Clinical Policy: Progesterone (Crinone, Endometrin)

Reference Number: CP.PMN.243
Effective Date: 09.01.20
Last Review Date: 08.24
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%) and progesterone vaginal insert (Endometrin®).

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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:

- ***AR**: In vitro fertilization are convered when: 1) The patient is the policyholder or the spouse of the policyholder and a covered dependent member under the policy, and the member's oocytes are fertilized with the sperm of the patient's spouse, and the patient and the patient's spouse have a history of unexplained infertility of at least two years' duration; OR 2) The infertility is associated with one or more of the following medical conditions: endometriosis; exposure in utero to diethylstilbestrol, commonly known as DES; Blockage of or removal of one or both fallopian tubes (lateral or bilateral salpingectomy) not a result of voluntary sterilization; or abnormal male factors contributing to the infertility.*
- ***CA**: Fertility Preservation – covers medically necessary services and supplies for established fertility preservation treatments in connection with iatrogenic Infertility; Infertility - with the exception of covered fertility preservation services, services or supplies that are intended to impregnate a woman are not covered. Excluded procedures include, but are not limited to:*
  - *Conception by medical procedures, such as artificial insemination, in-vitro fertilization (IVF), gamete intrafallopian transfer (GIFT), zygote intrafallopian transfer (ZIFT), or any process that involves harvesting, transplanting or manipulating a human ovum. Also not covered are services and supplies (including injections and injectable medications) which prepare the covered person to receive these services;*
  - *Services and supplies for the purpose of diagnosing the cause of infertility.*
- ***IL:** Fertility Preservation Services – Coverage for medically necessary expenses for standard fertility preservation services when a necessary medical treatment may directly or indirectly cause iatrogenic infertility to a member; Infertility Expense Benefits – Infertility coverage for the diagnosis and treatment of infertility including, but not limited to, in vitro fertilization, uterine embryo lavage, embryo transfer, artificial insemination, gamete intrafallopian tube transfer, zygote intrafallopian tube transfer, low tubal ovum transfer, oocyte retrieval and intracytoplasmic sperm injection, to the extent the treatment is legal under applicable law.*
- ***LA**: Fertility Preservation – Medically necessary fertility preservation services for enrollees when a medical treatment will directly or indirectly result in "iatrogenic infertility," which is an impairment of fertility by surgery, radiation, chemotherapy, or other medical treatment affecting reproductive organs or processes. Cost-sharing such as deductibles, copayments, and coinsurance may be imposed on fertility preservation services if the cost-sharing is consistent with other benefits in the contract and place of service. Services include the collecting, freezing, preserving of ova or sperm, and other standard services that are not experimental or investigational. Coverage includes up to three (3) years of storage costs associated with oocytes and sperm during the enrollee's membership. Infertility – Covered services under this benefit are provided for medically necessary diagnostic and exploratory procedures to determine infertility and surgical procedures to correct a medically diagnosed disease or condition of the reproductive organs including, but not limited to, treatment of the following: 1. Endometriosis; 2. Collapsed/clogged fallopian tubes; or 3. Testicular failure.*

- ***NV:*** *Limited diagnostic and therapeutic infertility services determined to be medically necessary and requires prior authorization. Covered services do not include those services specifically excluded herein, but do include limited: a. Laboratory studies; b. Diagnostic procedures; and c. Artificial insemination services, up to six (6) cycles per member per lifetime.*
- ***NJ****: Subject to pre-approval, covered charges include: artificial insemination; and standard dosages, lengths of treatment and cycles of therapy of prescription drugs used to stimulate ovulation for artificial insemination or for unassisted conception*
- ***NC****: Limited to diagnostic testing to find the cause of infertility, such as diagnostic laparoscopy, endometrial biopsy and semen analysis. Treatment of the underlying medical conditions that cause infertility (such as endometriosis, obstructed fallopian tubes and hormone deficiency)are considered a separate benefit. Treatment for infertility is limited to a lifetime benefit maximum, per member, of three medical ovulation induction cycles.*
- ***All other states****: No benefits will be paid under this benefit provision for services provided or expenses incurred for infertility drugs, unless otherwise listed on the formulary.*

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.

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 as supplementation or replacement of progesterone as part of ART treatment for infertile women;
5. Dose does not exceed one of the following (a or b):
   a. Crinone 8%: 180 mg per day for up to 12 weeks;
   b. Endometrin: 300 mg per day 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 one of the following (a or b):
   a. Crinone 4%: 45 mg every other day for up to 6 doses;
   b. Crinone 8%: 90 mg 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. Member has a short cervix as defined as a cervical length ≤ 25 mm;
7. Dose does not exceed one of the following (a or b):
   a. Crinone 8%: 90 mg per day;
   b. Endometrin: 200 mg perday.

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);
   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, new dose does not exceed any of the following (a, b, or c):
   a. ART treatment (i or ii):
      i. Crinone 8%: 180 mg per day for up to 12 weeks;
      ii. Endometrin: 300 mg per day for up to 10 weeks;
   b. Secondary amenorrhea (i or ii):
      i. Crinone 4%: 45 mg every other day for up to 6 doses;
      ii. Crinone 8%: 90 mg every other day for up to 6 doses;
   c. Prevention of preterm birth (i or ii):
      i. Crinone 8%: 90 mg per day;
      ii. Endometrin: 200 mg per day.

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:
    - Known sensitivity to progesterone or any other ingredients in Crinone or Endometrin
    - Active thrombophlebitis or thromboembolic disorders, or a history of hormone-associated thrombophlebitis or thromboembolic disorders
    - Known of suspected malignancy of the breast
    - Missed abortion or ectopic pregnancy
    - Liver dysfunction or disease
    - Known or suspected malignancy of the genital organs
  - Crinone:
    - 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 25 mm or less.
- According to ACOG, current evidence does not support the routine use of progesterone in women with multiple gestations or singleton pregnancy and prior spontaneous preterm birth.
- 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.
- On April 2023, ACOG released a practice advisory to serve as an update to Practice Bulletin No. 234 with the following recommendation: in the setting of a singleton pregnancy with a history of prior spontaneous preterm birth, and in the absence of a shortened cervix, vaginal progesterone should not be offered as a prevention option.

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 If 4% fails, 8% (90 mg) vaginally QOD up to a total of 6 doses.	4%: 45 mg/day 8%: 90 mg/day
	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

Drug Name	Indication	Dosing Regimen	Maximum Dose
	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

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)

VII. References

1. Crinone Prescribing Information. Irvine, CA: Allergan USA; June 2017. Available at: https://www.allergan.com/assets/pdf/crinone_pi. Accessed May 13, 2024.
2. Endometrin Prescribing Information. Parsippany, NJ: Ferring Pharmaceuticals Inc.; January 2018. Available at: https://www.ferringfertility.com/healthcare-professionals/product-information/. Accessed May 13, 2024.
3. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed May 23, 2024.
4. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2024. Available at: https://www.clinicalkey.com/pharmacology/. Accessed May 23, 2024.
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.
11. Practice bulletin no. 234: prediction and prevention of spontaneous preterm birth. Committee on Practice Bulletins – Obstetrics. The American College of Obstetricians and Gynecologists. Obstet Gynecol. 2021 August; 138 (2): e65-e90.
12. Simhan HN, Bryant A, Gandhi M, and Turrentine M. Updated clinical guidance for the use of progesterone supplementation for the prevention of recurrent preterm birth. The American College of Obstetricians and Gynecologists. Practice Advisory. April 2023. Available at: https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2023/04/updated-guidance-use-of-progesterone-supplementation-for-prevention-of-recurrent-preterm-birth. Accessed May 23, 2024.

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 shortened from 12 to 6 months and "to delivery or through week 36" added to continuation criteria per ACOG; references reviewed and updated.	05.12.20	08.20
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	
3Q 2023 annual review: for section I.C. removed "singleton pregnancy and history of spontaneous preterm birth" and added short cervix defined as a cervical length ≤ 25 mm per updated 2023 ACOG practice bulletin; references reviewed and updated.	04.11.23	08.23
3Q 2024 annual review: removed Milprosa from policy due to product discontinuation; evidence of coverage for infertility/fertility preservation language added for HIM line of business (AR, CA, Il,	05.13.24	08.24

Reviews, Revisions, and Approvals	Date	P&T Approval Date
LA, NV, NJ, NC, and all other states); references reviewed and updated.		

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.

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.