BlueCross BlueShield of Arizona
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PHARMACY COVERAGE GUIDELINES	**ORIGINAL EFFECTIVE DATE: 11/17/16**
SECTION: DRUGS	**LAST REVIEW DATE: 11/16/17**
	LAST CRITERIA REVISION DATE: 11/16/17
	ARCHIVE DATE:

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.

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.

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.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. 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 Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

CRINONE® (progesterone) vaginal gel (cont.)

Description:

Crinone (progesterone) 4% vaginal gel is indicated for the treatment of secondary amenorrhea. Crinone (progesterone) 8% vaginal gel is indicated for use in women with secondary ammenorrhea who failed to respond to treatment with 4% vaginal gel; 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 (the epithelial tissue of the endometrium), 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 agonadal women through the sixth decade of life. Progesterone administration decreases the circulatory levels of gonadotropins.

Secondary amenorrhea:

- Secondary amenorrhea is defined as the absence of menses for more than three months in girls or women who previously had regular menstrual cycles or six months in girls or women who previously had irregular menses

- Amenorrhea is often classified as either primary (absence of menarche by age 15 years) or secondary (absence of menses for more than three months in girls or women who previously had regular menstrual cycles or six months in girls or women who had irregular menses)

- Absence of menses can be a transient, intermittent, or permanent condition resulting from dysfunction of the hypothalamus, pituitary, ovaries, uterus, or vagina

- Missing a single menstrual period may not be important to assess, but amenorrhea lasting three months or more and oligomenorrhea (fewer than nine menstrual cycles per year or cycle length greater than 35 days) require investigation

- Pregnancy is the most common cause of secondary amenorrhea and should be excluded based on a sensitive pregnancy test (human chorionic gonadotropin [hCG])

- Systemic illness when it is severe enough to result in a decrease in hypothalamic GnRH secretion and/or when it is associated with nutritional deficiencies
    - Examples include type 1 diabetes mellitus and celiac disease

- The history, physical exam, and laboratory may provide clues about the possible cause of amenorrhea
    - After ruling out pregnancy, other helpful labs include follicle-stimulating hormone (FSH), serum prolactin, and thyroid-stimulating hormone (TSH) to test for primary ovarian insufficiency, hyperprolactinemia, and thyroid disease

CRINONE® (progesterone) vaginal gel (cont.)

- An assessment of estrogen status should be done in some cases to help with interpreting the FSH values and in others to help guide therapy such as hypoestrogenic patients need estrogen therapy for prevention of bone loss, while those making estrogen need endometrial protection with progesterone

- The overall goals of management include:
  - Correct and treat the underlying pathology, if possible
  - Helping the woman to achieve fertility, when desired
  - Preventing complications of the disease process (estrogen replacement to prevent osteoporosis)

Assisted Reproductive Technology (ART)

- ART a group of non-coital manipulations and processes that involve the in vitro handling of both human oocytes and sperm, or of embryos, with the objective of establishing a pregnancy

- Processes involved will depend on individual circumstance and may include:
  - Use of drugs to stimulate growth of multiple ovarian follicles
  - Use of drugs to suppress the natural menstrual cycle and down-regulate the pituitary gland
  - Monitoring to assess the growth of the follicles
  - Once follicles are an appropriate size, use drugs to bring about final maturation of the eggs (known as ovulation triggering)
  - Egg collection and, in some cases of male infertility, sperm retrieval
  - Fertilization (by in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI))
  - Endometrial preparation
  - Embryo placement into the uterus
  - Luteal phase support (several options are available including administration of progesterone, estrogen (E2), and human chorionic gonadotropin (hCG)
  - Management of ovarian hyperstimulation syndrome

- A cycle of ART may be any of the following:
  - Stimulate ovulation for coital reproduction
  - Stimulate ovulation for ART
  - IVF (fresh embryos or frozen embryo) transfer
  - GIFT– gamete intrafallopian tube transfer, involves removing a woman's eggs, mixing them with sperm, and immediately placing them into fallopian tube
  - ZIF – 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
  - Artificial insemination (AI)
  - Intravaginal insemination (IVI)
  - Intracervical insemination (ICI)
  - Intracytoplasmic sperm injection (ICSI)
  - Intrauterine insemination (IUI)
  - TET – tubal embryo transfer, involves transfer of zygote at a more advanced stage of development

- Endometrial receptivity plays a major role in the success or failure of embryo implantation after IVF
  - To optimize endometrial receptivity, it is common to administer a progesterone supplement during the luteal phase

- The optimum duration of supplementation has not been established
  - It is used to maintain pregnancy until placental autonomy (when the placenta produces progesterone) is achieved
- Intramuscular progesterone (progesterone in oil) and the various vaginal progesterone preparations (suppositories, tablets, gel, or ring) are equally effective
  - Intramuscular progesterone is more painful for the patient, but associated with less luteal phase bleeding than vaginal progesterone, and is commonly used

- Pregnancy is diagnosed by identification of rising serum hCG levels after transfer

- Implantation is thought to occur no earlier than seven days after retrieval; hCG levels may be detected one or two days later
  - However, late implantations can occur

Crinone (progesterone gel)

Medication class:
Progestin

FDA-approved indication(s):
- 4% vaginal is indicated for the treatment of secondary ammenorrhea
- 8% vaginal is indicated for progesterone supplementation as part of an Assisted Reproductive Technology (ART) treatment for infertile women with progesterone deficiency and is indicated for use in women who have failed to respond to treatment with Crinone 4%.

Recommended Dose:
- Secondary amenorrhea:
  - Crinone 4% is administered vaginally every other day up to a total of six doses
  - For women who fail to respond, a trial of Crinone 8% every other day up to a total of six doses may be instituted
- Assisted Reproductive Technology:
  - 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

Maximum dosage
- Not stated
  - But dosing in secondary amenorrhea is for total of six doses for each strength
  - Dosing in ART is until placental autonomy is achieved

Available Dosage Forms:
- 4% gel (45 mg) single use, disposable applicator, each contains 1.3 g gel and delivers 1.125 g of gel in a carton that contains 6 applicators

CRINONE® (progesterone) vaginal gel (cont.)

- 8% gel (90mg) single use, disposable applicator, each contains 1.3 g gel and delivers 1.125 g of gel in a carton that contains 15 applicators

Warnings and Precautions:

- Pretreatment exam should include examination of breasts and pelvis and should include a Papanicolaou smear
- The drug should be discontinued if any thrombotic disorder such as thrombophlebitis, cerebrovascular disorder, pulmonary embolism, and retinal thrombosis) is suspected
- The drug should be discontinued if depression occurs in a patient with a history of depression
- There is no adequate evidence that progesterone and progestins are effective when used to prevent miscarriage in a woman with a history of recurrent spontaneous pregnancy losses

Criteria:

- **Criteria for initial therapy:** Crinone (progesterone) vaginal gel is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Individual is 18 years of age or older

2. A confirmed diagnosis of **ONE** of the following:
   - For Crinone 4%: secondary amenorrhea
   - For Crinone 8%: **EITHER** of the following:
     - Woman with secondary amenorrhea
     - 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. Individual has failure, contraindication or intolerance to use preferred step therapy products:
   - Crinone 4% preferred step therapy products for treating secondary amenorrhea includes **ALL** of the following:
     - Prometrium oral micronized capsules
     - Progesterone intramuscular injection
   - Crinone 8% preferred step therapy products for treating secondary amenorrhea or as progesterone therapy as part of ART for individuals whose benefit design includes ART as a covered benefit includes **ALL** of the following:
     - Previous use of Crinone 4%
     - Prometrium oral micronized capsules
     - Progesterone intramuscular injection

4. There are **NO** contraindications:
   - Contraindications include:
     - 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

CRINONE® (progesterone) vaginal gel (cont.)

- Missed abortion
- Active thrombophlebitis or thromboembolic disorders, or a history of hormone-associated thrombophlebitis or thromboembolic disorders

Initial approval duration:
- 12 months when used for secondary amenorrhea
- 9 months when used as part of ART for individuals whose benefit design includes ART as a covered benefit

➢ **Criteria for continuation of coverage (renewal request):** Crinone (progesterone) vaginal gel is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Individual's secondary amenorrhea responded while on therapy
   - Response is defined as:
     - Normal menstrual periods
2. Individual has been adherent with the medication
3. Individual has not developed any contraindications or other significant level 4 adverse drug effects that may exclude continued use
   - Contraindications as listed in the criteria for initial therapy section

Renewal duration: 12 months when used for secondary amenorrhea

Resources:

Crinone. Package Insert. Revised by manufacturer 8/2014. Accessed 10/12/16.

UpToDate: In vitro fertilization. Current through Sep 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/in-vitro-fertilization?source=search_result&search=Assisted%20Reproductive%20Technology&selectedTitle=2~67#H32

UpToDate: Epidemiology and causes of secondary amenorrhea. Current through Sep 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/epidemiology-and-causes-of-secondary-amenorrhea?source=search_result&search=secondary%20amenorrhea&selectedTitle=2~54

UpToDate: Evaluation and management of secondary amenorrhea. Current through Sep 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/evaluation-and-management-of-secondary-amenorrhea?source=search_result&search=secondary%20amenorrhea&selectedTitle=1~54

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Fax completed prior authorization request form to 602-864-3126 or email to pharmacyprecert@azblue.com.
Call 866-325-1794 to check the status of a request.
All requested data must be provided. **Incomplete forms or forms without the chart notes will be returned.**
Pharmacy Coverage Guidelines are available at www.azblue.com/pharmacy.

Pharmacy Prior Authorization Request Form

Do not copy for future use. Forms are updated frequently.
REQUIRED: Office notes, labs, and medical testing relevant to the request that show medical justification are required.

Member Information

Member Name (first & last):	Date of Birth:	Gender:	BCBSAZ ID#:
Address:	City:	State:	Zip Code:

Prescribing Provider Information

Provider Name (first & last):	Specialty:	NPI#:	DEA#:
Office Address:	City:	State:	Zip Code:
Office Contact:	Office Phone:	Office Fax:	

Dispensing Pharmacy Information

Pharmacy Name:	Pharmacy Phone:	Pharmacy Fax:

Requested Medication Information

Medication Name:	Strength:		Dosage Form:
Directions for Use:	Quantity:	Refills:	Duration of Therapy/Use:

☐ Check if requesting **brand** only ☐ Check if requesting **generic**

☐ Check if requesting continuation of therapy (prior authorization approved by BCBSAZ expired)

Turn-Around Time For Review

☐ Standard ☐ Urgent. Sign here: _____ ☐ Exigent (requires prescriber to include a written statement)

Clinical Information

1. **What is the diagnosis? Please specify below.**

   ICD-10 Code: _____ **Diagnosis Description:** _____

2. ☐ Yes ☐ No **Was this medication started on a recent hospital discharge or emergency room visit?**

3. ☐ Yes ☐ No **There is absence of ALL contraindications.**

4. **What medication(s) has the individual tried and failed for this diagnosis? Please specify below.**
Important note: Samples provided by the provider are not accepted as continuation of therapy or as an adequate trial and failure.

Medication Name, Strength, Frequency	Dates started and stopped or Approximate Duration	Describe response, reason for failure, or allergy

5. **Are there any supporting labs or test results? Please specify below.**

Date	Test	Value

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Pharmacy Prior Authorization Request Form

6. Is there any additional information the prescribing provider feels is important to this review? Please specify below.
For example, explain the negative impact on medical condition, safety issue, reason formulary agent is not suitable to a specific medical condition, expected adverse clinical outcome from use of formulary agent, or reason different dosage form or dose is needed.

Signature affirms that information given on this form is true and accurate and reflects office notes

Prescribing Provider's Signature: Date:

Please note: Some medications may require completion of a drug-specific request form.

Incomplete forms or forms without the chart notes will be returned.

Office notes, labs, and medical testing relevant to the request that show medical justification are required.