Ethinylestradiol + etonogestrel

ATC codes: G02BB01

Indication	Contact with health services for contraceptive management ICD11 code: QA21.Z
INN	Ethinylestradiol + etonogestrel
Medicine type	Chemical agent
List type	Core
Formulations	**Local > Vaginal > vaginal ring:** 2.7 mg + 11.7 mg
EML status history	First added in 2021 (TRS 1035)
Sex	Female
Age	Adolescents and adults
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Ethinylestradiol + etonogestrel
DrugBank	Ethinylestradiol (Ethinyl Estradiol), Etonogestrel

Expert Committee recommendation

The Expert Committee noted target 3.7 of the SDGs to ensure universal access to sexual and reproductive health care services, including for family planning, information and education, and the integration of reproductive health into national strategies and programmes by 2030. The Committee acknowledged that effective contraception contributes to advancing maternal and child health, and reduces unintended pregnancies and the need for abortion (particularly unsafe abortion). Access to family planning reinforces people's rights to determine the number and spacing of their children. The Committee noted that the unmet need for contraception in many settings is high and is highest among the most vulnerable in society. The Committee agreed with the WHO Sexual and Reproductive Health and Research Department in supporting the principle of choice for people in the provision of family planning and contraception. The Expert Committee noted that the available evidence supports the comparable effectiveness of the combined contraceptive vaginal ring to alternative hormonal contraceptive methods. It also noted that the contraceptive vaginal ring had a safety profile largely consistent with well-established safety profiles of other combined hormonal contraceptives, but had unique device-related effects (e.g. vaginitis and discharge). The Committee noted that combined contraceptive vaginal rings are included in the WHO medical eligibility criteria for contraceptive use, and that the WHO technical department supported the inclusion of the ethinylestradiol + etonogestrel vaginal ring in the Model List. The Committee noted that the ethinylestradiol + etonogestrel vaginal ring is widely available including in generic forms. Based on the evidence for efficacy and safety, recommendations in WHO guidelines, and in line with the philosophy of offering multiple contraceptive choices for people seeking family planning and contraception, the Committee recommended inclusion of the

ethinylestradiol + etonogestrel vaginal ring on the core list of the EML.

Background

Ethinylestradiol + etonogestrel contraceptive vaginal ring has not previously been considered by the Expert Committee for inclusion on the Model List. Ethinylestradiol is included on the EML as a component of combined oral contraceptives. Etonogestrel is included on the EML in an implantable contraceptive rod formulation. In 2015, the Expert Committee recognized that many factors can influence a person's choice and use of contraception, including cultural and religious values, individual preferences, medical conditions, delivery methods, cost and convenience. The Committee strongly supported the principle of choice for people in the provision of family planning and contraception (1).

Public health relevance

Unintended pregnancy is well recognized as a serious public health issue both in developed and developing countries. Even though the rate of unintended pregnancy has declined globally in the past decade, it remains high, particularly in low- and middle-income countries (2). Unintended pregnancy is associated with adverse physical, mental, social and economic outcomes, and contributes to both maternal and infant mortality (3). 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 method for reasons related to the method such as health concerns, side-effects or inconvenience of use (4). Target 3.7 of the Sustainable Development Goals (SDGs) is to ensure, by 2030, universal access to sexual and reproductive health care services, and the integration of reproductive health into national strategies and programmes (5).

Benefits

The contraceptive efficacy of ethinylestradiol + etonogestrel vaginal ring was evaluated in two open-label, non-comparative studies in Europe and North America involving 2322 women for 23 298 cycles, equivalent to 1786 women years (intention-to-treat population) (6,7). From the pooled results of the two studies, 21 pregnancies occurred during the study period, giving a pearl index (contraceptive failures per 100 women years) of 1.18 (95% confidence interval (CI) 0.73 to 1.80). Eleven of the pregnancies were attributable to non-compliance; the pearl index for the women in the per-protocol group was 0.77 (95% CI 0.37 to 1.40) (8). The comparative efficacy of ethinylestradiol + etonogestrel vaginal ring versus ethinylestradiol + levonorgestrel combined oral contraceptive was evaluated in a phase III, open-label, multicentre randomized trial of 1030 women, conducted in nine European and two South American countries (9). Ten pregnancies occurred during treatment in the intention-to-treat population, five in each treatment arm. Five pregnancies occurred in the per-protocol population, three in the vaginal ring arm and two in the combined oral contraceptive arm. No significant differences were seen in contraceptive efficacy between treatment groups. Pearl indices for the intention-to-treat populations for the vaginal ring and combined oral contraceptive groups were 1.23 (95% CI 0.40 to 2.86) and 1.19 (95% CI: 0.39 to 2.79), respectively. For the intention-to-treat population, the cumulative probability of in-treatment pregnancy was 1.20% (95% CI 0.14 to 2.26%) and 1.07% (95% CI 0.13 to 2.00%), for the vaginal ring and combined oral contraceptive groups, respectively. For the per-protocol population, the estimated probabilities of pregnancy were 0.71% (95% CI 0.00 to 1.52%) for the vaginal ring group and 0.43% (95% CI 0.00 to 1.01%) for the combined oral contraceptive group. Similar results were observed in another open-label, multicentre randomized controlled trial involving 983 women in 10 European countries that compared ethinylestradiol + etonogestrel vaginal ring with a combined oral contraceptive containing ethinylestradiol + drospirenone (10). Five pregnancies occurred during the study, one in the vaginal ring group and four in the combined oral contraceptive group. Pearl indices for the intention-to-treat population were not significantly different between treatment groups: 0.25 (95% CI 0.01 to 1.36) for the vaginal ring group and 0.99 (95% CI 0.27 to 2.53) for the combined oral contraceptive group. An open-label, prospective, single-arm, non-randomized study assessed real-life use of the ethinylestradiol + etonogestrel vaginal ring over three cycles in 252 women in India (11). No pregnancies were reported during the study period. Three postmarketing observational studies in Germany (12), the Netherlands (13) and Switzerland (14) support the contraceptive efficacy findings of the clinical trials. Good user and partner acceptability of the vaginal ring has

been reported in several studies (6,7,10,11,15,16).

Harms

In the two non-comparative studies of contraceptives (6,7), 65.5% of participants reported at least one adverse event, of which 37.5% were considered to be possibly, probably or definitely treatment-related; 15.1% of participants discontinued the contraceptive due to adverse events. The most commonly reported treatment-related adverse events were headache (5.8%), vaginitis (5.6%), vaginal discharge (4.8%) and device-related events (foreign body sensation, sexual problems and expulsion (4.4%). The most common adverse events leading to treatment discontinuation were device-related events, headache, emotional lability and weight gain. Over the study period, mean weight gain was less than 1 kg from baseline. No clinically relevant changes in systolic or diastolic blood pressure were reported (6). The most commonly reported treatment-related adverse events in both arms of the comparative trials were headache, vaginitis, method-related events, vaginal discharge, breast pain and nausea, which occurred more frequently in the vaginal ring treatment arms (9,10).

Additional evidence

A Cochrane systematic review compared contraceptive effectiveness, cycle control, patient adherence and safety of combined hormonal contraceptives in transdermal patch and vaginal ring formulations versus combined oral contraceptives (17). The review included 11 randomized controlled trials that compared ethinylestradiol + etonogestrel vaginal contraceptive ring with combined oral contraceptives. No significant difference between treatment methods was observed for contraceptive effectiveness. Women using the vaginal ring generally had fewer adverse events than oral contraceptive users – less nausea, acne, irritability, depression and emotional liability – but they experienced more vaginal irritation and discharge. The incidence of deep vein thrombosis among users of the vaginal ring was estimated to be 149 per 100 000 women years (95% CI 18 to 538), based on two events. The authors stated that due to the rarity of events reported, these trials do not provide adequate evidence on the comparative risk of deep vein thrombosis. A second systematic review of 14 randomized controlled trials also compared the efficacy and side-effects of the vaginal ring versus combined oral contraceptives (18). This review found a trend towards higher efficacy for the vaginal ring for preventing pregnancy (Peto odds ratio (OR) 0.52, 95% CI 0.26 to 1.04), as well as significantly less nausea and breakthrough bleeding reported (Peto OR for nausea 0.66 95% CI 0.49 to 0.99; Peto OR for breakthrough bleeding 0.68, 95% CI 0.51 to 0.91). No significant differences were found between contraceptive methods in measures of compliance.

Cost / cost effectiveness

The cost–effectiveness of contraception for preventing unintended pregnancy is widely recognized (20). The application described a study that assessed the cost–effectiveness of different combined hormonal contraceptive methods in Spain (21). This study used a Markov model of three methods: reimbursed oral contraceptive, contraceptive patch and vaginal ring. The most cost-effective method from the perspective of the National Health Service was the vaginal ring. However, the vaginal ring was the most expensive method for patients.

WHO guidelines

The WHO Medical eligibility criteria for contraceptive use (19) notes that based on the available evidence, the combined contraceptive vaginal ring has a comparable safety and pharmacokinetic profile and has similar effects on ovarian function to combined oral contraceptives with similar hormone formulations in healthy women. Weight gain did not differ between vaginal ring users and combined oral contraceptive users who had a body mass index ≥ 30 kg/m2. Limited evidence on use by women after medical and surgical abortion found no serious adverse events and no infection related to use during three cycles of follow-up after abortion. In addition, in women with low-grade squamous intraepithelial lesions, use of the vaginal ring did not worsen the condition. Pending further evidence, the guideline development group concluded that the evidence available for combined oral contraceptives applies also to the combined contraceptive vaginal ring. Therefore, the combined contraceptive vaginal ring should have the same categories for use as combined oral contraceptives.

Availability

Nuvaring®, the innovator device developed by Organon (Merck), is registered in more than 50 countries. Generic brands are available. The ethinylestradiol + etonogestrel vaginal ring manufactured by the applicant is registered in several European countries, including Belgium, Czechia, Denmark, Finland, France, Italy, the Netherlands, Poland, Portugal and Spain. No information was presented on the availability of ethinylestradiol + etonogestrel vaginal ring in low- and middle-income settings.

1. The selection and use of essential medicines. Report of the WHO Expert Committee, 2015 (including the 19th WHO Model List of Essential Medicines and the 5th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2015 (WHO Technical Report Series, No. 994; https://apps.who.int/iris/handle/10665/189763, accessed 6 June 2021)
2. Bearak J, Popinchalk A, Ganatra B, Moller A-B, Tunçalp Ö, Beavin C, et al. Unintended pregnancy and abortion by income, region, and the legal status of abortion: estimates from a comprehensive model for 1990–2019. Lancet Glob Health. 2020;8(9):e1152–e61.
3. Tsegaye AT, Mengistu M, Shimeka A. Prevalence of unintended pregnancy and associated factors among married women in west Belessa Woreda, Northwest Ethiopia, 2016. Reprod Health. 2018;15(1):201.
4. Bellizzi S, Mannava P, Nagai M, Sobel HL. Reasons for discontinuation of contraception among women with a current unintended pregnancy in 36 low- and middle-income countries. Contraception. 2020;101(1):26–33.
5. United Nations Sustainable Development Goals. Goal 3: Ensure healthy lives and promote well-being for all at all ages [online]. New York: United Nations; 2015 (https://www.un.org/sustainabledevelopment/health/, accessed 6 June 2021).
6. Dieben TO, Roumen FJ, Apter D. Efficacy, cycle control, and user acceptability of a novel combined contraceptive vaginal ring. Obstet Gynecol. 2002;100(3):585–93.
7. Roumen FJ, Apter D, Mulders TM, Dieben TO. Efficacy, tolerability and acceptability of a novel contraceptive vaginal ring releasing etonogestrel and ethinyl oestradiol. Hum Reprod. 2001;16(3):469–75.
8. Bjarnadóttir RI. Update on contraceptive vaginal rings. Rev Gynaecol Pract. 2003;3(3):156–9.
9. Oddsson K, Leifels-Fischer B, de Melo NR, Wiel-Masson D, Benedetto C, Verhoeven CH, et al. Efficacy and safety of a contraceptive vaginal ring (NuvaRing) compared with a combined oral contraceptive: a 1-year randomized trial. Contraception. 2005;71(3):176–82.
10. Ahrendt HJ, Nisand I, Bastianelli C, Gómez MA, Gemzell-Danielsson K, Urdl W, et al. Efficacy, acceptability and tolerability of the combined contraceptive ring, NuvaRing, compared with an oral contraceptive containing 30 microg of ethinyl estradiol and 3 mg of drospirenone. Contraception. 2006;74(6):451–7.
11. Pandit SN, Chauhan AR, Anagani M, Reddy S, Birla A, Ray SK. Multicenter study of contraceptive vaginal ring (NuvaRing(®)) in normal daily practice in Indian women. J Obstet Gynaecol India. 2014;64(6):409–16.
12. Brucker C, Karck U, Merkle E. Cycle control, tolerability, efficacy and acceptability of the vaginal contraceptive ring, NuvaRing: results of clinical experience in Germany. Eur J Contracept Reprod Health Care. 2008;13(1):31–8.
13. Roumen FJ, op ten Berg MM, Hoomans EH. The combined contraceptive vaginal ring (NuvaRing): first experience in daily clinical practice in The Netherlands. Eur J Contracept Reprod Health Care. 2006;11(1):14–22.
14. Merki-Feld GS, Hund M. Clinical experience with NuvaRing in daily practice in Switzerland: cycle control and acceptability among women of all reproductive ages. Eur J Contracept Reprod Health Care. 2007;12(3):240–7.
15. Novák A, de la Loge C, Abetz L, van der Meulen EA. The combined contraceptive vaginal ring, NuvaRing: an international study of user acceptability. Contraception. 2003;67(3):187–94.
16. Schafer JE, Osborne LM, Davis AR, Westhoff C. Acceptability and satisfaction using Quick Start with the contraceptive vaginal ring versus an oral contraceptive. Contraception. 2006;73(5):488–92.
17. Lopez LM, Grimes DA, Gallo MF, Stockton LL, Schulz KF. Skin patch and vaginal ring versus combined oral contraceptives for contraception. Cochrane Database Syst Rev. 2013;2013(4):CD003552.
18. López-Picado A, Lapuente O, Lete I. Efficacy and side-effects profile of the ethinylestradiol and etonogestrel contraceptive vaginal ring: a systematic review and meta-analysis. Eur J Contracept Reprod Health Care. 2017;22(2):131–46.
19. Medical eligibility criteria for contraceptive use. Fifth edition. Geneva: World Health Organization; 2015. https://apps.who.int/iris/handle/10665/181468, accessed 6 June 2021).
20. Blumenthal PD, Edelman A. Hormonal contraception. Obstet Gynecol. 2008;112(3):670–84.
21. Guerra S, Sánchez F, Encinas A, Ugarte L, Barbadillo N, Lete I. Costes de la anticoncepción hormonal combinada en España: ¿hay algún método más coste-efectivo [Cost–effectiveness of combined hormonal contraception in Spain: which is the most cost-effective method?] Prog Obstet Ginecol. 2015;58(5):221–6.

