CRINONE® (progesterone) vaginal gel

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member’s specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as “Description” defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as “Criteria” defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms “experimental” and “investigational” are considered to be interchangeable.

BLUE CROSS®, BLUE SHIELD® and the Cross and Shield Symbols are registered service marks of the Blue Cross and Blue Shield Association, an association of independent Blue Cross and Blue Shield Plans. All other trademarks and service marks contained in this guideline are the property of their respective owners, which are not affiliated with BCBSAZ.

Description:

Crinone (progesterone) 4% vaginal gel is indicated for the treatment of secondary amenorrhea. Crinone (progesterone) 8% vaginal gel is indicated for use in a woman who failed to respond to treatment with 4% vaginal gel and it is also indicated for progesterone supplementation or replacement as part of an Assisted Reproductive Technology (ART) treatment for an infertile woman with progesterone deficiency. Crinone (progesterone) 8% vaginal gel has been used to support embryo implantation and maintain pregnancies through its use as part of ART treatment regimens.

Progesterone is a naturally occurring steroid secreted by the ovary, placenta, and adrenal gland. In the presence of adequate estrogen, progesterone transforms a proliferative endometrium into a secretory endometrium. It is essential for the development of decidual tissue, and the effect of progesterone on the differentiation of glandular epithelia and stroma has been extensively studied.
Progesterone is necessary to increase endometrial receptivity for implantation of an embryo. Once an embryo is implanted, progesterone acts to maintain the pregnancy. Normal or near-normal endometrial responses to oral estradiol and intramuscular progesterone have been noted in functionally agonalad women through the sixth decade of life. Progesterone administration decreases the circulatory levels of gonadotropins.

**Definitions:**

**Assisted Reproductive Technology:**
A cycle of ART may be any of the following: IVF (fresh embryos) transfer, IVF (frozen embryo) transfer, GIFT or ZIFT

IVF – in vitro fertilization

GIFT – gamete intrafallopian tube transfer, involves removing a woman’s eggs, mixing them with sperm, and immediately placing them into fallopian tube

ZIFT – zygote intrafallopian tube transfer, involves removing a woman’s eggs, mixing them with sperm, and then on the day after they become fertilized they are placed into fallopian tube

TET – tubal embryo transfer, involves transfer of zygote at a more advanced stage of development

**Drug related events:**

- Ineffective / failure
  Use of a drug employing optimal doses (FDA-recommended doses) for optimal duration; where the condition being treated has not improved or worsened

  A request for branded agent due to generic drug failure or ineffectiveness will be assessed for potential approval with documentation of use of optimal dose / duration of the generic product and meeting other criteria within the coverage guideline. When the drug in question is a combination product, there must be documentation of failure / ineffectiveness of concurrent use (each ingredient used at the same time) of individual generic components. When the drug in question is a low dose formulation, there must be documentation of failure / ineffectiveness of low dose generic formulation.

  **Adverse Drug Event:** Allergic reaction / Hypersensitivity / Intolerance
  Use of a drug produced a significant reaction where continued use of the drug places the individual at risk for either lack of improvement or worsening of the condition being treated or at risk for harm and the concern is documented in medical record. A significant adverse drug event is when an individual's outcome is death, life-threatening, hospitalization (initial or prolonged), disability resulting in a significant, persistent, or permanent change, impairment, damage or disruption in the individuals' body function/structure, physical activities or quality of life, or requires intervention to prevent permanent impairment or damage.

  *Allergic reaction / hypersensitivity* – may or may not involve the active ingredient. When the active ingredient is involved, use of same or a chemically similar agent places the individual at risk for harm when the same or chemically similar agent is used. The subsequent reaction may be the same as the
original reaction or a more exaggerated response may be seen, potentially placing the individual at even greater risk for harm.

If the reaction occurred from the active/main generic ingredient; request for branded agent with same active ingredient will not be considered unless it is proven (documented) that active ingredient did not cause reaction and the request meets other criteria within the coverage guideline

**Intolerance** – these events represent circumstance(s) where use of a drug produced a significant reaction and continued use may result in non-adherence to proposed therapy and this concern is documented in medical record

**Contraindication**
Use of a drug that is not recommended by the manufacturer or FDA labelling

Use of any drug in the face of a contraindication is outside of the FDA and manufacturer’s labelled recommendation and is considered investigational or experimental

**Non-adherence**
Individual does not follow prescribe regimen that places the individual at risk for lack of improvement or worsening of the condition being treated and this concern is documented in medical record

---

**Precertification:**

Precertification (Prior Authorization) is required for members with a Blue Cross Blue Shield of Arizona (BCBSAZ) pharmacy benefit for medication(s) or product(s) indicated in this guideline.

This Pharmacy Coverage Guideline does not apply to FEP or other states’ Blues Plans.

Information about medications that require precertification is available at [www.azblue.com/pharmacy](http://www.azblue.com/pharmacy).

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

---

**Criteria:**

See “Resources” section for FDA-approved dosage.

- Precertification for Crinone (progesterone) vaginal gel requires completion of the specific request form in its entirety. All requested data must be provided. Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacy precert@azblue.com. Incomplete forms will be returned.
CRINONE® (progesterone) vaginal gel (cont.)

- FDA-approved product labeling (indication, age, dosage, testing, contraindications, exclusions, etc.) of Crinone (progesterone) vaginal gel is considered **medically necessary** when **ALL** of the following criteria are met:

1. Individual is 18 years of age or older

2. Medical record documentation of a confirmed diagnosis of **ONE** of the following:
   - For Crinone 4%: Secondary amenorrhea
   - For Crinone 8%: **EITHER** of the following:
     - Woman who has failed to respond to treatment with Crinone 4% vaginal gel
     - Infertile woman with progesterone deficiency for progesterone supplementation or replacement as part of an Assisted Reproductive Technology (ART) for individuals whose benefit design includes ART as a covered benefit

3. Unable to use preferred products due to intolerance, failure, or contraindication:
   - For Crinone 4% in treating amenorrhea, unable to use **ALL** of the following:
     - Prometrium oral micronized capsules
     - Progesterone intramuscular injection
   - For Crinone 8% as part of ART who has failed Crinone 4%

4. **ALL** of the following baseline tests have been completed before initiation of treatment:
   - Recent physical examination that includes breast and pelvic exam
   - Recent or most current Papanicolaou smear

5. Absence of **ALL** of the following contraindications:
   - Known sensitivity to Crinone (progesterone or any of the other ingredients)
   - Undiagnosed vaginal bleeding
   - Liver dysfunction or disease
   - Known or suspected malignancy of the breast or genital organs
   - Missed abortion
   - Active thrombophlebitis or thromboembolic disorders, or a history of hormone-associated thrombophlebitis or thromboembolic disorders

6. Absence of **ALL** of the following exclusions:
   - Used to prevent miscarriage in a woman with a history of recurrent spontaneous pregnancy losses

- Crinone (progesterone) vaginal gel for all other indications not previously listed is considered **experimental or investigational** based upon:

1. Lack of final approval from the Food and Drug Administration, and
2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
3. Insufficient evidence to support improvement of the net health outcome, and
4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
5. Insufficient evidence to support improvement outside the investigational setting.
CRINONE® (progesterone) vaginal gel (cont.)

Resources:


FDA-approved indication and dosage:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommended Dose</th>
</tr>
</thead>
</table>
| Assisted Reproductive Technology| Assisted Reproductive Technology
Crinone 8% is indicated for progesterone supplementation or replacement as part of an Assisted Reproductive Technology ("ART") treatment for infertile women with progesterone deficiency. |
| Secondary Amenorrhea            | Secondary Amenorrhea
Crinone 4% is indicated for the treatment of secondary amenorrhea. Crinone 8% is indicated for use in women who have failed to respond to treatment with Crinone 4%. Crinone 8% is administered vaginally at a dose of 90 mg once daily in women who require progesterone supplementation. Crinone 8% is administered vaginally at a dose of 90 mg twice daily in women with partial or complete ovarian failure who require progesterone replacement. If pregnancy occurs, treatment may be continued until placental autonomy is achieved, up to 10 to 12 weeks. |

It is important to note that a dosage increase from the 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.