



PHARMACY COVERAGE GUIDELINES  
SECTION: DRUGS

ORIGINAL EFFECTIVE DATE: 8/15/19  
LAST REVIEW DATE: 8/15/19  
LAST CRITERIA REVISION DATE:  
ARCHIVE DATE:

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## HYDROXYPROGESTERONE THERAPY

- Hydroxyprogesterone caproate 1.25 g/5 mL intramuscular injection
- Hydroxyprogesterone caproate 250 mg/mL intramuscular injection
- Makena® (hydroxyprogesterone caproate) 250 mg/mL intramuscular injection
- Makena® (hydroxyprogesterone caproate) 275 mg/1.1 mL subcutaneous injection

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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.

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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.

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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](mailto:Pharmacyprecert@azblue.com). **Incomplete forms or forms without the chart notes will be returned.**

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**Generic hydroxyprogesterone caproate 250 mg/mL for intramuscular injection**  
**Makena hydroxyprogesterone caproate 250 mg/mL for intramuscular injection**  
**Makena hydroxyprogesterone caproate 275 mg/1.1 mL auto-injector for subcutaneous injection**

### Criteria:

- **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** of the following criteria are met:
  1. Prescriber is a physician specializing in gynecology or is in consultation with Obstetrics Gynecologist
  2. Individual is 16 years of age or older
  3. A confirmed diagnosis of a woman with a singleton pregnancy who has a history of singleton spontaneous preterm birth before 37 weeks gestation; treatment is to reduce the risk of preterm birth
  4. Use is according to member plan benefit design
  5. There are **NO** contraindications.
    - Contraindications include:
      - Current or history of thrombosis or thromboembolic disorders
      - Known or suspected breast cancer other hormone-sensitive cancer, or history of these conditions
      - Undiagnosed abnormal vaginal bleeding unrelated to pregnancy
      - Cholestatic jaundice of pregnancy
      - Liver tumors (benign or malignant) or active liver disease
      - 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



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### Approval duration:

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

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## Hydroxyprogesterone caproate 1.25 gm/5mL for intramuscular injection

### Criteria:

- **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. Prescriber is a physician specializing in cancer or gynecology 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:
    - Treatment of advanced (stage III or IV) uterine adenocarcinoma **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
    - Management of amenorrhea (primary and secondary) or abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology (e.g., submucous fibroids or uterine cancer) **AND**
      - Failure, contraindication or intolerance to **BOTH**:
        - progesterone (Prometrium or generic) oral micronized capsules **or** progesterone intramuscular injection **AND**
        - medroxyprogesterone oral **or** intramuscular injection
    - Use is for production of secretory endometrium and desquamation
    - Use is for a test for endogenous estrogen production
  4. Use is according to member plan benefit design
  5. Will not be used to prevent miscarriage in a woman with a history of recurrent spontaneous preterm pregnancy losses

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6. **ALL** of the following baseline tests have been completed before initiation of treatment with continued monitoring as clinically appropriate:
- Papanicolaou smear
  - Breast exam
  - Pelvic exam
7. There are **NO** contraindications
- Contraindications include:
    - Current or history of thrombosis or thromboembolic disorders
    - Known or suspected breast cancer other hormone-sensitive cancer, or history of these conditions
    - Undiagnosed abnormal vaginal bleeding
    - Liver dysfunction or disease
    - Missed abortions
    - As a diagnostic test for pregnancy
    - Hypersensitivity to hydroxyprogesterone caproate or any component of the formulation

**Initial 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

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no 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:
1. Individual continues to be seen by a physician specializing in cancer or gynecology or is in consultation with an Oncologist or Obstetrics Gynecologist, depending upon indication or use
  2. Individual's condition responded while on therapy
    - Response is defined as:
      - No evidence of disease progression
      - Documented evidence of efficacy, disease stability and/or improvement
  3. Use is according to member plan benefit design
  4. Will not be used to prevent miscarriage in a woman with a history of recurrent spontaneous preterm pregnancy losses
  5. Individual has been adherent with the medication
  6. 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
    - Significant adverse effect such as:
      - Thrombosis or thromboembolism (arterial or venous)
      - New or worsening depression
  7. There are no significant interacting drugs

**Renewal duration:** 12 months

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### **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.

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.

Hydroxyprogesterone caproate injections are commercially available as:

- Generic hydroxyprogesterone caproate 1.25 gm/5mL for intramuscular injection
- Generic hydroxyprogesterone caproate 250 mg/mL for intramuscular injection
- Brand Makena hydroxyprogesterone caproate 250 mg/mL for intramuscular injection
- Brand Makena hydroxyprogesterone caproate 275 mg/1.1 mL auto-injector for subcutaneous injection

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### **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



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### 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 is metastases to the rectum, bladder, and/or distant organs.

### 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

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### Resources:

Makena (hydroxyprogesterone caproate) product information accessed 08-09-19 at DailyMed

Hydroxyprogesterone caproate product information accessed 08-09-19 at DailyMed

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.

UpToDate: Evaluation and management of primary amenorrhea. Current through Jul 2019.

UpToDate: Evaluation and management of secondary amenorrhea. Current through Jul 2019.

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