

Segesterone Acetate/Ethinyl Estradiol Contraceptive Vaginal System (ANNOVERA) National Drug Monograph December 2021

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information. [Annovera PI Aug 2018](#)

FDA Approval Information¹

Description/Mechanism of Action

- Segesterone acetate/ethinyl estradiol (SA/EE) contraceptive vaginal system (CVS) is a combination hormonal contraceptive that prevents pregnancy primarily by suppressing ovulation. SA/EE is released from a flexible, contraceptive vaginal ring. The progestin component, SA, is a new molecular entity and derivative of 19-norprogesterone. SA is not orally active.

Indication(s) Under Review in This Document

- For use in females of reproductive potential for the prevention of pregnancy
- *Limitation:* SA/EE CVS has not been adequately studied in females with a body mass index (BMI) of greater than 29 kg/m².

Dosage Form(s) Under Review

- SA/EE CVS is a silicone elastomer vaginal ring containing 103 mg SA and 17.4 mg EE, releasing an average of 0.15 mg of SA and 0.013 mg of EE daily.
- SA/EE CVS is inserted by the patient into the vagina and must remain in place continuously for 3 weeks (21 days) followed by a 1 week (7 day) ring-free interval. The **reusable** ring is stored in a case for the ring-free interval. One SA/EE CVS will provide contraception for 13 cycles (each cycle is 28 days in length, with 21 days in and 7 days out for a total of 273 days) or 1 year.

Clinical Evidence Summary

Efficacy Considerations^{1,2,3}

- FDA approval of the SA/EE CVS was based on pooled data from two one-year, multicenter, open-label, phase 3 studies evaluating the effectiveness in preventing pregnancy. One study was conducted in the U.S. and the other study included subjects from the U.S. and internationally. Enrolled women were healthy, sexually active, and between the ages of 18 and 40 years old with normal menstrual cycles. When about 50% of the women were enrolled, a change was made to the study to exclude women with a BMI greater than 29 kg/m² after two nonfatal venous thromboembolic events (VTEs) were reported, both in patients with a BMI greater than 29 kg/m².
- The primary endpoint was the Pearl Index (number of pregnancies per 100 woman-years) for women who were 35 years of age and younger. The Pearl Index was calculated as the number of on-treatment pregnancies that occurred during all cycles except those where adjunctive contraception use was reported or that occurred after a conception.³

- **Baseline/disposition:** A total of 2,265 participants were enrolled in both studies with a median follow-up time of 11 cycles. The mean age of the population was 27 years, 67% were from the U.S., and 71% of the women were Caucasian.
- **Results:** The efficacy population included 2,111 females who were ≤ 35 years old contributing 17,427 cycles (where no back-up contraception was used). The Pearl Index for the primary efficacy group was 2.98 (95% confidence interval [CI] 2.13 – 4.06) per 100 woman-years. The cumulative probability of not becoming pregnant over 13 cycles was 97.5%, and there were no apparent signals of changing efficacy over time.³

Safety Considerations^{1,2}

- **Safety results from clinical trials:** Safety data used to support the FDA approval of the SA/EE CVS included 2,308 females contributing 21,590 cycles of exposure; 43% of subjects completed 13 cycles.
- **Contraindications:** Contraindications with the SA/EE CVS are very similar to other combination hormonal contraceptives and include patients with a high risk of arterial or venous thrombotic disease, current or history of breast cancer or other estrogen- or progestin-sensitive cancer, liver tumors, acute hepatitis or severe (decompensated) cirrhosis, undiagnosed abnormal uterine bleeding, hypersensitivity to ingredients, and use of hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to the potential for alanine transaminase elevations.
- **Other warnings / precautions:** Warnings and precautions with the SA/EE CVS are very similar to other combination hormonal contraceptives. Consult prescribing information for a complete list. Examples include warnings to inform and minimize the risk of venous thromboembolic events (VTE) and arterial events (e.g., stroke and myocardial infarction), liver enzyme elevations, hypertension, the potential for gall bladder disease, abnormal uterine bleeding, depression, and others. (See more information below).
 - **VTE**
 - Of note, the rate estimate of VTE was higher for the SA/EE CVS than other combination hormonal contraceptives. The estimated rate of VTE for the SA/EE CVS was 24 cases per 10,000 woman years (95% CI 6.6 – 61.7) based on 4 VTE events in the clinical trials. Two of the women had a BMI >29 kg/m², and 1 woman had factor V Leiden mutation. Further postmarketing study will be required evaluating the risk of VTE with the SA/EE CVS.
 - The increased risk of VTE with combination hormonal contraceptives is well known and estimated to be in the range of 3 to 12 cases per 10,000 woman-years. For the other FDA approved vaginal ring (etonogestrel/ethinyl estradiol), the incidence of VTE was 8.3 per 10,000 woman-years and 11.4 per 10,000 woman-years based on two epidemiologic studies.⁴
 - For perspective, the base rate of VTE in nonpregnant women of childbearing age is 1 to 5 cases per 10,000 woman-years. During pregnancy, the rate of VTE is 5 to 20 cases per 10,000 woman-years, and in the highest risk post-partum period, the rate is 40 to 65 cases per 10,000 woman-years.
 - **Unique to vaginal contraceptives:** 1) Toxic shock syndrome (TSS) has been reported by users of vaginal ring contraceptives, tampons, and some barrier contraceptives. No cases of TSS were reported in clinical trials with the SA/EE CVS. 2) Vaginal and cervical erosion and/or ulceration has been reported by females using vaginal contraceptives. 3) The risk of vaginal infection with the use of the same vaginal ring for 13 cycles was evaluated in a microbiology sub-study. Per the FDA review, no unexpected vulvar or vaginal findings were noted with SA/EE.²
- **Adverse reactions:** The most common adverse reactions reported were headaches and nausea/vomiting. See Table 1 for more details.

Table 1. Adverse reactions occurring in more than 5% of subjects¹

	SE/EE CVS N=2,308
Headache, including migraine	39%
Nausea, vomiting	25%
≥1 complete vaginal expulsion	25%
Vulvovaginal mycotic infection, vaginal candidiasis	15%
Abdominal pain, lower or upper	13%
Dysmenorrhea	13%
Vaginal discharge	12%
UTI, cystitis, pyelonephritis, genitourinary tract infection	10%
Breast pain, tenderness, discomfort	10%
Metrorrhagia, menstrual disorder	8%
Diarrhea	7%
Genital pruritus	6%

- **Deaths:** none
- **Serious adverse events:** VTEs, psychiatric events, hypersensitivity reactions, and spontaneous abortions were reported in 2 or more subjects in clinical trials.
- **Discontinuations due to adverse events:** In clinical trials, 12% of subjects discontinued due to adverse reactions. Metrorrhagia/menorrhagia, vaginal expulsions, headache/migraine, vaginal discharge/vulvovaginal mycotic infections, and nausea/vomiting were the most commonly reported reactions leading to discontinuation.

Other Considerations

- **Return of fertility¹** In a sub study evaluating return to pregnancy within a 6 month follow-up period, all 290 women reported a return to fertility (defined as return of menses or pregnancy).¹
- **Use of vaginal products with the SA/EE CVS¹**
 - Oil-based (including silicone-based) vaginal lubricants and medications (e.g., oil-based vaginal suppositories) will alter the vaginal system and/or exposure to SA and EE and should not be used. Water-based vaginal lubricants and vaginal creams are compatible and can be used with the CVS.
 - Male condoms are compatible with the CVS.
 - Tampon use with the CVS has not been studied.
- **Cleaning and storage¹** When removed, the SA/EE CVS should be cleaned with mild soap and water, dried, and stored in provided case for the 1-week ring-free interval. The product should be cleaned again prior to re-insertion.
- **FDA approval²**
 - The trial design was changed at about 50% enrollment to exclude women with a BMI greater than 29 kg/m² after two women with a BMI greater than 29 kg/m² developed non-fatal venous thromboembolism in the studies.
- **Pharmacologic properties³** The vaginal ring releases approximately 150 mcg of SA and 13 mcg of EE daily. Plasma EE exposure is comparable-to-lower-than a low-dose oral combination hormonal contraceptive.

- **Pregnancy**¹ There is no indication for the use for the SA/EE CVS in pregnancy.
- **Lactation**¹ Contraceptive hormones and/or their metabolites are found in human milk. Combination hormonal contraceptives may reduce milk production in nursing females. It is recommended to use an alternative method of contraception in breastfeeding females.
- **Sexually transmitted infections**¹ The SA/EE CVS does not protect against sexually transmitted infections including HIV. The SA/EE CVS is compatible with condoms made with natural rubber latex, polyisoprene, and polyurethane.

Other Therapeutic Options

Table 2. Tier 2 Hormonal Contraceptive Alternatives⁵

Drug	VANF	Other Considerations
Contraceptive ring, <u>reusable</u> (Annovera)	TBD	<ul style="list-style-type: none"> • Vaginal ring inserted for 3 wks, removed for 1 wk • Ring is washed and reused for 13 cycles • No refrigeration required
Contraceptive ring, <u>disposable</u> (NuvaRing, EluRyng)	Yes	<ul style="list-style-type: none"> • Vaginal ring inserted for 3 wks, removed for 1 wk and discarded • New ring needed after each cycle • Stable outside refrigerator for 4 mos
DMPA injection (Depo-Provera)	Yes	<ul style="list-style-type: none"> • Injection that lasts 12 wks • Typically requires healthcare visit
Oral contraceptives	Yes	<ul style="list-style-type: none"> • Pills containing progestin +/- estrogen • Need for daily compliance
Contraceptive patch (Xulane, Zafemy, Twirla)	No	<ul style="list-style-type: none"> • Weekly transdermal patch with estrogen and progestin • Higher exposure to estrogen

DMPA=depo-medroxyprogesterone; IUD=intrauterine device; OTC=over the counter

Projected Place in Therapy

- In the U.S., the rate of unintended pregnancy was nearly 45% based on data from 2011.⁶
- The SA/EE CVS appears to have comparable efficacy as other combination hormonal contraceptives, with a Pearl Index of 2.98 (95% CI 2.13 – 4.06) pregnancies per 100 woman-years, though no direct comparisons have been made.
- The safety profile of the SA/EE CVS appears to be comparable to other combination hormonal contraceptives, with the exception of a possible increased risk of VTE (see below).
- The rate estimate for VTE was higher with the SA/EE CVS (24 per 10,000 woman-years; 95% CI 6.6 – 61.7) than reported with other combination hormonal contraceptives, though the risk estimate was associated with wide confidence interval indicating uncertainty. VTE risk will be further evaluated in a postmarketing study.
- The SA/EE CVS has not been adequately evaluated in females with a BMI >29 kg/m². Two of four VTEs reported in clinical trials occurred in patients with a BMI >29 kg/m².
- The SA/EE CVS is the second FDA approved combination hormonal vaginal ring contraceptive in the U.S. Both the SA/EE CVS and etonogestrel/ethinyl estradiol ring (Nuvaring, Eluryng, and equivalents) are inserted for 3 continuous weeks followed by a 1 week ring-free interval. One of the main practical differences between the products for patients is that the SA/EE CVS is **reusable** for up to 13 cycles, and etonogestrel/EE is **disposable**, with a new etonogestrel/EE ring required each month. The SA/EE CVS requires cleaning and storage during the 1 week ring-free interval. The etonogestrel/EE rings are supplied in boxes of 3, which are stable for 4 months outside of the refrigerator. Of note, the etonogestrel/EE ring was not evaluated in patients with BMI ≥30 kg/m².
- The SA/EE CVS has not been studied for indications other than pregnancy prevention (e.g., endometriosis) or in dosing regimens outside of the product label (e.g., altering the ring-free interval).
- There is moderate quality evidence to support the effectiveness of SA/EE CVS as a contraceptive based on data from two open-label, noncomparative studies evaluating pregnancy as an outcome.
- **Contraceptive vaginal rings including the SA/EE CVS offer patients an effective, convenient, non-daily, non-oral method for pregnancy prevention. The monthly, disposable etonogestrel/EE ring is available generically and at a lower annual cost compared to the new 12-month, reusable SA/EE CVS. The SA/EE CVS may be considered when a 12-month product is preferred due to clinical or other patient specific needs (e.g., extended travel or deployment, limited or no access to refrigeration, or history of or potential difficulties with obtaining timely refills).**

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References:

- ¹ ANNOVERA (segesterone acetate and ethinyl estradiol vaginal system). Prescribing Information. Therapeutics MD for Population Council, New York, NY. August 2018.
- ² Food and Drug Administration: Center for Drug Evaluation and Research. Annovera Multidiscipline Review. Accessed at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/209627Orig1s000MultidisciplineR.pdf Accessed on September 10, 2021.
- ³ Archer DF, Merkatz RB, Bahamondes L, et al. Efficacy of the 1-year (13-cycle) segesterone acetate and ethinylestradiol contraceptive vaginal system: results of two multicentre, open-label, single-arm, phase 3 trials. *Lancet Glob Health* 2019;7:31-54-64.
- ⁴ NUVARING (etonogestrel and ethinyl estradiol vaginal ring). Prescribing Information. Merck Sharp & Dohme Corp., Whitehouse Station, NJ. May 2019.
- ⁵ Centers for Disease Control and Prevention. Reproductive Health: Contraception: Contraceptive Effectiveness. Accessed at: <https://www.cdc.gov/reproductivehealth/contraception/index.htm#Contraceptive-Effectiveness> Accessed on March 4, 2021.
- ⁶ Centers for Disease Control and Prevention. Reproductive Health: Contraception: Unintended Pregnancy. Accessed at: <https://www.cdc.gov/reproductivehealth/contraception/unintendedpregnancy/index.htm> . Accessed on March 3, 2021.