Cigna Drug and Biologic Coverage Policy

Subject: Hydroxyprogesterone caproate injection

Effective Date: 8/15/2018
Next Review Date: 8/15/2019
Coverage Position Number: 1108

Table of Contents
Coverage Policy: 1
General Background: 2
Coding/Billing Information: 3
References: 3

Related Coverage Resources

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer’s particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer’s benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer’s benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Coverage Policy

Cigna covers hydroxyprogesterone caproate injection (Makena®) as medically necessary to reduce the risk of preterm birth when ALL of the following are met:

- current singleton pregnancy
- previous singleton spontaneous preterm birth due to spontaneous preterm labor or premature rupture of membranes between week 20, 0 days and week 36, 6 days of pregnancy
- treatment will be initiated between week 16, 0 days and week 20, 6 days of gestation and not continue beyond week 36, 6 days of gestation or time of delivery (whichever occurs first)

Cigna does not cover hydroxyprogesterone caproate injection (Makena®) for any other indications, including but not limited to the following, because they are considered experimental, investigational, or unproven:

- Cervical insufficiency and/or cerclage in place
- Prevention of preterm birth in twin gestation
- Prolonging pregnancy in women with a sonographic short cervix

When coverage is available and medically necessary, the dosage, frequency, site of administration, and duration of therapy should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to hydroxyprogesterone caproate injection (Makena®)

Note: Receipt of sample product does not satisfy any criteria requirements for coverage
FDA Approved Indications
Makena is a progestin indicated to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. The effectiveness of Makena 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.

Limitation of use: Makena is not intended for use in women with multiple gestations or other risk factors for preterm birth.

FDA Recommended Dosing
Makena (single and multi-dose vials): Administer intramuscularly at a dose of 250 mg (1 mL) once weekly (every 7 days) by a healthcare provider.

Makena auto-injector: Administer subcutaneously using auto-injector at a dose of 275 mg (1.1 mL) once weekly (every 7 days) in the back of either upper arm by a healthcare provider.

Begin treatment between 16 weeks, 0 days and 20 weeks, 6 days of gestation. Continue administration once weekly until week 37 (through 36 weeks, 6 days) of gestation or delivery, whichever occurs first.

Drug Availability
Each single dose 1 ml vial contains hydroxyprogesterone caproate USP, 250 mg/mL (25% w/v), in castor oil USP (30.6% v/v) and benzyl benzoate USP (46% v/v).

Each multidose 5 mL vial contains hydroxyprogesterone caproate USP, 250 mg/mL (25% w/v), in castor oil USP (28.6% v/v) and benzyl benzoate USP (46% v/v) with the preservative benzyl alcohol NF (2% v/v).

Each auto-injector is supplied as 1.1 mL of a clear yellow sterile preservative-free solution in an auto-injector containing a pre-filled syringe. Each 1.1 mL auto-injector contains hydroxyprogesterone caproate USP, 250 mg/mL (25% w/v), in castor oil USP (30.6% v/v) and benzyl benzoate USP (46% v/v).

General Background
Pharmacology
Hydroxyprogesterone caproate is a synthetic progestin. 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 shows slight estrogenic, androgenic, or corticoid effects as well, but should not be relied upon for these effects. It’s mechanism for preventing preterm birth in women with a history of preterm delivery is unknown.

Guidelines
American College of Obstetricians and Gynecologists (ACOG)
In 2016, ACOG reaffirmed the 2012 Prediction and Prevention of Preterm Birth Practice Bulletin, which addresses use of progesterone. In order to minimize the risk of recurrent spontaneous preterm birth, the bulletin suggests administration of progesterone beginning at weeks 16-24 of gestation in a woman with a singleton pregnancy and a history of previous singleton spontaneous preterm delivery. ACOG concludes that evidence does not demonstrate use of progesterone reduces preterm delivery in twin or triplet pregnancies and does not support it’s use in multiple gestations.

Clinical Efficacy
Makena
The pivotal trial evaluating the efficacy of hydroxyprogesterone caproate in reducing singleton preterm birth in women with a history of preterm delivery found preterm delivery prior to 37 weeks occurred less frequently in patients receiving hydroxyprogesterone caproate (36.3%) compared to patients receiving placebo (54.9%, p<0.001) (Meis, 2003). Two published meta-analyses report the pooled results of clinical trials evaluating hydroxyprogesterone caproate for the prevention of preterm delivery in high risk women. Both analyses found
Hydroxyprogesterone caproate significantly reduced the incidence of preterm birth (16-29%) compared to placebo (28-41%). Hydroxyprogesterone caproate (10-20%) also significantly reduced the risk of birthweight less than 2.5 kg compared to placebo (20-28%). Perinatal mortality was not significantly different between treatment groups in either meta-analysis (Sanchez-Ramos, 2005; Kierse, 1990).

**Experimental, Investigational, Unproven uses**
There are no published, randomized, controlled trials evaluating the use of Makena in singleton pregnancy with spontaneous twin preterm birth in prior pregnancy. There is insufficient evidence in the peer-reviewed published scientific literature to support safety and efficacy of Makena combined with cerclage for the prevention of preterm birth in high risk women, prolonging pregnancy in women with a sonographic short cervix, or for the prevention of preterm birth in twin gestation. (Awwad 2015; Dodd 2017; Samson 2018; Sanchez-Ramos 2018; Schuit 2015; Sinkey 2017; Su 2010; Szychowski 2012; Winer 2015)

**Coding/Billing Information**

**Note:**
1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

**Covered when medically necessary**

<table>
<thead>
<tr>
<th>HCPCS Codes</th>
<th>Description</th>
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<tbody>
<tr>
<td>J1726</td>
<td>Injection, hydroxyprogesterone caproate (Makena), 10 mg</td>
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<tr>
<td>Q9986</td>
<td>Injection, hydroxyprogesterone caproate (Makena), 10 mg (Code deleted 12/31/2017)</td>
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**References**
