Clinical Policy: Progesterone (Crinone, Endometrin)

Reference Number: CP.CPA.03
Effective Date: 11.16.16
Last Review Date: 08.19
Line of Business: Commercial

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 (Crinone®), progesterone (Endometrin®).

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 Assisted Reproductive Technology (ART) treatment program for infertile women.

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 and Endometrin 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% 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: 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%;
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. 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: 12 months

D. Other diagnoses/indications
1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial.

II. Continued Therapy

A. All Indications in Section I (must meet all)**:**
1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
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:
Secondary amenorrhea: 4 weeks
All other indications: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.
   Approval duration: Duration of request or 12 months (whichever is less); or
2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial.

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 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 and Endometrin: Known sensitivity to progesterone or any other ingredients in Crinone or Endometrin; 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 only: Undiagnosed vaginal bleeding
- 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 (Crinone)	Progesterone supplementation in ART	8% (90 mg) PV QD	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
	Prophylaxis of premature birth	90 mg vaginally QD 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

VI. Product Availability

Drug Name	Availability
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)

VII. References

1. Crinone Prescribing Information. Irvine, CA: Allergan USA; June 2017. Available at: https://www.allergan.com/assets/pdf/crinone_pi. Accessed May 8, 2019.
2. Endometrin Prescribing Information. Parsippany, NJ: Ferring Pharmaceuticals Inc.; January 2018. Available at: https://www.ferringfertility.com/products/endometrin/. Accessed May 8, 2019.
3. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed May 8, 2019.
4. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2018. Available at: http://www.clinicalpharmacology-ip.com/. Accessed May 8, 2019.
5. Hassan SS, Romero R, Vidyadhari D, et al. Vaginal progesterone reduces the rate of preterm birth in women with a sonographic short cervix: a multicenter, randomized, double-blind, placebo controlled trial. Ultrasound in Obstet Gynecol. 2011;38:18-31.
6. 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.
7. 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.
8. 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.
9. Norwitz E, Phaneuf L, Caughey Progesterone Supplementation and the Prevention of Preterm Birth. Obstetrics and Gynecology. 2011; 4(2): 60-72.
10. 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
Converted to new template; clarified use in ART for women with partial or complete ovarian failure per AHFS Drug Info.	01.31.17	08.17
3Q 2018 annual review: no significant changes; added age restriction and dosing limits; references reviewed and updated.	05.08.18	08.18
No significant changes: modified approval duration from length of benefit to 4 weeks for secondary amenorrhea, 12 weeks for all other indications.	10.03.18	

Reviews, Revisions, and Approvals	Date	P&T Approval Date
3Q 2019 annual review: no significant changes; combined luteal phase support criteria set with ART criteria set which already includes use for support of embryo implantation; references reviewed and updated.	05.08.19	08.19

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.

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