



An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

ORIGINAL EFFECTIVE DATE: 8/15/2019
LAST REVIEW DATE: 8/19/2021
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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

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.

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

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

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 the patient's diagnosis 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, 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 a Non-cancer Medications**

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2. Off-Label Use of a Cancer Medication for the Treatment of Cancer without a Specific Coverage Guideline

Hydroxyprogesterone caproate 1.25 g/5mL intramuscular solution 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 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:
 - 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
 - g. Hypersensitivity to hydroxyprogesterone caproate or any component of the formulation

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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 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 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
 - a. Response is defined as:
 - i. No evidence of disease progression
 - ii. 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
 - a. Contraindications as listed in the criteria for initial therapy section
 - b. Significant adverse effect such as:

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- i. Thrombosis or thromboembolism (arterial or venous)
- ii. New or worsening depression

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

7. There are no significant interacting drugs

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 a Non-cancer Medications**

4. **Off-Label Use of a Cancer Medication for the Treatment of Cancer without a Specific Coverage Guideline**

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

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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 (250 mg/mL) intramuscular injection formulated in castor oil in a multiple dose 5 mL vial
- Generic hydroxyprogesterone caproate 250 mg/mL intramuscular injection formulated in castor oil in a single dose 1 mL vial or a multiple dose 5 mL vial depending on manufacturer
- Brand Makena hydroxyprogesterone caproate 250 mg/mL intramuscular injection formulated in castor oil in a single dose 1 mL vial or a multiple dose 5 mL vial
- Brand Makena hydroxyprogesterone caproate 275 mg/1.1 mL subcutaneous formulated in castor oil in a single use auto-injector prefilled syringe

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.

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:

Hydroxyprogesterone caproate product information, revised by Mylan Institutional LLC. 01-2017. Available at DailyMed <http://dailymed.nlm.nih.gov>. Accessed on July 16, 2021.

Hydroxyprogesterone caproate product information, revised by Mylan Institutional LLC. 04-2019. Available at DailyMed <http://dailymed.nlm.nih.gov>. Accessed on July 16, 2021.

Makena (hydroxyprogesterone caproate) product information, revised by AMAG Pharmaceuticals, Inc. 02-2018. Available at DailyMed <http://dailymed.nlm.nih.gov>. Accessed on July 16, 2021.

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>. Accessed on July 18, 2021.

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>. Accessed on July 18, 2021.

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.
