request for inclusion is for an individual medicine.

Treatment details, public health relevance and evidence appraisal and synthesis

7. **Treatment details (requirements for diagnosis, treatment and monitoring).**

The therapeutic indication of Ethinylestradiol/Etonogestrel Vaginal Ring is contraception.
The proposed therapeutic dosage regimen is 0.120 mg/day of etonogestrel and 0.015 mg/day of ethinylestradiol. Ethinylestradiol/Etonogestrel Vaginal Ring works just like a combined contraceptive pill (the Pill) but instead of taking a pill every day, the ring is used for 3 weeks in a row. It contains 11.7 mg of etonogestrel and 2.7 mg of ethinylestradiol.

Ethinylestradiol/Etonogestrel Vaginal Ring 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 Ethinylestradiol/Etonogestrel Vaginal Ring should take into consideration the individual woman's current risk factors.

The woman herself can insert Ethinylestradiol/Etonogestrel Vaginal Ring in the vagina. The physician should advise the woman how to insert and remove it. 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. It should be compressed and inserted into the vagina until it feels comfortable. The exact position of Ethinylestradiol/Etonogestrel Vaginal Ring in the vagina is not critical for the contraceptive effect of the ring.

Once Ethinylestradiol/Etonogestrel Vaginal Ring has been inserted it is left in the vagina continuously for 3 weeks. Advise women to regularly check for the presence of the Vaginal Ring in the vagina. It 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. It 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.

8. Information supporting the public health relevance.

Unintended pregnancy is regarded as a serious public health issue both in developed and developing countries and has received growing research and policy attention during last few decades (1). It is a major global concern due to its association with adverse physical, mental, social and economic outcomes. It affects all segments of the community and contributes greatly to maternal and infant mortality (2). Globally, the maternal mortality ratio (MMR) was 216 maternal deaths per 100,000 live births in 2015. Developing countries account for approximately 99% of the global maternal deaths in 2015, with sub-Saharan Africa alone accounting for roughly 66% (2). Even though the incidence of unintended pregnancy has declined globally in the past decade, the rate of unintended pregnancy remains high, particularly in developing regions. (3)

Between 20 and 40% of all births that occur in developing countries are unwanted, posing a hardship for families and jeopardizing the health of millions of women and children. Women who experience an unintended pregnancy are less likely to have prenatal, perinatal and postnatal care. (2)
Unintended pregnancies can result from a lack of contraceptive use, contraceptive failure and incorrect use of contraceptives (5). Multiple studies have also shown other variables that influence the likelihood of unintended pregnancies including sociodemographic and economic conditions as well as reproductive and environmental factors. (2)

An understanding of the available contraceptive methods allows clinicians to counsel women about methods that are most consistent with their lifestyle and beliefs, and therefore most likely to be successful.

Modern methods of contraception have a vital role in preventing unintended pregnancies. Among women who experienced an unintended pregnancy leading to an abortion, half had discontinued their contraceptive methods due to issues related to use of the method such as health concerns, side effects or inconvenience of use. (14)

Regarding the use of contraceptive vaginal rings, updated bibliography (4–6) states that contraceptive vaginal rings (CVR) offer an effective contraceptive option, expanding the available choices of hormonal contraception. The main advantages of CVRs are their effectiveness (similar or slightly better than the pill), ease of use without the need of remembering a daily routine, user ability to control initiation and discontinuation, nearly constant release rate allowing for lower doses, greater bioavailability and good cycle control with the combined ring, in comparison with oral contraceptives.

The target population for the Ethinylestradiol/Etonogestrel Vaginal Ring is intended for women of fertile age. The safety and efficacy have been established in women aged 18 to 40 years.

9. Review of benefits: summary of evidence of comparative effectiveness.

Clinical evidence from reviews

As previously referred, the basic indication recognized for Ethinylestradiol/Etonogestrel Vaginal Ring is contracepcion.

The contraceptive efficacy was studied in 2322 women using Ethynilnilestradiol/Etonogestrel combined contraceptive vaginal ring for 23,298 cycles equivalent to 1786 women-years. This was carried out in two identical studies, one in 52 European centers, the other in 48 centers in Canada and the United States. Twenty-one pregnancies occurred, giving a Pearl Index of 1.18 (95% confidence interval 0.73–1.80). Eleven of the pregnancies were attributable to non-compliance; the Pearl Index for the women adhering to the protocol was 0.77 (95% confidence interval 0.37–1.40). (15)

Two large multi-center registration studies, 1 large daily clinical practice study, and 6 randomized controlled trials (RCTs) comparing Ethinylestradiol/Etonogestrel Vaginal Ring and a combined oral contraceptives (COC) were identified. Contraceptive efficacy was high showing no significant differences in comparison with the COC; cycle control was good and consistently better than that of the COC and compliance was high and comparable with that of the pill. (16)

The ring's effectiveness is similar to other combined hormonal contraceptive methods, with pregnancy rates less than 1% in large efficacy trials. Increased effectiveness may result from ease of use and the minimal user intervention required. Once the ring was on the market, three studies examined effectiveness in everyday practice. One study recruited 5823 women from gynecology clinics in Germany. A total of nine on-treatment pregnancies occurred, of which six could be attributed to noncompliance or pregnancy occurring prior to starting treatment. A Dutch study found that in a cohort of 854 women seen by family practitioners, of which 82.6% completed the three cycles, one pregnancy occurred during the 3-month trial. A Swiss study found that three pregnancies occurred among 2642 women using the ring for a total of 151900 cycles. These three studies thus reaffirmed the efficacy demonstrated in the randomized controlled trials (RCTs). (17)

Clinical evidence from clinical trials

Reference	Objectives and design	Comments
Ahrendt et al (18)	This randomized multicenter, open-label, trial compared efficacy, acceptability, tolerability and compliance of Ethynilestradiol/etonogestrel combined contraceptive vaginal ring with a combined oral contraceptive (COC), containing 30 mcg of ethinyl estradiol (EE) and 3 mg of drospirenone.	To sum up Ethynilestradiol/etonogestrel combined contraceptive vaginal ring had comparable efficacy and tolerability to a COC containing 30 mcg of EE and 3 mg drospirenone. User acceptability of both methods was high.
Mohamed et al (19)	Randomized, open-label trial developed to compare the adverse effects, cycle control, and metabolic effects of a Ethynilestradiol/etonogestrel combined contraceptive vaginal ring and a combined oral contraceptive (COC).	600 women seeking contraception received a Ethynilestradiol/etonogestrel combined contraceptive vaginal ring (n=300) or a COC (n=300) for 12 cycles. The results demonstrate that Ethynilestradiol/etonogestrel combined contraceptive vaginal ring is a reasonable alternative means of hormonal contraception when compared with a COC containing 30 µg of EE and 3 mg of drospirenone.
Oddsson et al (20,21)	This was an open-label, randomized, multi-center comparative study performed in Health centers in 11 countries in Europe and South America. To compare the efficacy and safety of the Ethynilestradiol/etonogestrel combined contraceptive vaginal ring with combined oral contraception (COC) for women seeking birth control.	A total of 1030 women, aged ≥18 years, who were seeking a form of contraception were included in this study. The Ethynilestradiol/etonogestrel combined contraceptive vaginal ring released 15 mg of ethinylestradiol (EE) and 120 mg of etonogestrel daily, and COC released 150 mg levonorgestrel (LNG) and 30 mg of EE daily for 13 cycles (3 weeks with pill/ring followed by 1 week with no exposure).The Pearl indices for the intent-to-treat analyses were 1.23 (95% CI, 0.40 - 2.86) for the Ring group and 1.19 (95% CI, 0.39 - 2.79) for the COC group as compared to 0.71 (95% CI, 0.00 - 1.52) in the Ring group and 0.43 (95% CI, 0.00 - 1.01) for the COC group in the per protocol analyses. Compliance was similar in both the Ring (87.4%) and COC groups (86.6%). Both contraceptives were well tolerated.

Pandit et al (22)	This open-label, prospective, single-arm, nonrandomized, interventional study enrolled 252 women aged >18 years, seeking contraception with no contraindications to the use of combined hormonal contraceptive. It was a multicenter study at six specialty hospitals, to assess the real-life usage of the vaginal ring in daily clinical practice.	Women were provided the ring with a monthly follow-up schedule for three cycles. Cycle control, acceptability, tolerability, and safety assessments were recorded at each visit.Regular menstrual bleeding was reported by 76.2 % (192/252) at baseline. In study completers, regular bleeding was seen in 94.1 % (192/204), 97.5 % (199/204), and 98 % (200/204) in the 1st, the 2nd, and the 3rd cycles, respectively. Most (94.2 % [195/207]) women were very satisfied or satisfied with the ring, and 93.2 % (193/207) would recommend it to others. No pregnancies or serious adverse events were reported. The study demonstrated that Ethynilestradiol/etonogestrel combined contraceptive vaginal ring is a highly effective contraceptive method with an excellent cycle control. It is well tolerated and accepted by Indian women.

10. Review of harms and toxicity: summary of evidence of safety.

Studies previously commented in the efficacy paragraph (18-22) have also evaluated the safety of Ethynilestradiol/Etonogestrel combined contraceptive vaginal ring.

Specifically related with safety, there are different references in Literature that offer information related to exposure to Ethynilestradiol/Etonogestrel combined contraceptive vaginal ring. Those references have shown that the use of the vaginal ring was not found to significantly affect blood pressure. No clinically relevant change from baseline was seen during observational trials or post-marketing surveillance in either diastolic or systolic blood pressure. In a trial comparing COC and Ethynilestradiol/Etonogestrel combined contraceptive vaginal ring use, ≤ 4% of subjects in each treatment group experienced hypertension. No significant changes in cervical cytology have been attributed to Ethynilestradiol/Etonogestrel combined contraceptive vaginal ring use. In an observational trial, a total of 1.3% of subjects changed from normal cytology to low-grade squamous intraepithelial lesions and 0.4% of subjects changed to high-grade squamous intraepithelial lesion/carcinoma in situ. Normal shifts in cervical cytology may have been detected because of the frequent screening during the study. (8,10)

Novak et al (23) assessed the acceptability of a combined contraceptive Ethynilestradiol/Etonogestrel vaginal ring, during two trials conducted in North America and Europe. Women completed a questionnaire about the ring's clarity of instructions, ease of use, sexual comfort, cycle-related characteristics and satisfaction after 3, 6 and 13 cycles of use. A total of 1950 women (82% of those recruited) completed a questionnaire at cycle 3. At baseline, 66% of participants preferred oral contraceptives, but after three cycles of ring use 81% preferred the ring. On study completion, 97% agreed that the instructions for use were clear; 85% of women and 71% of their partners never/rarely felt the ring during intercourse and 94% of partners never/rarely minded that the woman was using the ring. Overall acceptance was high, 96% were satisfied with the ring and 97% would recommend the ring. Similar responses were seen for women who prematurely discontinued from the studies, except that slightly fewer women were satisfied (60%) and would recommend the ring (75%). Reasons for liking the ring included 'not

having to remember anything' (45%) and 'ease of use' (27%). In conclusion, there is a high level of user and partner acceptability for a contraceptive ring.

Additionally, Schafer et al (24) assessed user satisfaction and method continuation 3 months after ring or pill initiation. Data for this study were collected as part of a randomized clinical trial on 201 women comparing immediate start of vaginal ring use with immediate start of low-dose oral contraceptive use. At 3 months, 174 of 201 subjects (87%) had follow-up interviews. Among the 174 study participants with follow-up data, 61% of ring subjects and 34% of pill subjects were very satisfied with their methods (p=.003). For posttrial contraception, 79% of ring subjects chose to continue with the ring whereas 59% of pill subjects chose to continue with the pill (pb.001). Women who reported greater comfort in touching their genitals, greater frequency of masturbation, more comfort with intercourse and past use of vaginal contraceptives and products were not more likely than others to be satisfied with the ring or to continue using it for birth control. In conclusion, women who were allocated to vaginal ring use, regardless of their baseline characteristics or behavior, were likely to be highly satisfied with the method and to continue its use.

Adverse events

The most frequently reported undesirable effects in the clinical trials with a Ethynilestradiol/Etonogestrel combined contraceptive vaginal ring were headache and vaginal infections and vaginal discharge, each reported by 5-6% of the women. (8,10)

Description of selected adverse reactions

An increased risk of arterial and venous thrombotic and thromboembolic events, including myocardial infarction, stroke, transient ischemic attacks, venous thrombosis and pulmonary embolism has been observed in women using CHCs (combined hormonal contraceptives).
Adverse drug reactions that have been reported in clinical trials, observational studies, or during post-marketing use with Ethynilestradiol/Etonogestrel combined contraceptive vaginal ring 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
Infections and infestations	Vaginal infection	Cervicitis, Cystitis, Urinary tract infection		
Immune system disorders				Hypersensitivity
Metabolism and nutrition disorders		Increased appetite		
Psychiatric disorders	Depression, Libido decreased	Affect lability, Mood altered, Mood swings		
Nervous system disorders	Headache, Migraine	Dizziness, Hypoesthesia		

System Organ Class	Common	Uncommon	Rare	Not known
Eye disorders		Visual disturbance		
Vascular disorders		Hot flush	Venous thromboembolism Arterial thromboembolism	
Gastrointestinal disorders	Abdominal pain, Nausea	Abdominal distension, Diarrhea, Vomiting, Constipation. The low incidence of gastrointestinal side effects (nausea, vomiting) may be related the low hormonal dose and to the vaginal delivery of hormones which avoids the gastrointestinal tract. (30)		
Skin and subcutaneous tissue disorders	Acne	Alopecia, Eczema, Pruritus, Rash		Chloasma Urticaria
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, Dysmenorrhea, Pelvic pain, Vaginal discharge	Amenorrhea, Breast discomfort, Breast enlargement, Breast mass, Cervical polyp, Coital bleeding, Dyspareunia, Ectropion of cervix, Fibrocystic breast disease, Menorrhagia, Metrorrhagia, Pelvic discomfort, Premenstrual syndrome, Uterine spasm, Vaginal burning sensation, Vaginal odor, Vaginal pain, Vulvovaginal discomfort, Vulvovaginal dryness	Galactorrhea	Penis disorders
General disorders and administration site conditions		Fatigue, Irritability, Malaise, Edema, Sensation of foreign body		
Investigations	Weight increased (30)	Blood pressure increased		
Injury, poisoning and procedural complications	Medical device discomfort, Vaginal contraceptive device expelled	Contraceptive device complication, Device breakage		

Table 6. List of adverse events. (8,10)

Safety in specific groups and situations

Combined hormonal contraceptives (CHCs) should not be used in the following conditions. Should any of the conditions appear for the first time during the use of Ethynilestradiol/Etonogestrel combined contraceptive vaginal ring, 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 immobilization.
- A high risk of venous thromboembolism due to the presence of multiple risk factors.
- 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 ischemic 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 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 tumors (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 (8,10)

11. Summary of available data on comparative cost and cost-effectiveness of the medicine.

A study to assess the cost-effectiveness of different combined hormonal contraceptive (CHC) methods in Spain shown that the most cost-effective CHC method is the vaginal ring. For women, the vaginal ring is most expensive method, but the excess price could be balanced by a greater protection against unwanted pregnancies due its effectiveness.

This pharmacoeconomic study was conducted using a Markov model of three CHC methods: a reimbursed oral contraceptive, a contraceptive patch, and a vaginal ring. (25)

Furthermore, since February 2020, Ethynilestradiol/Etonogestrel combined contraceptive vaginal ring was included in the Public Health System because of the commercialization of generic versions.

12. Summary of regulatory status and market availability of the medicine.

Nuvaring ®, the innovator device, is registered in more than 50 countries and it is developed by Organon (Merck).

The Ethinylestradiol/Etonogestrel Vaginal Ring manufactured by Chemo is registered in several countries, which includes Netherlands, Poland, Denmark, France, Italy, Spain, Portugal, Belgium, Czech Republic and Finland, among others.

13. Availability of pharmacopoeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia, European Pharmacopeia).

N/A

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