CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	209627
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Reviewer Name(s)	Courtney Cunningham, PharmD
Team Leader	Laura Zendel, PharmD
Deputy Division Director	Jamie Wilkins, PharmD
Review Completion Date	July 16, 2018
Subject	Evaluation of Need for a REMS
Established Name	Segesterone Acetate/Ethinyl Estradiol Vaginal System
Trade Name	Annovera
Name of Applicant	The Population Council
Therapeutic Class	Combined hormonal contraceptive (CHC)
Formulation(s)	Vaginal System
Dosing Regimen	Insert 1 system vaginally; remain in place for 21 days, remove for 7 days system free for 13 cycles

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Annovera (segesterone acetate/ethinyl estradiol) vaginal system is necessary to ensure the benefits outweigh its risks. The Population Council submitted a New Drug Application (NDA # 209627) for Annovera with the proposed indication of prevention of pregnancy. The most serious risks associated with Annovera include venous thrombotic events (VTEs), and serious cardiovascular events in women who are over 35 years of age and smoke cigarettes. The applicant's proposed REMS consisted of a Medication Guide and Communication Plan.

DRISK and the Division of Bone, Reproductive, and Urologic Products (DBRUP) agree that a REMS is not needed to ensure the benefits of Annovera outweigh its risks. The product demonstrated efficacy in prevention of pregnancy. Currently approved combined hormonal contraceptives use professional labeling to communicate the risk of VTEs. Although the Applicant submitted a REMS, at this time, labeling can serve as sufficient risk mangement.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for Annovera, which contains the new molecular entity (NME) segesterone acetate, is necessary to ensure the benefits outweigh its risks. The Population Council submitted a New Drug Application (NDA 209627) for Annovera with the proposed indication of prevention of pregnancy. This application is under review in the Division of Bone, Reproductive, and Urologic Products (DBRUP). The applicant's proposed REMS consisted of a Medication Guide and a Communication Plan, however, this product does not currently demonstrate a risk which necessitates a risk management approach beyond labeling.

2 Background

2.1 Product Information

Annovera, with segesterone acetate being a new molecular entity, is a progestin/estrogen combination hormonal contraceptive vaginal ring proposed for the indication of the prevention of pregnancy in adult females. This contraceptive vaginal ring lowers the risk of pregnancy using a progestin and estrogen to suppress ovulation by inhibiting the release of gonadotropin from the pituitary, preventing follicular maturation, and decreasing the release of luteinizing hormone releasing hormone from the hypothalamus. Other potential mechanisms of action include changes to cervical mucus which inhibit sperm penetration and changes to the endometrium which reduce likelihood of implantation. [1]

The proposed strength and dosage form of Annovera is a vaginal ring, inserted by the patient and worn consecutively for 21 days, during which it releases 150 mcg segesterone acetate and 15 mcg ethinyl estradiol daily. The ring is removed by the patient on day 22, washed with lukewarm water and soap, then stored in the provided storage case for 7 days. The ring is proposed effective for the duration of 13

twenty-eight day cycles. The combined hormonal contraceptive, (CHC), class has a boxed warning regarding the increased risk of cardiovascular adverse events in patients who use CHCs and smoke cigarettes. Segesterone acetate is an NME, while ethinyl estradiol has been used in CHCs since 1964. This CHC in a vaginal ring is not marketed in any other jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA #209627 relevant to this review:

- 08/17/2017: NDA 209627 submission for prevention of pregnancy received
- 02/01/2018: A Post Mid-cycle Face to Face Meeting was held between the Agency and Population Council. The Agency informed Population Council that based on the currently available data, there were no safety issues that require a REMS for segesterone

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Family planning and its many available methods are of great importance to women of childbearing years. In 2015, the CDC conducted a survey of the preferred contraceptive methods of women ages 15-44. 15.9% reported using oral hormonal contraception, 8% an IUD or contraceptive implant, female sterilization was reportedly used by 14.3% of respondents and male sterilization rates were reported at 4.5%.[2] However, not all women chose birth control, nor do they or their partner use it correctly. In that year alone, the CDC reported 3,978,497 births, which translates into 62.5 births/1,000 women ages 15-44.[a3] 45% of these pregnancies were unintended as of 2011 data. When used as per manufacturers' instructions, contraceptive methods can range from over 99% effective down to 80% for a female condom. Simple fertility tracking with avoidance during fertile time periods fails typically 24% of the time.

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

The options for contraception are numerous and vary in efficacy. Many varieties and strengths of combination oral contraceptive (COC) tablets are available in mono, bi, and tri-phasic formulations. Monophasic low dose progestin only tablets are also available. A weekly transdermal patch and single cycle vaginal ring containing an estrogen and progestin are also available. Progestin only containing long term use products vary from an intramuscular injection and a subdermal implant to an IUD. The progestin only formulations can be active for months to years. Non-pharmacological therapies include male and female sterilization, copper IUDs, along with male and female condoms and diaphragms and contraceptive sponges, which can be used alone or with a spermicide. Tracking fertile periods in the menstrual cycle and avoiding intercourse during these times is also used as a form of birth control. Even

[a] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

the more reliable forms of contraception are not infallible, however. Progestin containing implants and all IUDs have a failure rate of 0.05%-0.8%. Male and female surgical sterilization fail between 0.15%-0.5% of the time. Progestin injections fail approximately 6% of the time and the pill, patch, and vaginal contraceptive ring all have about a 9% failure rate. Barrier methods, including male and female condoms and sponges fail 12-24% of the times used, and withdrawal fails approximately 22% of the time.[4] A chart summarizing estrogen containing options for prevention of pregnancy is appended.

4 Benefit Assessment

Two pivotal Phase 3 studies, Study 300A (NCT00263341) and 300B (NCT00455156), were used to support the findings of safety and efficacy. A third Phase 3 pharmacokinetic study, Study 300PK, was used to support the safety findings. Study 300PK enrolled 39 women into 3 sites in the US and Latin America, for thirteen 28 day cycles. It was an open label study to evaluate safety, pharmacokinetics/pharmacodynamics, and cycle control.

Studies 300A and 300B were multicenter, open-label, trials that analyzed enrolled women 18 to less than 40 years of age who were generally healthy, sexually active, and had a history of regular menstrual cycles when not using hormonal contraceptives. Study 300A was performed at 15 sites in the United States and analyzed 1129 of 1135 enrollees, while 300B consisted of 12 sites in the US, Europe, Latin America, and Australia and analyzed 1135 enrolled subjects. Patients who completed Study 300B were allowed to enter into the Phase 3 safety, cycle control, and efficacy extension Study 300B-Ex. Twelve subjects entered this prospective, open-label, study at sites in Europe, South America, and Australia. Data from this study was used in the safety analysis.[5] Both trials lasted for thirteen 28 day cycles; 21 days when the contraceptive ring was worn vaginally, followed by 7 days when the ring was not worn. At approximately 55% of enrollment of Phase 3 studies, the Data and Safety Monitoring Board recommended exclusion of women with a BMI >29.0 kg/m^2 due to an observed occurrence of 2 venous thrombotic events in subjects with BMI >29.0 kg/m^2. The prior exclusion criteria had been a weight of >95kg (209 lbs.). This led to protocol amendments for both studies 300A and 300B.

Both studies 300A and 300B were combined to form the Summary of Clinical Effectiveness (SCE). The primary endpoint to determine effectiveness in both studies was the total number of pregnancies that occurred over a maximum 13-cycle period using the Pearl Index.

The Pivotal 13-Cycle Pearl Index Analysis Set, comprised of subjects in Studies 300A and 300B, analyzed the Pearl Index, (a method of comparison of contraception; a higher pearl index denotes a higher chance for unintended pregnancy while using a specific form of contraception), for the subgroup of women <35 years of age in cycles with no adjunctive contraception use. The Pearl Index of these 1923 was 3.01 (95% CI [2.15, 4.07]) per 100 women-years of contraceptive vaginal ring (CVR) use. The Pearl Index for females <35 years of age with a BMI <29.0 kg/m2 was 2.99 (95% CI [2.12, 4.08]). The Pearl Index for women <35 years of age with a BMI >29.0 kg/m2 was 3.43 (95% CI [0.57, 10.6]). The total number of pregnancies that occurred during ring use or within 7 days of last ring use was 38 out of

16405 cycles. The estimate of the cumulative probability of not becoming pregnant during or within 7 days of last CVR use was 0.9749 (95% CI [0.9654, 0.9818]), or 97.5%.

Thirty-nine total confirmed pregnancies occurred in the 2 pivotal trials, 38 of which were within 7 days of last CVR use. This falls within the 28-day cycle, during which a subject should have been protected from pregnancy. Six pregnancies occurred 8-14 days after the last CVR use, which would have been days 1-7 of a new cycle if the CVR had still been in use. A recalculation of the Pearl Index, including these pregnancies in women in all Phase 3 trials (N=2303) was 3.38 (95% CI [2.97, 3.83]).[5]

It has been concluded by the clinical reviewer that "overall the CVS (contraceptive vaginal system) is effective in preventing pregnancy in females of reproductive potential."

5 Risk Assessment & Safe-Use Conditions

The Summary of Clinical Safety was comprised of 2308 subjects in studies 300A, 300B, 300B-Ex, and 300PK, who used the CVR for a total of 21590 cycles. Of the total number of subjects, 999 completed the full 1 year of use (13 cycles). The most common treatment emergent adverse events (TEAEs) reported in ≥10% of subjects in studies were headache, nausea, nasopharyngitis, uterine spasm, vaginal discharge, upper respiratory tract infections, and vulvovaginal mycotic infection. The TEAE of greatest concern is the risk of venous thrombotic event (VTE), noted in 4 women in the trials.

5.1 SERIOUS ADVERSE EVENTS (SAES)

5.1.2 Venous Thrombotic Events

There were 4 VTEs seen in clinical trials. A 26-year-old African American female with a BMI of 30.3 kg/m^2 was diagnosed with a deep vein thrombosis (DVT) 1 week after after driving in a seated position for 5 hours. This occurred in cycle 6 use of the CVR. The condition resolved with medical intervention. A 23-year-old African American female, baseline BMI 29.1 kg/m^2 and BMI at time of event was 28.5 kg/m^2, had no predisposing factors when she presented with a pulmonary embolism during cycle 2 of CVR use. This resolved with medical treatment. During the 7th cycle of CVR use in the clinical trial, a 28-year-old Caucasian female with a baseline BMI of 25.3 kg/m^2 and BMI at time of event 25.0 kg/m^2, with a past medical history of prior combined oral contraceptive use, former smoker, and depression/anxiety suffered a cerebral venous thrombosis. This subject had not given the Principal Investigator permission to examine her medical records, and did not respond to repeated attempts at follow-up. She was listed as lost to follow-up, but recovering per her primary care physician. The final VTE was a DVT diagnosed in a 39-year-old Caucasian female with a BMI of 24.7 kg/m^2 during cycle 3 of the CVR study. It is noteworthy that this patient was later found to be Factor 5 Leiden positive, which would contraindicate the use of hormonal contraceptives.[6] The Clinical Reviewer finds the limitation of use at BMI 29.0kg/m^2 arbitrary recommends discussion of all four VTEs seen in clinical trials in the Warnings and Precautions section of labeling.

In the initial application, the applicant proposed [redacted] (b) (4)

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(b) (4), it will be noted in Warnings and Precautions that this product has insufficient evidence of safety and efficacy in females with BMI >29.0 kg/m^2.

The clinical safety reviewer has concluded that the CVS has "an acceptable safety profile," and recommended a post-marketing requirement study to better characterize the risk of VTEs.

6 Expected Postmarket Use

The most likely prescribers are gynecologists, with fewer prescriptions written by family or general practitioners. Annovera will most likely be used on an outpatient basis. Due to other combination hormonal birth control products having a documented increased risk for VTE, these providers should have an understanding of this risk when prescribing Annovera and other combined hormonal contraceptives.

7 Risk Management Activities Proposed by the Applicant

The applicant submitted a proposed REMS with their submission. It included a goal statement of informing patients of the risks associated with the product, a Medication Guide, and a Communication Plan.

7.1 Review of Applicant's Proposed REMS

The applicant proposed a goal of informing patients of, "the serious risks associated with the use" of the combination hormonal contraceptive product. The applicant then outlined using The Guide for Using the Hormonal Contraceptive as a Medication Guide in accordance with 21 CFR 208.24. A Communication Plan was also listed, but did not have Communication Plan activities, but rather a timetable for submission of assessments. At the conclusion of a REMS Discussion Meeting on 1/12/18, DBRUP and DRISK agreed that a REMS was not necessary for the benefits to outweigh the risks associated with Annovera. Currently approved combined contraceptive products, also carry the risk of thrombotic events, but use boxed warnings and labeling to convey this risk to prescribers and patients. The clinical reviewer determined that the VTE rate per 10000 woman-years of use for this product was 24.1 (95% CI 6.6, 61.7). Other CHC had rates of 11.7 (OrthoEvra), 5.3 (NuvaRing), and 16.7 (LoLoestrin Fe), all of which communicate VTE risk via a boxed warning in labeling, which prescribers of these products should be familiar with. The applicant was subsequently informed in the post Mid-cycle communication that a REMS would not be necessary. Postmarketing requirements and commitments are currently under review, and labeling will reflect the indeterminate safety and efficacy in women with BMIs over 29.0 kg/m^2.

7.2 OTHER PROPOSED RISK MANAGEMENT ACTIVITIES

The applicant proposed no other risk management activities with their submission. Postmarketing requirements/commitments of the applicant are still underway, but are expected to include studies powered to better characterize the risk of VTE and a study on the PK effects of stong CYP3A inducers and inhibitors on Annovera.

8 DISCUSSION OF NEED FOR A REMS

The Clinical Reviewer recommends approval of Annovera based on the efficacy and safety information currently available. The most common TEAEs reported were headache, nausea, nasopharyngitis, uterine spasm, vaginal discharge, upper respiratory tract infections, and vulvovaginal mycotic infection. Annovera is expected to be prescribed predominantly by OB/GYN, who should be familiar with the associated risks of the system, due to approved combination hormonal birth control products having a documented increased risk of VTEs. As data was limited in subjects with BMI > 29.0 kg/m^2, labeling will reflect the uncertainty of efficacy and safety in that population, as well as an increased risk of VTE in the overall population who use this drug. Labeling will be maximixed to include boxed warning to reflect the increased risk of VTE as well as increased risk of cardiovascular events in women over 35 who smoke cigarettes. This is consistent with labeling of approved combined hormonal contraceptives that also carry this risk. Therefore, based on currently available data, mitigation measures going beyond professional labeling are not necessary to ensure the benefits of Annovera outweigh its risks.

9 Conclusion & Recommendations

Based on the available data a REMS is not necessary to ensure the benefits outweigh the risks. The safety concern of increased VTE associated with Annovera use has been well documented in previously approved combined hormonal contraceptives, and in general, healthcare providers who prescribes these medications should be familiar with the increase risk of VTE.

Should DBRUP have any concerns or questions or if new safety information becomes available, please send a consult to DRISK.

10 Appendices

10.1 REFERENCES

1. Council TP. Proposed segesterone acetate/ethinyl estradiol vaginal ring labeling. August 17, 2017.
2. Centers for Disease Control and Prevention-National Center for Health Statistics-Contraceptive Use July 15, 2016.

3. Centers for Disease Control and Prevention- National Center for Health Statistics-Births and Natality. October 13, 2016.
4. Centers for Disease Control and Prevention-Reproductive Health-Contraception-Effectiveness of Contractive Methods
February 9,2017.
5. Council TP. Summary of Clinical Efficacy of (segesterone acetate)/ethinyl estradiol vaginal ring. August 17, 2017.
6. Council TP. Summary of Clinical Safety of (segesterone acetate)/ethinyl estradiol vaginal ring. August 17, 2017.

Estrogen Containing Contraception Options

Brand Name (Generic Name)	Year of Approval	Dosing and Administration	Warnings and Precautions	Boxed Warnings
NuvaRing Vaginal Ring (Ethinyl estradiol(EE)/etonorgestrel)	2014	0.015mg EE/0.12mg etonorgestrel in 24 hr Insert 1 ring vaginally; leave in for 21 days, remove for 7 days	-Must be discontinued if venous/arterial thrombotic event -Retinal vascular thrombosis, cholestasis, (b) (4) hypertension	-Cigarette smoking increases risks of cardiovascular side effects

Xulane (Ethinyl estradiol and norelgestromin transdermal patch)	1992	0.035mg EE/0.15mg norelgestromin daily Apply 1 patch weekly for 3 weeks, then 1 patch free week	-Contraindicated in smokers over 35 years old, history of estrogen dependent or hepatic cancers, or at high risk of venous or arterial thrombotic diseases -Potential lower efficacy in women weighing over 90 kg(198lbs) -Thromboembolic disorders, retinal vascular thrombosis, hypertension, use with caution in patients at risk for cardiovascular disease	-Cigarette smoking increases risks of cardiovascular side effects-increases with age, particularly over 35 years old and number of cigarettes smoked-not to be used by smokers -Higher risk of venous thromboembolism than oral contraceptives (OC) -Patch pharmacokinetic profile different than OC; steady state EE concentrations avg. 60% higher in patch users than COC, and EE peak 25% lower-unknown if this contributes to adverse events
Ortho Tri-Cyclen (Ethinyl estradiol(EE) norgestimate) oral tablets	2001/2006	7 tablets of 0.180mg norgestimate and 0.035mg EE, 7 tablets of 0.215 mg norgestimate and 0.035mg EE, 7 tablets of 0.250mg norgestimate and 0.035mg EE 7 inert tablets	-Should be stopped surrounding major surgery -Hypertension, dyslipidemia, headache	-Cigarette smoking increases risks of serious cardiac side effects from COC use -Ortho Tri-Cyclen is contraindicated in women over 35 years old who smoke

Yasmin/YAZ (Ethinyl estradiol/drospirenone) Oral Tablets		Yasmin-21 tablets containing 0.03mg EE and 3 mg drospirenone-7 inert tablets YAZ-24 tablets containing 0.02mg EE and 3mg drospirenone, 4 inert tablets	-Bolded Warning- Drospirenone has antimineralocorticoid activity, including hyperkalemia potential (comparable to 25mg spironolactone)-do not use in patients with conditions that predispose to hyperkalemia; women receiving daily long term medications that may cause hyperkalemia should have potassium checked in 1st cycle -Must be stopped surrounding major surgery, liver disease, lipid effects, hypertension -Contraindicated in renal impairment -Higher risk ratio for VTE's when compared with other COCs	-Smokers over 35 years old should not use Yasmin -Cigarette smoking increases risk of serious cardiovascular events from COC use -YAZ Boxed Warning- Cigarette smoking increases risk of serious cardiovascular events from COC use

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