

<b>Clinical Policy Title:</b>	progesterone
<b>Policy Number:</b>	RxA.367
<b>Drug(s) Applied:</b>	Crinone®, Endometrin®, Prometrium
<b>Original Policy Date:</b>	03/06/2020
<b>Last Review Date:</b>	09/14/2020
<b>Line of Business Policy Applies to:</b>	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 nonhysterectomized, 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) PV once daily	90 mg/day
	Partial or complete ovarian failure requiring progesterone replacement in ART	8% (90 mg) PV BID	180 mg/day
	Secondary amenorrhea	4% (45 mg) PV QOD up to a total of 6 doses  If 4% fails, 8% PV QOD up to a total of 6 doses.	4%: 45 mg/day 8%: 90 mg/day

This clinical policy has been developed to authorize, modify, or determine coverage for individuals with similar conditions. Specific care and treatment may vary depending on individual need and benefits covered by the plan. This policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. This document may contain prescription brand name drugs that are trademarks of pharmaceutical manufacturers that are not affiliated with RxAdvance.

	Prophylaxis of premature birth	90 mg vaginally once daily  Begin treatment prior to 24 weeks gestation	90 mg/day
Progesterone (Endometrin®)	As supplementation in ART	100 mg PV BID or TID	300 mg/day
	Prophylaxis of premature birth	200 mg vaginally at bedtime  Begin treatment prior to 24 weeks gestation	200 mg/day
Progesterone (Prometrium®)	Prevention of endometrial hyperplasia in nonhysterectomized	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.

#### 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  $\geq 18$  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  $\geq 18$  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  $\geq 18$  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. 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

*This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.*

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

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

#### 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): none reported

#### APPENDIX D: General Information

- Micromedex recommendation IIa for the use of progesterone as prophylaxis for premature birth of newborn 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	07/30/2020	09/14/2020

<ol style="list-style-type: none"><li>2. Added alternative authorized brand (Prometrium®)</li><li>3. Added Prometrium initial and continued therapy approval criteria for prevention of endometrial hyperplasia associated with conjugated estrogen replacement therapy</li><li>4. Initial Therapy and Continued Therapy Approval duration separated for Commercial &amp; Medicaid</li><li>5. Continued Therapy criteria II.A.1 was rephrased to "Currently receiving medication that has been authorized by RxAdvance..."</li><li>6. Reference reviewed and updated.</li></ol>		
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