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	201110
PDUFA Goal Date	April 29, 2020
OSE RCM #	2016-789
Reviewer Name(s)	Theresa Ng, PharmD, BCPS, CDE
Team Leader	Laura Zendel, PharmD, BCPS
Division Director	Jamie Wilkins, PharmD
Review Completion Date	April 29, 2020
Subject	Evaluation of Need for a REMS
Established Name	Progesterone Vaginal (b) (4)
Trade Name	Milprosa
Name of Applicant	Ferring Pharmaceuticals Inc. (Ferring)
Therapeutic Class	Progesterone
Formulation(s)	(b) (4) progesterone in a non-biodegradable, (b) (4) vaginal Ring containing (b) (4) gram progesterone releasing an average of 11 mg/day of progesterone over a 7-days.
Dosing Regimen	One ring inserted vaginally (b) (4) the day after oocyte retrieval. The vaginal ring is replaced weekly, continuing for up to 10 weeks total duration.

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for Milprosa (Progesterone Vaginal (b) (4)) is necessary to ensure the benefits outweigh its risks. Ferring Pharmaceuticals Inc. (Ferring) submitted a New Drug Application (NDA 201110) for Milprosa with the proposed indication to support embryo implantation and early pregnancy (up to 10 weeks post-embryo transfer) by supplementation of corpus luteal function as part of an Assisted Reproductive Technology (ART) treatment program for infertile women up to 34 years of age.

The risks associated with Milprosa include adverse events related to the device such as vaginal irritation and discomfort, adverse events associated with pregnancy including nausea, spontaneous abortion, and headache, and other known risks associated with progesterone. The Applicant did not submit a proposed REMS or risk management plan with this application.

The Division of Risk Management (DRM) has determined that a REMS is not needed to ensure the benefits of Milprosa outweigh its risks. The product has demonstrated efficacy in supporting embryo implantation and early pregnancy (up to 10 weeks post-embryo transfer) by supplementation of corpus luteal function as part of an ART treatment program for infertile women up to and including 34 years of age. However, efficacy in women 35 years old and greater was not established with this product and therefore a limitation of use will be included in the labeling to inform prescribers and a postmarketing commitment (PMC) will be conducted to evaluate the efficacy and safety in this subgroup of women, the likely population that will be prescribed Milprosa for luteal support after undergoing ART for infertility. As the adverse events are comparable to other progesterone products with the same indication, labeling should be sufficient to communicate the expected risks associated with Milprosa.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for Milprosa (progesterone vaginal (b) (4)), a new drug-device combination product, is necessary to ensure the benefits outweigh its risks. Ferring submitted a New Drug Application (NDA) 201110 for Milprosa with the proposed indication to support embryo implantation and early pregnancy (up to 10 weeks post-embryo transfer) by supplementation of corpus luteal function as part of an Assisted Reproductive Technology (ART) treatment program for infertile women up to and including 34 years of age. This application is under review in the Division of Urology, Obstetrics and Gynecology (DUOG) (previously under review in the Division of Bone Reproductive, Urologic Products (DBRUP)). The Applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Milprosa is a drug-device product with the active ingredient progesterone embedded in a non-biodegradable (b) (4) vaginal ring. Milprosa is proposed to support embryo implantation and early pregnancy (up to 10 weeks post-embryo transfer) by supplementation of corpus luteal function as part of an Assisted Reproductive Technology (ART) treatment program for infertile women. Milprosa is not a

new molecular entity, however, it is under review as an NDA 505(b)(1)[a] application. Milprosa is proposed to be available as a (b) (4) gram progesterone vaginal ring, releasing an average of 11 mg/day of progesterone over 7 days. The patient inserts one ring vaginally starting the day after oocyte retrieval and replaces the vaginal ring weekly at home, continuing for up to 10 weeks total duration[b]. There are currently no REMS requirements for any progesterone products approved for luteal support for use in women with infertility. Currently approved progesterone products for luteal support include the risks of cardiovascular and cerebral thromboembolic disorders and depression in the warnings and precaution sections of labeling.[1,2] Milprosa is currently not approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for Milprosa (NDA 201110) relevant to this review:

- 04/30/2010: Teva Women's Health Inc., submitted NDA 201110 for Milprosa to support embryo implantation and early pregnancy (up to 10 weeks post-embryo transfer) by supplementation of corpus luteal function as part of an Assisted Reproductive Technology (ART) treatment program for infertile women.
- 02/28/2011: The Agency issued a Complete Response Letter (CRL) for deficiencies in: (1) Product quality and (2) efficacy in 35-42-year-old females. The Agency recommended that the Applicant conduct, prior to approval of Milprosa, a randomized, active-controlled clinical trial to evaluate the efficacy of Milprosa in women 35-42 years of age. However, the CRL provide a possible pathway for approval if appropriate labeling with a limitation of use statement and a postmarketing commitment (PMC) to conduct clinical trials to evaluate the efficacy of Milprosa in women 35-42 year of age.[3]
- 08/05/2015: Ownership of NDA 201110 was transferred from Teva to Ferring Pharmaceuticals Inc.
- 02/25/2016: Ferring submitted a Class 2 Resubmission to address the deficiencies identified in the original submission CRL dated 02/28/2011. The Applicant did not submit further efficacy or safety information with this resubmission. The Applicant proposed labeling with limitation of use and a PMC as requested by the Agency.
- 11/23/2016: The Agency issued a CRL for deficiencies in: (1) biocompatibility information, (2) clinical safety bridge between the legacy progesterone vaginal ring used in the phase 3 clinical trials and the revised progesterone vaginal ring product which uses a new (b) (4) process and recommended that the applicant conduct a study to evaluate the clinical safety of the new progesterone vaginal ring product, and (3) efficacy in the subgroup of women 35-42 years of age. The Agency reiterated its recommendation that the Applicant conduct a clinical trial to

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

evaluate efficacy in the older women subgroup or to revise the labeling with a limitation of use along with a postmarketing commitment (PMC) to conduct the needed clinical trial.[4]

- 10/29/2019: Ferring submitted a Class 2 Resubmission to address the deficiencies identified in the second CRL dated 11/23/2016.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

Infertility, as defined by the World Health Organization, is the failure to become pregnant despite regular unprotected sexual intercourse for one year or more.[5] It can cause considerable social distress and is accompanied by numerous psychological and social problems such as depression, anxiety, social isolation, and sexual dysfunction impacting negatively on the quality of life, particularly in the female.[6] Infertility can be due to male factors, female factors, or factors contributed by both partners. Identifiable male factors include hypogonadism, post-testicular defects, and seminiferous tubule dysfunction. Diagnosable female factors include ovulatory dysfunction, tubal damage, endometriosis, and cervical factor. In some cases, infertility is due to coital problems or is unexplained.[7] Infertility affects approximately 10-15% of couples.[8] Of the approximately 61 million women in United States (US) aged 15–44 years in 2011–2015, more than 7 million, or 12%, had received any infertility services, and almost 7% of married women in this age group were unable to get pregnant after at least 12 consecutive months of trying to conceive.[9]

Based on the Centers for Disease Control's (CDC) 2017 Fertility Clinic Success Rates Report, there were 284,385 ART cycles performed at 448 reporting clinics in the US during 2017, resulting in 68,908 live births (deliveries of one or more living infants) and 78,052 live born infants.[8c] Although the use of ART is still relatively rare as compared to the potential demand, its use has doubled over the past decade. Today, approximately 1.7% of all infants born in the US every year are conceived using ART.[9] In 2016, the average age of women using ART service was 36 years of age. Women, aged 35-42 years, comprise 50% (21.5% in 35-37 years of age, 19.1% in 38-40 years of age, and 9.6% in 41-42 years of age) of women undergoing ART treatment. Women greater than 42 years of age comprise 11.5% (6% in 43-44 years of age and 5.5% in women greater than 44 years of age).[10d]

[c] 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.*

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

The normal menstrual cycle can be divided into two phases: follicular and luteal. The follicular phase results in estrogen-stimulated endometrial proliferation, whereas the luteal phase produces progesterone, which inhibits endometrial proliferation and determines endometrial receptivity. Treatments that encompass ART include invitro fertilization (IVF), intracytoplasmic sperm injection (ICSI), and frozen embryo transfer (FET) which results in a luteal phase deficiency.[11] Progesterone supplementation after ART treatment induces secretory transformation of endometrial tissue, increasing endometrial receptivity for implantation of an embryo and helps maintain pregnancy when an embryo is implanted; and is therefore essential for embryo implantation.[12] During controlled ovarian stimulation (COS) for IVF and ICSI cycles, administration of gonadotropin-releasing hormone (GnRH) agonists and antagonists compromise the production of progesterone by the corpus luteum.[13] Additionally, the oocyte retrieval process destroys the corpus luteum. Thus, administration of exogenous progesterone for luteal support is standard of care for IVF and ICSI cycles. Progesterone supplementation is also standard of care in embryo recipients [ovum donation, embryo adoption, gestational surrogacy, or frozen embryo transfers (FETs).[14] Progesterone is administered to initially align embryo recipient cycles with the stage of the embryos and to ultimately support embryo implantation until adequate production of progesterone by the placenta at approximately ten weeks of gestation.

Various formulations of progesterone are used for luteal support and can be administered orally, vaginally, or by intramuscular (IM) injections. However, because of poor availability of progesterone administered orally, IM injections and vaginal administration of progesterone are the primary routes used in clinical practice with vaginal administration of progesterone providing for greater endometrial tissue concentration and lower serum levels and greater convenience.[14] The Applicant proposes Milprosa as an alternative vaginal formulation of progesterone supplementation with greater convenience, less mess, and less frequent dosing than other available progesterone vaginal supplements.[15] The following table describes both approved and non-approved progesterone products for support of the luteal phase in women who had undergone ART.

Table 1: Available Progesterone Products Used to Support the Luteal Phase in Women who Have Undergone ART[e]

Products approved for support of the luteal phase, Implantation and early pregnancy					
Drug Name	**Active Ingredient**	**Strength**	**Dosage (Form/Route)**	**Company**	**Date of Approval**
Endometrin® NDA 22057	Micronized Progesterone	100 mg	Twice or Three Times Daily as a Vaginal Insert	Ferring Pharmaceuticals, Inc.	6/21/2007
Crinone® 8%	Micronized Progesterone	90 mg	Once Daily as a Vaginal Gel	Allergan Sales, LLC	5/13/1977
Un-approved products for support of the luteal phase, implantation and early pregnancy					
Progesterone NDA 017362 (off-label use)	Progesterone in oil	50 mg	Once Daily Intramuscular (IM)	Watson Labs	5/11/1978
Prometrium® NDA 019781 NDA 020843 (off-label use)	Oral Micronized Progesterone	200 mg	Three Times Daily as a Vaginal Tablet	Vitrus Pharmaceuticals	5/14/1985

4 Benefit Assessment

The Applicant did not submit additional efficacy studies in the February 2016 and October 2019 NDA resubmissions. The Applicant did submit biocompatibility and clinical safety bridge studies between the legacy progesterone vaginal ring (PVR) used in the phase 3 clinical studies and the to-be-marketed product due to changes to the (b) (4) process conditions.[16] The following summarizes the efficacy results from the original application in 2010.[17]

The primary efficacy and safety information for Milprosa is derived from the US Study DR-PGN-302 (NCT03565211), a randomized, investigator (single) blind, active controlled, multicenter study. The Applicant submitted this study with the intent to evaluate the clinical pregnancy rate using progesterone supplementation with Milprosa also known as DR-2011 (progesterone vaginal ring) compared to a progesterone product, approved for luteal support, Crinone® 8% (progesterone vaginal gel, 90 mg/day) at two time points following embryo transfer:

- 6 weeks post-embryo transfer (8 weeks of pregnancy) and
- 10 weeks post-embryo transfer (12 weeks of pregnancy)

Efficacy was assessed by the co-primary endpoints of clinical pregnancy rate, defined as the presence of at least one fetal heartbeat seen on ultrasound at 6 weeks and 10 weeks post-embryo transfer

[e] This information is from the clinical review by Hearns-Stewart, R, DBRUP, dated February 25, 2016

(8 and 12 weeks of pregnancy). Secondary efficacy outcomes included evaluations of live birth rate, rate of spontaneous abortion, rate of biochemical pregnancy, and rate of ectopic pregnancy for each treatment group, and safety and tolerability.

The Agency and the Applicant prospectively agreed upon a non-inferiority (NI) margin defined as the lower bound of the two-sided 95% confidence interval (CI) or one-sided 97.5% CI of the difference of Milprosa versus Crinone® 8% of -10%. Treatment with the progesterone vaginal ring would be declared non-inferior to Crinone if the lower bound of the 95% CI for the difference in pregnancy rate was greater than -10% based on the modified intention to treat (MITT) population.

A total 1299 subjects were randomized into the study. Subjects ranged in age from 21.05 to 42.31 years (mean 31.64 years, median 31.81 years) for the Crinone group and 20.03 to 42.84 years (mean 31.70 years, median 31.71 years) for the DR-2011 group respectively. The majority of subjects in terms of race and ethnicity were primarily Caucasians (80%) followed by African-American (5%), Hispanic (5%), and Asians (5%). Subjects weight ranged from 94 to 261 lbs. (mean 152.2 lbs., median 145 lbs.) for the Crinone group and 97 to 264 lbs. (mean 154.5 lbs., median 147 lbs.) for the DR-2011 group while the BMI for the respective groups ranged from: 15 to 38.2 (mean 25.7 kg/m2, median 24.4kg/m2) and 16 to 38 (mean 25.3 kg/m2, median 24.4 kg/m2). The clinical reviewer determined that the study population adequately represented the targeted population in the US and are fairly balanced and there were no differences in the duration and diagnosis of infertility between the two treatment groups.

Results of Study DR-PGN-302 for the indicated population showed non-inferiority of DR-2011 in comparison to Crinone, with a margin of -4.6% at 6 weeks post embryo transfer (8 weeks pregnancy) and -3.7% at 10 weeks post embryo transfer (12 weeks pregnancy), which is well within the prospectively agreed upon margin of -10%. This lower bound margin of the two-sided 95% CI was maintained for the whole study population (ages 18-42 years) at -4.6 (at 8 weeks of pregnancy) and -4.1% (at 12 weeks of pregnancy), respectively. However, Study DR-PGN-302 failed to show non-inferiority for the sub-group of women 35-42 years of age. These margins were -16.4 and -18.5% respectively. The primary endpoints results are summarized in Table 2.

Table 2: Clinical pregnancy rates per retrieval – MITT Cohort

	Weeks of Pregnancy	DR-2011 N=646		Crinone® N=651		DIFF (DR 2011-Crinone®)	95% C.I. for DIFF
		N	%	N	%		
Ages 18-34	8	558	275 (49.3%)	560	269 (48.0%)	1.2%	(-4.6%, 7.1%)
	12		269 (48.2%)		258 (46.1%)	2.1%	(-3.7%, 8.0%)
All Ages (18-42)	8	646	310 (48.0%)	651	307 (47.2%)	0.8%	(-4.6%, 6.3%)
	12		300 (46.4%)		294 (45.2%)	1.3%	(-4.1%, 6.7%)
Ages 35-42	8	88	35 (39.8%)	91	38 (41.8%)	-2.0%	(-16.4%, 12.4%)
	12		31 (35.2%)		36 (39.6%)	-4.3%	(-18.5%, 9.8%)

Source: NDA DR-PGN-302 Clinical Study Report, Table 17, p76

Secondary endpoint results for 18-34 years old in each of the treatment groups DR-2011 and Crinone, respectively, include:

(1) the evaluation of live birth rate per retrieval (47.0%, 44.5%)
(2) cycle cancellation rate (overall: 5.6%)

(3) rate of spontaneous abortion (4.8%, 8% 5.4%)
(4) rate of biochemical pregnancy (62.5%, 63.6%)
(5) rate of ectopic pregnancy (0.9%, 1.1%)

The clinical reviewer agreed with the Applicant's results and determined that the data showed similar rates between the two treatment groups and are consistent with reported background rates for adverse pregnancy outcomes for women undergoing ART.

5 Risk Assessment & Safe-Use Conditions

The following summarizes the safety evaluation for Milprosa from the original review cycle in 2010. The Applicant did not submit new safety information in the February 2016 and October 2019 Class 2 resubmissions.

The Applicant submitted results from Study DR-PGN-302 to support the safety of Milprosa also known as DR-2011. The safety analysis included a total of 647 subjects in the DR-2011 group and 650 subjects in the Crinone group.

There were no maternal deaths in either study group. There were two neonatal deaths, one in each treatment group. The total number of adverse events was 542, with 266 for DR-2011 and 276 for Crinone. Forty-four (44) or 6.8% subjects in the DR-2011 group versus 36 (5.5%) in the Crinone group discontinued the study due to adverse events (AEs).

The most commonly reported treatment-emergent adverse events (≥2% of all subjects [18-42 years]) with DR-2011 in Study DR-PGN-302 were as follows: headache (6.8%), vaginal discharge (4.0%), nausea (3.8%), breast tenderness (3.7%), post procedural discomfort (3.7%), abdominal distension (3.4%), abdominal pain (2.9%), pelvic pain (2.9%), and constipation (2.6%).

5.1 Serious Adverse Events

Most of the AEs leading to discontinuation were related to pregnancy loss (such as intrauterine death, missed abortion, blighted ovum, spontaneous abortion, ectopic pregnancy, and hyperemesis gravidarum) and therefore are classified as serious adverse events (SAEs). A total of 155 subjects (12.8% DR-2011 and 11.1% Crinone) in the safety cohort, reported SAEs with 89% related to pregnancy and 11% were not pregnancy related. Intrauterine death, missed abortion, and blighted ovum accounted for the majority of SAEs related to pregnancy for the Crinone group. Accounting for all the capture terms indicating early pregnancy loss, the rates for DR-2011 and Crinone are comparable and within the range of usual expectation for invitro fertilization trials (6.5% and 6.1%, respectively). Of the 18 SAEs that were unrelated to pregnancy, 11 (6.8%) were related to ovarian hyperstimulation syndrome (OHSS) [4 (2.5%) of 83 subjects with SAEs in the DR-2011 treatment group and 7 (4.3%) of 72 subjects with SAEs in the Crinone treatment group]. The Applicant provided tabulation of SAEs during the follow-up period (Maternal and Neonatal) by MedDRA system Organ Class and Preferred Term. See table 3 below.

Table 3: SAEs by MedDRA System Organ Class and Preferred Term

MedDRA System Organ Class and Preferred Term	DR-2011 (N=647) N	DR-2011 (N=647) %	Crinone® (N=650) N	Crinone® (N=650) %	Total (N=1297) N	Total (N=1297) %
ANY AE						
Total Disorders	91	14.06	79	12.15	170	13.11
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS						
Total Disorders	80	12.36	66	10.15	146	11.26
PREMATURE BABY	56	8.66	40	6.15	96	7.40
PREMATURE LABOUR	12	1.85	12	1.85	24	1.85
PRE-ECLAMPSIA	10	1.55	5	0.77	15	1.16
PREMATURE RUPTURE OF MEMBRANES	6	0.93	1	0.15	7	0.54
NEONATAL DISORDER	5	0.77	5	0.77	10	0.77
PREGNANCY INDUCED HYPERTENSION	5	0.77	1	0.15	6	0.46
ABORTION SPONTANEOUS	3	0.46	2	0.31	5	0.39
HELLP SYNDROME	3	0.46	1	0.15	4	0.31
OLIGOHYDRAMNIOS	3	0.46	0	0.00	3	0.23
CONGENITAL, FAMILIAL AND GENETIC DISORDERS						
Total Disorders	9	1.39	10	1.54	19	1.46
CONGENITAL ANOMALY IN OFFSPRING	5	0.77	8	1.23	13	1.00
FOETAL CHROMOSOME ABNORMALITY	2	0.31	1	0.15	3	0.23
KLINEFELTER'S SYNDROME	1	0.15	0	0.00	1	0.08
MULTIPLE CONGENITAL ABNORMALITIES	1	0.15	0	0.00	1	0.08
HOLOPROSENCEPHALY	0	0.00	1	0.15	1	0.08

Source: NDA DR-PGN-302 Clinical Study Report, Table 54, p112-3

The clinical reviewer concluded that the adverse events and serious adverse events (SAEs) were similar for both treatment groups (DR-2011 and Crinone), and no significant safety trends were noted for DR-2011. Treatment-related adverse events were generally similar between the groups and consistent with the known safety profile of progesterone. Rates of subject discontinuation due to an adverse event were similar between the treatment groups. Adverse events related to vaginal bleeding were also similar between the two groups. No subject discontinued because of vaginal bleeding, and no subject was switched to an alternative progesterone product because of a bleeding issue. There were no increased rates of cervical/vaginal abrasions or irritation associated with use of a vaginal ring compared with vaginal gel. Weekly PVR insertion appeared to be safe and well tolerated.

6 Expected Postmarket Use

The likely prescribers for Milprosa are infertility specialists who should be familiar with the risks associated with progesterone supplementation in women who had undergone ART. Milprosa is intended for home administration by the patient.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for Milprosa beyond routine pharmacovigilance and labeling. The Applicant agreed to include a limitation of use in labeling for women less than age 35 and to conduct a PMC to address the deficiencies in efficacy and safety data for this subpopulation.

8 Discussion of Need for a REMS

The clinical reviewer recommends approval of Milprosa on the basis of the efficacy and safety information currently available with a limitation of use in women less than 35 years old and a PMC to study the effectiveness and safety in women 35 to 42 years old.

Infertility affects 10-15% of the couples and in the US approximately 1.7% of all infants born every year are conceived using ART. Progesterone supplementation is a standard of care for women who had undergone ART treatment and is essential to increase endometrial receptivity and to maintain implantation of embryo.

The pivotal study, DR-PGN-302, supports the efficacy and safety of Milprosa in women less than 35 years old showing non-inferiority in their primary endpoints of pregnancy at 8 and 12 weeks of pregnancy (6 weeks and 10 weeks after egg retrieval) with Milprosa vs. Crinone 8%, a progesterone vaginal gel product approved for luteal support in women who had undergone ART for infertility with non-inferiority CI margins of -4.6% at 8 weeks of pregnancy (6 weeks post embryo transfer) and -3.7% at 12 weeks pregnancy (10 weeks post embryo transfer). No significant safety signals and trends were detected in the Milprosa clinical development program and the adverse events are comparable to Crinone 8%. The most common adverse events were mostly related to pregnancy, such as headache, nausea, and abdominal distension and are consistent with known safety profile of progesterone. Post-procedural adverse events such as vaginal irritation and bleeding are comparable to Crinone 8%.

Due to underpowering of the study, there is insufficient data to support effectiveness and safety in women 35 years old or greater, the most likely group to be prescribed Milprosa for luteal support after undergoing ART for infertility.[18] The clinical reviewer noted in the original Milprosa review cycle that with Milprosa, the issue is not just one of efficacy (pregnancy) but safety as well, because failure to maintain the pregnancy, leading to spontaneous abortion (SAB) or miscarriage, is a safety issue and a woman's age is a significant predictor of SAB as there is a direct correlation of advanced age with miscarriage, especially in the 35 to 42 years age group.[5] In addition, there is concern for off-label use of

Milprosa in women age 35 years or older. Thus, a limitation of use in labeling and a PMC to evaluate the efficacy and safety in women 35-42 years old are necessary.

Given progesterone supplementation for luteal support is a standard of care for women who had undergone ART for infertility, prescribers of Milprosa will likely be familiar with the risks associated with progesterone supplementation. DRM is not recommending a REMS for Milprosa; the risks are comparable to currently available progesterone supplementation. As with other marketed progesterone products for luteal support, Milprosa will contain similar risks for cardiovascular and cerebral thromboembolic disorders and depression in labeling.

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable and a REMS is not necessary for Milprosa to ensure the benefits outweigh the risks. Labeling should be sufficient to communicate the limitation of use and known risks related to progesterone and adverse events related to the vaginal ring device. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Appendices

10.1 References

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