Clinical Policy: Progesterone (Crinone, Endometrin, Milprosa)

Reference Number: CP.PMN.243
Effective Date: 09.01.20
Last Review Date: 08.22
Line of Business: Commercial*, HIM*, Medicaid* Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

The following are progesterone products requiring prior authorization: progesterone gel (Crinone® 4%, Crinone® 8%), progesterone vaginal insert (Endometrin®), and progesterone vaginal system (Milprosa™).

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*Sections I.A., I.B., II.A., II.B. Infertility/Fertility Preservation Treatment
All lines of business: pharmacy benefit coverage is required.
HIM line of business - pharmacy benefit coverage restrictions by state:
States without pharmacy benefit restriction: AR, FL, IL, IN, KS, NC, NV, SC, TN, WA
(Policy may be used for formulary and non-formulary drugs.)
States with pharmacy benefit restriction: AZ, GA, MO, MS, NH, OH, PA, TX
(Policy may be used for formulary drugs only; non-formulary drugs are a pharmacy benefit exclusion.)

FDA Approved Indication(s)

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 ART treatment program for infertile women.

Milprosa is indicated to support 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.

- Limitation of use: Efficacy in women 35 years of age and older has not been established.

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Crinone, Endometrin, and Milprosa are **medically necessary** when the following criteria are met:

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%, Endometrin, or Milprosa;
4. Prescribed as supplementation or replacement of progesterone as part of ART treatment for infertile women;
5. Request meets one of the following (a, b, or c):
   a. Crinone 8%: Dose does not exceed 180 mg per day for up to 12 weeks;
   b. Endometrin: Dose does not exceed 300 mg per day for up to 10 weeks;
   c. Milprosa: Dose does not exceed one vaginal system per week for up to 10 weeks.

Approval duration: 6 months

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

1. Diagnosis of secondary amenorrhea;
2. Age ≥ 18 years;
3. Request is for Crinone 4% or 8%;
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.

Approval duration: 4 weeks

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

1. Prescribed for prevention of preterm birth;
2. Age ≥ 18 years;
3. Request is for Crinone 8% or Endometrin;
4. Gestational age is ≥ 16 weeks;
5. The requested agent is not prescribed concurrently with Makena®;
6. Documentation of one of the following (a or b):
   a. Short cervix;
   b. Singleton pregnancy and history of spontaneous preterm birth;
7. Dose does not exceed 90 mg per day Crinone 8% or 200 mg per day Endometrin.

Approval duration: 6 months

D. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business:

CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or

2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

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

1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*
2. Member is responding positively to therapy;
3. Member meets one of the following (a, b, or c):
   a. If request is for ART treatment, both (i and ii):
      i. Member must have infertility coverage (optional pharmacy benefit);
      ii. Member has not yet received more than 12 weeks of therapy (Crinone 8%) or 10 weeks of therapy (Endometrin and Milprosa);
   b. If request is for secondary amenorrhea, member has not yet received 6 doses of Crinone 4% or 8%;
   c. If request is for prevention of preterm birth, week 37 (through 36 weeks, 6 days) of gestation or delivery has not yet been reached;
4. If request is for a dose increase, request meets one of the following (a, b, or c):
   a. ART treatment (i, ii, or iii):
      i. Crinone 8%: New dose does not exceed 180 mg per day for up to 12 weeks;
      ii. Endometrin: New dose does not exceed 300 mg per day for up to 10 weeks;
      iii. Milprosa: New dose does not exceed one vaginal system per week for up to 10 weeks;
   b. Secondary amenorrhea: New dose does not exceed 45 mg Crinone 4% or 90 mg Crinone 8% every other day for up to 6 doses;
   c. Prevention of preterm birth: New dose does not exceed 90 mg per day Crinone 8% or 200 mg per day Endometrin.

Approval duration:
Secondary amenorrhea: 4 weeks total
ART treatment: 6 months total
Prevention of preterm birth: 6 months total

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):

a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or

2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviations

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 QD for 5 to 10 days	10 mg/day x 10 days
norethindrone acetate (Aygestin®)	Secondary amenorrhea: 2.5 to 10 mg PO QD for 5 to10 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, Endometrin, Milprosa:
    - Known sensitivity to progesterone or any other ingredients in Crinone, Endometrin, or Milprosa.
    - Active thrombophlebitis or thromboembolic disorders, or a history of hormone-associated thrombophlebitis or thromboembolic disorders.

        - Known of suspected malignancy of the breast
    - Crinone, Endometrin
        - Missed abortion or ectopic pregnancy
        - Liver dysfunction or disease
        - Known or suspected malignancy of the genital organs
    - Crinone, Milprosa:
        - Undiagnosed vaginal bleeding
    - Milprosa
        - Severe hepatic impairment or disease
- 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.

V. Dosage and Administration

Drug Name	Indication	Dosing Regimen	Maximum Dose
Progesterone gel (Crinone 4% and Crinone 8%)	Progesterone supplementation in ART	8% (90 mg) vaginally QD	90 mg/day
	Partial or complete ovarian failure requiring progesterone replacement in ART	8% (90 mg) vaginally BID	180 mg/day
	Secondary amenorrhea	4% (45 mg) vaginally QOD up to a total of 6 doses	4%: 45 mg/day 8%: 90 mg/day

Drug Name	Indication	Dosing Regimen	Maximum Dose
		If 4% fails, 8% (90 mg) vaginally QOD up to a total of 6 doses.	
	Prophylaxis of premature birth (off-label)	90 mg vaginally QD Starting 16 to 24 weeks gestation and continuing through 34 weeks gestation; some studies extend through week 36 (Clinical Pharmacology, ACOG)	90 mg/day
Progesterone vaginal insert (Endometrin)	Progesterone supplementation in ART	100 mg vaginally BID or TID	300 mg/day
	Prophylaxis of premature birth (off-label)	200 mg vaginally at bedtime Starting 16 to 24 weeks gestation and continuing through 34 weeks gestation; some studies extend through week 36 (Clinical Pharmacology, ACOG)	200 mg/day
Progesterone vaginal system (Milprosa)	Progesterone supplementation in ART	One vaginal system inserted vaginally initially on the day after oocyte retrieval and then replaced weekly, continuing for up to 10 weeks total duration.	11 mg/day

VI. Product Availability

Drug Name	Availability
Progesterone gel (Crinone 4% and Crinone 8%)	Gel: 4% (45 mg of progesterone, 6 single-use applicators) Gel: 8% (90 mg of progesterone, 15 single-use applicators)
Progesterone vaginal insert (Endometrin)	Vaginal insert: 100 mg (21 inserts and disposable applicators)
Progesterone vaginal system (Milprosa)	Vaginal system: silicone ring containing 1.78 grams of progesterone and releases an average of 11 mg/day of progesterone over a 7-day period of use.

VII. References

1. Crinone Prescribing Information. Irvine, CA: Allergan USA; June 2017. Available at: https://www.allergan.com/assets/pdf/crinone_pi. Accessed April 14, 2022.
2. Endometrin Prescribing Information. Parsippany, NJ: Ferring Pharmaceuticals Inc.; January 2018. Available at: https://www.ferringfertility.com/products/endometrin/. Accessed April 14, 2022.
3. Milprosa Prescribing Information. Parsippany, NJ: Ferring Pharmaceuticals, Inc.; April 2020. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/201110s000lbl.pdf. Accessed April 14, 2022.
4. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed April 14, 2022.
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7. Fonseca EB, Celik E, Parra M, et al. Progesterone and the Risk of Preterm Birth among Women with a Short Cervix. NEJM. 2007;357:462-469.
8. DeFranco E, Obrien JM, Adair CD et al. Vaginal progesterone is associated with a decrease in risk for early preterm birth and improved neonatal outcome in women with a short cervix: a secondary analysis from a randomized, double-blind, placebo-controlled trial. Ultrasound Obstet Gynecol. 2007;30:697-705.
9. daFonseca EB, Bittar RE, Carvalho MHB et al. Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: A randomized placebo-controlled double-blind study. Am J Obstet Gynecol 2003;188:419-424.
10. Norwitz E, Phaneuf L, Caughey Progesterone Supplementation and the Prevention of Preterm Birth. Obstetrics and Gynecology. 2011; 4(2): 60-72.
11. Practice bulletin no. 130: prediction and prevention of preterm birth. Committee on Practice Bulletins – Obstetrics. The American College of Obstetricians and Gynecologists. Obstet Gynecol. 2012; 120 (4): 964-73. Reaffirmed 2018.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created: adopted from CP.CPA.03 (retired); HIM and Medicaid lines of business added; new progesterone vaginal ring formulation (Milprosa) added; ART indications collapsed from three to one for clarity; ART total doses per FDA label added and approval duration shortened from 12 to 6 months; infertility/fertility preservation benefit exclusion added for HIM line of business except for HIM Illinois; infertility/fertility preservation pharmacy benefit requirement added for all lines of business; for preterm birth, request for Crinone 8% or Endometrin, not prescribed concurrently with Makena, and at least 16 weeks gestational age added, Crinone dosing changed from 180 to 90 mg per ACOG/compendia, approval duration	05.12.20	08.20

Reviews, Revisions, and Approvals	Date	P&T Approval Date
shortened from 12 to 6 months and "to delivery or through week 36" added to continuation criteria per ACOG; references reviewed and updated.		
Ad hoc "Milrone" typo corrected to Milprosa.	11.13.20	
3Q 2021 annual review: no significant changes; updated reference for HIM off-label use to HIM.PA.154 (replaces HIM.PHAR.21); references reviewed and updated.	03.23.21	08.21
3Q 2022 annual review: no significant changes; references reviewed and updated.	04.14.22	08.22
Template changes applied to other diagnoses/indications and continued therapy section.	10.06.22	

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise

professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.