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# Subject: Hydroxyprogesterone Caproate

**THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.**



## DESCRIPTION:

Progesterone is a progestinic hormone secreted mainly from the corpus luteum of the ovary during the latter half of the menstrual cycle. Progesterone is formed from steroid precursors in the ovary, testis, adrenal cortex, and placenta. Luteinizing hormone (LH) stimulates the synthesis and secretion of progesterone from the corpus luteum. Progesterone is necessary for nidation (implantation) of the ovum and for maintenance of pregnancy. Although the hormone is secreted mainly during the luteal phase of the menstrual cycle, small amounts of progesterone are also secreted during the follicular phase. High concentrations of the hormone are secreted during the latter part of pregnancy. Amounts comparable to those secreted in women during the follicular phase have been shown to be secreted in males.

Progesterone shares the pharmacologic actions of the progestins. In women with adequate endogenous estrogen, progesterone transforms a proliferative endometrium into a secretory one. The abrupt decline in the secretion of progesterone at the end of the menstrual cycle is principally responsible for the onset of menstruation. Progesterone also stimulates the growth of mammary alveolar tissue and relaxes uterine smooth muscle. Progesterone has minimal estrogenic and androgenic activity.

Hydroxyprogesterone caproate (Makena®) is used to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. Hydroxyprogesterone caproate was designated an orphan drug by the US Food and Drug Administration (FDA) for this use in 2007. Efficacy of the drug for this use is based on improvement in the proportion of women who delivered at less than 37 weeks of gestation. Direct clinical benefit (e.g., improvement in neonatal morbidity and mortality) has not been established. While there are many risk factors for preterm birth, safety and efficacy of hydroxyprogesterone caproate have been demonstrated only in women with a prior spontaneous singleton birth. Hydroxyprogesterone is not intended for use in women with multiple gestations or other risk factors for preterm birth. The American College of Obstetricians and

Gynecologists (ACOG) recommends that progesterone supplementation for the prevention of recurrent preterm birth be offered to women with a singleton pregnancy and a prior spontaneous preterm birth at less than 37 weeks of gestation due to spontaneous preterm labor or premature rupture of membranes. The ACOG also states that physicians should be able to prescribe Makena or compounded hydroxyprogesterone caproate based on accepted medical indications after discussion with the patient.

Safety and efficacy of hydroxyprogesterone caproate for risk reduction of spontaneous preterm birth have been evaluated in a multicenter, randomized, double-blind, placebo-controlled study in 463 women 16 to 43 years of age with a singleton pregnancy who had a documented history of singleton spontaneous preterm birth (defined as delivery at less than 37 weeks of gestation following spontaneous preterm labor or premature rupture of membranes). Members were randomized to receive weekly IM injections of either hydroxyprogesterone caproate 250 mg or placebo starting between 16 weeks, 0 days and 20 weeks, 6 days of gestation and continuing until 37 weeks of gestation or delivery, whichever occurred first. The proportion of women who delivered preterm at less than 37 weeks of gestation, the primary end point, was lower in members receiving hydroxyprogesterone caproate compared with those receiving placebo (37.1 versus 54.9%). The proportion of women delivering at less than 35 and 32 weeks of gestation also was lower in members receiving hydroxyprogesterone caproate (21.3 and 11.9%, respectively) compared with those receiving placebo (30.7 and 19.6%, respectively).

In a follow-up safety study, neurodevelopmental and other health outcomes of 278 surviving infants (mean age: 48 months) born to women enrolled in the randomized, double-blind, placebo-controlled study were evaluated to assess whether there were adverse effects of hydroxyprogesterone caproate evident after in utero exposure. The proportion of children whose scores met the screening threshold for developmental delay in each developmental domain of the Ages and Stages Questionnaire (i.e., communication, gross motor, fine motor, problem solving, and personal/social parameters) was similar in both the hydroxyprogesterone caproate and placebo groups. In addition, no substantial differences were observed in health status; physical examination; or scores for gender-specific roles in both groups.

One of the generic formulations of hydroxyprogesterone caproate injection is available that was previously marketed as Delalutin. The product is FDA approved in non-pregnant women for the treatment of advanced adenocarcinoma of the uterine corpus (Stage III or IV), primary and secondary amenorrhea, abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, as a test for endogenous estrogen production, and for the production of secretory endometrium and desquamation.

## POSITION STATEMENT:

I. Hydroxyprogesterone caproate injection, including compounded products, meet the definition of **medical necessity** when used to reduce the risk of preterm birth in a female member and **ALL** of the following criteria are met:

   1. The member has a current singleton pregnancy.
   2. The member has a documented previous singleton spontaneous preterm birth that occurred at less than 37 weeks gestation due to spontaneous preterm labor or premature rupture of membranes.
   3. Member has not had any preterm labor or premature rupture of membranes during the current pregnancy.
   4. Treatment is initiated between 16 weeks, 0 days and 20 weeks, 6 days of gestation.
   5. Injections are not to be administered more often than weekly until 36 weeks of gestation or time of delivery (whichever occurs first) for a maximum total of no more than 21 injections.

6. Dose does not exceed the following:
    a. 250 mg per intramuscular injection
    b. 275 mg per subcutaneous injection

II. Hydroxyprogesterone caproate injection (generic for Delalutin), **meets the definition of medical necessity** when the dose does not exceed the FDA labeled dosing for **ONE** of the following indications:
    a. Advanced adenocarcinoma of the uterine corpus (Stage III or IV)
    b. Amenorrhea (primary or secondary)
    c. Abnormal uterine bleeding in the absence of organic pathology
    d. As a test for endogenous estrogen production
    e. For production of secretory endometrium and desquamation
    f. Dose does not exceed indication specific FDA labeled dosing

**Note: Coverage of Compounded Hydroxyprogesterone Caproate**

Florida Blue continues to provide coverage under an individual's benefit plan for both compounded hydroxyprogesterone caproate as well as the brand medication Makena in accordance with the physician's prescription. Both the ACOG and the Society for Maternal-Fetal Medicine support access to compounded hydroxyprogesterone caproate for the appropriate clinical indication. In its most current 2012 statement, the FDA emphasized that it is applying its normal enforcement policies for compounded drugs to compounded hydroxyprogesterone caproate. The compounding of any drug, including hydroxyprogesterone caproate, should not exceed the scope of traditional pharmacy compounding. As the Agency has previously explained, FDA generally prioritizes enforcement actions related to compounded drugs using a risk-based approach, giving the highest enforcement priority to pharmacies that compound products that are causing harm or that amount to health fraud.

The following is a link to the complete statement:

http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm308546.htm

Approval duration: 180 days

## DOSAGE/ADMINISTRATION:

**THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.**

**Hydroxyprogesterone Caproate Injection for use in pregnancy:**

**Usual dosage:**

**Intramuscular:** 250 mg (1 mL) administered intramuscularly (IM) once weekly (every 7 days) in the upper outer quadrant of the gluteus maximus by a health care provider. Begin treatment between 16 weeks, 0 days and 20 weeks, 6 days of gestation.

**Subcutaneous (auto-injector only):** 275 mg (1.1 mL) administered subcutaneously once weekly (every 7 days) in the back of the upper arm by a health care provider. Begin treatment between 16 weeks, 0 days and 20 weeks, 6 days of gestation.

**Duration of therapy:** Continue administration once weekly until week 37 (through 36 weeks, 6 days) of gestation or delivery, whichever occurs first.

See prescribing information for dosing of hydroxyprogesterone caproate injection in non-pregnant members.

**NOTE:** Counsel members that hydroxyprogesterone caproate injections may cause pain, soreness, swelling, itching, or bruising. Inform the member to contact her physician if she notices increased discomfort over time, oozing of blood or fluid, or inflammatory reactions at the injection site.

## PRECAUTIONS:

**Contraindications**

- Current thrombosis or thromboembolic disorders or history of these conditions
- Known or suspected breast cancer, other hormone-sensitive cancer, or history of these conditions
- Undiagnosed abnormal vaginal bleeding
- Cholestatic jaundice of pregnancy
- Liver tumors (benign or malignant) or active liver disease
- Uncontrolled hypertension
- Hypersensitivity to the medication
- Use as a diagnostic test for pregnancy

**Warnings:**

- **Thromboembolic disorders:** Hydroxyprogesterone caproate should be discontinued if an arterial or deep venous thrombotic or thromboembolic event occurs.
- **Sensitivity Reactions:** Allergic reactions, including urticaria, pruritus, and angioedema, have been reported with hydroxyprogesterone caproate and other products containing castor oil. Discontinuance of hydroxyprogesterone caproate should be considered if such reactions occur.
- **Decreased Glucose Tolerance:** Decreased glucose tolerance has been observed in some persons receiving progestin therapy. Members with prediabetes or diabetes should be carefully monitored during hydroxyprogesterone caproate therapy.
- **Fluid Retention:** Because progestational agents may cause some degree of fluid retention, members with conditions that may be aggravated by fluid retention (e.g., preeclampsia, epilepsy, migraine, asthma, cardiac or renal dysfunction) should be carefully monitored.
- **Depression:** Members with a history of clinical depression should be monitored during therapy with hydroxyprogesterone caproate. Hydroxyprogesterone caproate should be discontinued if clinical depression recurs.
- **Jaundice**: Monitor women who develop jaundice and consider if the benefit of use warrants continuation.
- **Hypertension:** Monitor women who develop hypertension and consider if the benefit of use warrants continuation.

## BILLING/CODING INFORMATION:

The following codes may be used to describe:

### HCPCS Coding, Hydroxyprogesterone Caproate Injection

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|---|---|
| J3490 | Unclassified drugs [for compounded hydroxyprogesterone caproate ONLY] |
| J1726 | Injection, hydroxyprogesterone caproate, (makena), 10 mg |
| J1729 | Injection, hydroxyprogesterone caproate, not otherwise specified, 10 mg |

### ICD-10 Diagnosis Codes That Support Medical Necessity, Hydroxyprogesterone caproate injection in pregnancy (all HCPCS codes)

| | |
|---|---|
| O09.212 | Supervision of pregnancy with history of pre-term labor, second trimester |
| O09.213 | Supervision of pregnancy with history of pre-term labor, third trimester |
| O09.219 | Supervision of pregnancy with history of pre-term labor, unspecified trimester |
| Z87.51 | Personal history of pre-term labor |

### ICD-10 Diagnosis Codes That Support Medical Necessity, Hydroxyprogesterone caproate injection in non-pregnant members (J1729 only)

| | |
|---|---|
| C54.0 – C54.9 | Neoplasm of uterine corpus |
| N91.0 | Primary amenorrhea |
| N91.1 | Secondary amenorrhea |
| N91.2 | Amenorrhea, unspecified |

## REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

## PROGRAM EXCEPTIONS:

**Federal Employee Program (FEP):** Follow FEP guidelines.

**State Account Organization (SAO):** Follow SAO guidelines.

**Medicare Advantage Products:** No National Coverage Determination (NCD) or Local Coverage Determination (LCD) was found at the time of the last guideline revised date.

## DEFINITIONS:

**Singleton:** a person that is not a twin or other multiple births.

## RELATED GUIDELINES:

**Unclassified Codes and Compounded Drug Products, 09-J0000-58**

## OTHER:

None applicable.

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## COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Medical Policy & Coverage Committee on 06/12/19.

## GUIDELINE UPDATE INFORMATION:

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|---|---|
| 05/15/11 | New Medical Coverage Guideline. |
| 07/01/11 | Revision to guideline; consisting of updating coding. |
| 01/01/12 | Revision to guideline; consisting of updating coding. |
| 05/15/12 | Review and revision to guideline; consisting of updating references. |

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| 05/15/13 | Review and revision to guideline; consisting of updating description section, position statement, coding, references and exceptions. |
| 05/15/14 | Review and revision to guideline; consisting of reformatting the position statement and updating precautions and references. |
| 05/15/15 | Review and revision to guideline; consisting of updating description, updating and reformatting the position statement, reformatting and updating coding, and adding and updating references. |
| 07/01/15 | Revision to guideline; consisting of updating coding. |
| 11/01/15 | Revision: ICD-9 Codes deleted. |
| 01/01/16 | Annual HCPCS coding update: added code J7999 and deleted code Q9977. |
| 05/15/16 | Review and revision to guideline; consisting of updating position statement, warnings, and references. |
| 01/15/17 | Revision to guideline consisting of updating position statement. |
| 02/15/17 | Review and revision to guideline; consisting of updating position statement, dosing, precautions, coding and references. |
| 05/15/17 | Review and revision to guideline; consisting of updating references. |
| 07/01/17 | Addition of HCPCS codes Q9985 and Q9986 that replaces HCPCS code J1725. |
| 01/01/18 | Annual HCPCS coding update: added HCPCS codes J1726 and J1729, and deleted codes Q9985 and Q9986. |
| 05/15/18 | Review and revision to guideline; consisting of updating position statement, coding and references. |
| 07/15/19 | Review and revision to guideline; consisting of updating position statement and references. |