BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

HYDROXYPROGESTERONE THERAPY:

Hydroxyprogesterone caproate 1.25 g/5 mL (250 mg/mL) multi-dose vial intramuscular (IM) injection
Hydroxyprogesterone caproate 250 mg/mL single dose vial intramuscular (IM) injection
MAKENA® (hydroxyprogesterone caproate) 1 mL single dose & 5 mL multi-dose vials (250 mg/mL) intramuscular (IM) injection
MAKENA® (hydroxyprogesterone caproate) 275 mg/1.1 mL (250 mg/mL) subcutaneous (SC) single dose auto-injection

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require precertification is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Criteria:

Hydroxyprogesterone caproate 250 mg/mL single dose IM injection
Makena (hydroxyprogesterone caproate) 1 mL single dose & 5 mL multi-dose IM injection
Makena (hydroxyprogesterone caproate) 275 mg/1.1 mL SC auto-injector

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PHARMACY COVERAGE GUIDELINE

HYDROXYPROGESTERONE THERAPY

- **Criteria for therapy:** Hydroxyprogesterone caproate **250 mg/mL, Makena 250 mg/mL, or Makena 275 mg/1.1 mL** is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

  1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with an Obstetrics Gynecologist.
  2. Individual is 16 years of age or older.
  3. Individual has a confirmed diagnosis of a woman with a singleton pregnancy who has a history of singleton spontaneous preterm birth before 37 weeks gestation, use is to reduce the risk of preterm birth.
  4. If used for fertility, use is according to member plan benefit design.
  5. There are **NO** FDA-label contraindications, such as:
     a. Current or history of thrombosis or thromboembolic disorders
     b. Known or suspected breast cancer other hormone-sensitive cancer, or history of these conditions
     c. Undiagnosed abnormal vaginal bleeding unrelated to pregnancy
     d. Cholestatic jaundice of pregnancy
     e. Liver tumors (benign or malignant) or active liver disease
     f. Uncontrolled hypertension
  6. Will be initiated between 16 weeks, 0 days and 20 weeks, 6 days of gestation **and** continued until 36 weeks 6 days of gestation.

  Approval duration: Once weekly until week 37 (through 36 weeks, 6 days) of gestation or delivery, whichever comes first. No refills will be authorized.

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

  1. **Off-Label Use of Non-Cancer Medications**
  2. **Off-Label Use of Cancer Medications**

Hydroxyprogesterone caproate 1.25 g/5mL multi-dose IM injection

- **Criteria for initial therapy:** Hydroxyprogesterone caproate **1.25 gm/5mL** is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with an Oncologist or Obstetrics Gynecologist, depending upon indication or use.
  2. Individual is 16 years of age or older.
  3. A confirmed diagnosis in a non-pregnant woman with **ONE** of the following:

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a. Treatment of advanced uterine adenocarcinoma of the uterine corpus (stage III or IV) **OR** other request for a specific oncologic direct treatment use that is found and listed in the National Comprehensive Cancer Network (NCCN) Guidelines with Categories of Evidence and Consensus of 1 and 2A

b. Management of amenorrhea (primary and secondary) and abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology (e.g., submucous fibroids or uterine cancer) **AND**
   i. Failure, contraindication or intolerance to **BOTH**:
      1. Progesterone (Prometrium or generic) oral micronized capsules **or** progesterone intramuscular injection **AND**
      2. Medroxyprogesterone oral **or** intramuscular injection

c. Use is for production of secretory endometrium and desquamation.

d. Use is for a test for endogenous estrogen production.

4. Will not be used to prevent miscarriage in a woman with a history of recurrent spontaneous preterm pregnancy losses.

5. There are **NO** FDA-label contraindications, such as:
   a. Current or history of thrombosis or thromboembolic disorders
   b. Known or suspected carcinoma of the breast, other hormone-sensitive cancer, or history of these conditions
   c. Undiagnosed abnormal vaginal bleeding
   d. Liver dysfunction or disease
   e. Missed abortion
   f. As a diagnostic test for pregnancy

Approval duration: 6 months

- **Uterine adenocarcinoma (advanced):** 1,000 mg IM one or more times a week (1,000-7,000 mg/week); discontinue upon relapse

- **Amenorrhea (primary and secondary) or abnormal uterine bleeding due to hormonal imbalance:**
  - *Single dose therapy*: 375 mg IM as a single dose; begin at any time **OR**
  - *Cyclic therapy schedule*: 250 mg IM on day 15 of each 28-day cycle for 4 cycles (in combination with estradiol valerate); begin cyclic therapy schedule after 4 days of desquamation. If there is no bleeding, begin cyclic therapy schedule 21 days after the 375 mg IM single dose schedule

- **Production of secretory endometrium and desquamation:**
  - *Patients not on estrogen therapy*:
    Cyclic therapy schedule: 250 mg IM on day 15 of each 28-day cycle (in combination with estradiol valerate); may begin at any time; continue until cyclic therapy is no longer required
  - *Patients currently on estrogen therapy*:
    Single dose therapy: 375 mg IM as a single dose; begin at any time **OR**
  - *Cyclic therapy schedule*: 250 mg IM on day 15 of each 28-day cycle (in combination with estradiol valerate); begin cyclic therapy schedule after 4 days of desquamation. If there is no

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bleeding, begin cyclic therapy schedule 21 days after the 375 mg IM single dose schedule. Continue until cyclic therapy is no longer required

- **Test for endogenous estrogen production:** 250 mg IM as a single dose (bleeding 7-14 days after administration indicates endogenous estrogen); may repeat once 4 weeks after initial dose

- **Criteria for continuation of coverage (renewal request):** Hydroxyprogesterone caproate 1.25 gm/5mL is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met **(samples are not considered for continuation of therapy**):

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with an Oncologist or Obstetrics Gynecologist, depending upon indication or use

2. Individual's condition responded while on therapy with response defined as **ALL** of the following:
    a. No evidence of disease progression
    b. Documented evidence of efficacy, disease stability and/or improvement

3. Will not be used to prevent miscarriage in a woman with a history of recurrent spontaneous preterm pregnancy losses.

4. Individual has been adherent with the medication.

5. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use as follows:
    a. Contraindications as listed in the criteria for initial therapy section
    b. Significant adverse effect such as:
        i. Thrombosis or thromboembolism (arterial or venous) such as pulmonary emboli, deep vein thrombosis, myocardial infarction, or stroke
        ii. Sudden partial or complete loss of vision
        iii. New or worsening depression

6. If used for fertility, use is according to member plan benefit design.

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

3. **Off-Label Use of Non-Cancer Medications**

4. **Off-Label Use of Cancer Medications**

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HYDROXYPROGESTERONE THERAPY

Description:

Hydroxyprogesterone is a potent, long-acting, progestational steroid ester which transforms proliferative endothelium into secretory endothelium, induces mammary gland duct development, and inhibits the production and/or release of gonadotropic hormone; it also displays slight estrogenic, androgenic, or corticoid effects, but should not be relied upon for these effects.

In advanced adenocarcinoma of the uterine corpus, hydroxyprogesterone caproate injection in a dosage of 1,000 mg or more, one or more times each week, often induces regressive changes.

Amenorrhea (the absence of menses) can be a transient, intermittent, or permanent condition resulting from dysfunction of the hypothalamus, pituitary, ovaries, uterus, or vagina. It is often classified as either primary (absence of menarche by age 15 years or thereafter) or secondary (absence of menses for more than 3-months in girls or women who previously had regular menstrual cycles or 6-months in girls or women who had irregular menses).

Hydroxyprogesterone caproate in non-pregnant women is indicated for: a) the treatment of advanced (stage III or IV) uterine adenocarcinoma; b) management of amenorrhea (primary and secondary) and abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology (e.g., submucous fibroids or uterine cancer); c) as a test for endogenous estrogen production; and d) production of secretory endometrium and desquamation. It is available as a multi-dose 1.25 g/5 mL vial as a solution for intramuscular injection.
Makena (brand and generic) is indicated to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. While there are many risk factors for preterm birth, safety and efficacy of Makena brand and generic) has been demonstrated only in women with a prior spontaneous singleton preterm birth. It is not intended for use in women with multiple gestations or other risk factors for preterm birth. The effectiveness of Makena brand and generic) is based on improvement in the proportion of women who delivered < 37 weeks of gestation. There are no controlled trials demonstrating a direct clinical benefit, such as improvement in neonatal mortality and morbidity.

Definitions:

Singleton Pregnancy:
A pregnancy with one fetus

Singleton spontaneous preterm birth:
A pregnancy involving only one fetus in which birth is not induced and occurs before 37 weeks of pregnancy

Multiple Gestations:
A pregnancy with more than one fetus, e.g., twins, triplets

Adenocarcinoma of the Uterine Corpus Stage III and IV:
Cancer that begins in glandular (secretory) cells and involves the uterus. Glandular cells are a type of cells found in the cervix and the lining of the uterus (endometrium). These cells are involved in the menstrual cycle and in the production of cervical mucus. Stage III and IV Adenocarcinoma of the uterine corpus are endometrial cancers that have spread outside of the uterus. In stage III, the cancer has spread beyond the uterus but is still only in the pelvic area. Stage IV cancer is where there are metastases to the rectum, bladder, and/or distant organs.

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Amenorrhea:

Primary amenorrhea is defined as the failure to reach menarche, often, but not exclusively, due to a chromosomal irregularity leading to primary ovarian insufficiency or anatomic abnormality

Secondary amenorrhea is characterized as the cessation of previously regular menses for three months or previously irregular menses for six months. Most cases of secondary amenorrhea can be attributed to polycystic ovary syndrome (PCOS), hypothalamic amenorrhea, hyperprolactinemia, or primary ovarian insufficiency

Normal menstrual cycle typically occurs every 21-35 days

Resources:

Hydroxyprogesterone caproate 1 mL single dose vial product information, revised by American Regent, Inc. 07-2018. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed June 08, 2022.

Hydroxyprogesterone caproate 5 mL multi-dose vial product information, revised by Mylan Institutional LLC. 11-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed June 08, 2022.

Makena (hydroxyprogesterone caproate) 1.1 mL auto-injection, 1 mL single dose vial, & 5 mL multi-dose vial product information, revised by AMAG Pharmaceuticals, Inc. 02-2018. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed June 08, 2022.

Welt CK, Barbieri RL. Evaluation and management of primary amenorrhea. In: UpToDate, Crowley WF, Geffner ME, Martin KA (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Topic last updated on November 10, 2020. Accessed June 29, 2022.

Welt CK, Barbieri RL. Evaluation and management of secondary amenorrhea. In: UpToDate, Crowley WF, Geffner ME, Martin KA (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Topic last updated April 07, 2022. Accessed June 29, 2022.

Off Label Use of Cancer Medications: A.R.S. §§ 20-826(R) & (S). Subscription contracts; definitions.

Off Label Use of Cancer Medications: A.R.S. §§ 20-1057(V) & (W). Evidence of coverage by health care service organizations; renewability; definitions.

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