Clinical Policy Title:	progesterone
Policy Number:	RxA.367
Drug(s) Applied:	Crinone®, Endometrin®, Prometrium®
Original Policy Date:	03/06/2020
Last Review Date:	09/14/2021
Line of Business Policy Applies to:	All lines of business

Background

The following are progesterone products requiring prior authorization: progesterone (Crinone®), progesterone (Endometrin®), progesterone (Prometrium®).

Crinone® 4% is indicated for the treatment of secondary amenorrhea; Crinone® 8% is indicated:

- For progesterone supplementation or replacement as part of an Assisted Reproductive Technology (ART) treatment for infertile women with progesterone deficiency.
- For the treatment of secondary amenorrhea in women who have failed to respond to treatment with Crinone® 4%.

Endometrin® is indicated to support embryo implantation and early pregnancy by supplementation of corpus luteal function as part of an Assisted Reproductive Technology (ART) treatment program for infertile women.

Prometrium® is used for prevention of endometrial hyperplasia in non-hysterectomized, postmenopausal women who are receiving conjugated estrogens; treatment of secondary amenorrhea.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
progesterone (Crinone®)	Progesterone supplementation in ART	8% (90 mg) intravaginally once daily	90 mg/day
	Partial or complete ovarian failure requiring progesterone replacement in ART	8% (90 mg) intravaginally twice daily	180 mg/day
	Secondary amenorrhea	4% (45 mg) intravaginally every other day for up to a total of 6 doses If 4% fails, 8% intravaginally every other day for up to a total of 6 doses.	4%: 45 mg/day 8%: 90 mg/day

Drug Name	Indication	Dosing Regimen	Maximum Dose
	Prophylaxis of premature birth (Off- label indication)	8% (90 mg) intravaginally once daily Begin treatment prior to 24 weeks gestation	90 mg/day
progesterone (Endometrin®)	As supplementation in ART	100 mg intravaginally twice daily or three times daily	300 mg/day
	Prophylaxis of premature birth (Off- label indication)	200 mg intravaginally at bedtime Begin treatment prior to 24 weeks gestation	200 mg/day
progesterone (Prometrium®)	Prevention of endometrial hyperplasia in non-hysterectomized	200 mg orally once daily at bedtime for 12 days sequentially per 28-day cycle	200 mg/daily
	Secondary Amenorrhea	400 mg orally once daily at bedtime for 10 days	400mg/daily

Dosage Forms

- progesterone (Crinone®): Gel: 4% (45 mg of progesterone, 6 single-use applicators), 8% (90 mg of progesterone, in 15 single-use applicators)
- progesterone (Endometrin®): Vaginal insert: 100 mg (21 inserts and disposable applicators)
- progesterone (Prometrium®): Capsules: 100 mg, 200 mg

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria. The provision of provider samples does not guarantee coverage under the terms of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

I. Initial Approval Criteria

A. Assisted Reproductive Technology (ART) Treatment (must meet all)**:**

1. Member must have infertility coverage (optional pharmacy benefit);
2. Age ≥ 18 years;
3. Request is for Crinone® 8% or Endometrin®;
4. Prescribed for one of the following (a, b, or c):

a. ART treatment for infertile women with progesterone deficiency;
b. ART treatment in patients with partial or complete ovarian failure;
c. To support embryo implantation and early pregnancy (luteal phase support) by supplementation of corpus luteal function as part of an ART treatment program for infertile women;

5. Dose does not exceed 180 mg per day Crinone® or 300 mg per day Endometrin®.

Approval duration
Commercial: 12 months
Medicaid: 12 months

B. Secondary Amenorrhea (must meet all)**:**

1. Diagnosis of secondary amenorrhea;
2. Age ≥ 18 years;
3. Request is for Crinone® 4% or 8% or for Prometrium®;
4. Failure of a progestin product (e.g., medroxyprogesterone, norethindrone) unless contraindicated or clinically significant adverse effects are experienced;
5. Dose does not exceed 45 mg Crinone® 4% or 90 mg Crinone® 8% every other day for up to 6 doses or 400 mg per day for Prometrium®.

Approval duration
Commercial: 28 days
Medicaid: 28 days

C. Prevention of Preterm Birth (off-label) (must meet all)**:**

1. Prescribed for prevention of preterm birth;
2. Age ≥ 18 years;
3. Documentation of one of the following (a or b):
   a. Short cervix;
   b. Singleton pregnancy and a history of spontaneous preterm birth;
4. Dose does not exceed 180 mg per day Crinone® or 200 mg per day Endometrin®.

Approval duration
Commercial: 12 months
Medicaid: 12 months

D. Prevention of endometrial hyperplasia associated with conjugated estrogen replacement therapy (must meet all)**:**

1. Prescribed for the prevention of endometrial hyperplasia associated with conjugated estrogen replacement therapy
2. Age ≥18 years;
3. Postmenopausal with an intact uterus;
4. Request is for Prometrium®;
5. Dose does not exceed 200 mg per day Prometrium®.

Approval duration
Commercial: 28 days
Medicaid: 28 days

II. Continued Therapy Approval

A. All Indications in Section I (must meet all)**:**

1. Member is currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy;

2. Member is responding positively to therapy;
3. If request is for a dose increase, new dose does not exceed the FDA-approved maximum recommended dose for the relevant indication.

Approval duration

Commercial: 28 days (for secondary Amenorrhea and prevention of endometrial hyperplasia associated with conjugated estrogen replacement therapy); 12 months (for all other indication)

Medicaid: 28 days (for secondary Amenorrhea and prevention of endometrial hyperplasia associated with conjugated estrogen replacement therapy); 12 months (for all other indication)

III. Appendices

APPENDIX A: Abbreviations /Acronym Key

ACOG: American College of Obstetrics and Gynecologists
ART: Assisted Reproductive Technology
FDA: Food and Drug Administration

APPENDIX B: Therapeutic Alternatives

Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

Drug	Dosing Regimen	Dose Limit/ Maximum Dose
medroxyprogesterone (e.g., Provera®)	Secondary amenorrhea: 5 to 10 mg orally once daily for 5 to 10 days	10 mg/day x 10 days
norethindrone acetate (Aygestin®)	Secondary amenorrhea: 2.5 to 10 mg orally once daily for 5 to 10 days	10 mg/day x 10 days

Therapeutic alternatives are listed as generic (Brand name®) when the drug is available by both generic and brand; Brand name® when the drug is available by brand only and generic name when the drug is available by generic only.

APPENDIX C: Contraindications/Boxed Warnings

- Contraindication(s):
  - Crinone® and Endometrin® and Prometrium®: Known sensitivity to progesterone or any other ingredients in Crinone® or Endometrin® or Prometrium®; missed abortion or ectopic pregnancy; liver dysfunction or disease; known or suspected malignancy of the breast or genital organs; active thrombophlebitis or thromboembolic disorders, or a history of hormone-associated thrombophlebitis or thromboembolic disorders.
  - Crinone® and Prometrium®: Undiagnosed vaginal bleeding.
  - Prometrium® only: Prometrium® Capsules should not be used in patients with known hypersensitivity to its ingredients. Prometrium® capsules contain peanut oil and should never be used by patients allergic to peanuts.
- Boxed warning(s):
  - Prometrium®: Cardiovascular Disorders, Breast Cancer & Probable Dementia for Estrogen plus Progestin Therapy.

APPENDIX D: General Information

- Micromedex recommendation IIa for the use of progesterone as prophylaxis for premature birth of new born in women with short cervix. Studies cited used the following progesterone products: progesterone 90 mg vaginal gel once daily in women who had a singleton pregnancy and short cervix (with or without a history of early preterm delivery); or micronized progesterone 200 mg intravaginally at bedtime. In the micronized progesterone group women with a cervical length of 15 mm or less, with singleton or twin pregnancies, without regard to past early preterm delivery, were randomized to receive either placebo (n=125) or micronized progesterone 200 mg intravaginally at bedtime (n=125). Women with a history of ruptured membranes or cervical cerclage were excluded.
- In clinical trials, less than 25 mm is the length most frequently used to define short cervix measured mid-pregnancy (prior to 24 weeks gestation). American College of Obstetrics and Gynecologists (ACOG) recommends vaginal progesterone supplementation if cervical length is 20 mm or less before or at 24 weeks of gestation in women with singleton gestation and no prior spontaneous preterm birth.
- According to ACOG, current evidence does not support the routine use of progesterone in women with multiple gestations.
- The dosage increase from the Crinone® 4% gel can only be accomplished by using the 8% gel. Increasing the volume of gel administered does not increase the amount of progesterone absorbed.

References

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Review/Revision History	Review/Revised Date	P&T Approval Date
Policy established	01/2020	03/06/2020
Policy was reviewed. 1. Clinical policy table was updated 2. Added alternative authorized brand (Prometrium®) 3. Added Prometrium initial and continued therapy approval criteria for prevention of endometrial hyperplasia associated with conjugated estrogen replacement therapy 4. Initial Therapy and Continued Therapy Approval duration separated for Commercial & Medicaid 5. Continued Therapy criteria II.A.1 was rephrased to "Currently receiving medication that has been authorized by RxAdvance..." 6. Reference reviewed and updated.	07/30/2020	09/14/2020
Policy was reviewed. 1. Statement about provider sample ‘‘The provision of provider samples does not guarantee coverage…” was added to Clinical Policy. 2. Continued Approval Therapy Criteria II.A.1 was rephrased to “Member is currently receiving medication that has been authorized by RxAdvance…” 3. Therapeutic Alternatives verbiage was rephrased to "Below are suggested therapeutic alternatives based on clinical guidance..". 4. Statement about drug listing format in Appendix B is rephrased to "Therapeutic alternatives are listed as generic (Brand name®) when the drug is available by both generic and brand; Brand name® when the drug is available by brand only and generic name when the drug is available by generic only". 5. Appendix C was updated to include Boxed Warning for Prometrium®, “Prometrium®: Cardiovascular Disorders, Breast Cancer & Probable	5/31/2021	9/14/2021

Dementia…” 6. References were reviewed and updated.		