IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Hydroxyprogesterone caproate (Makena) is a synthetic progestin. It is a once weekly intramuscular injection administered by a healthcare provider to prevent preterm birth.
Policy/Criteria

I. Most contracts require prior authorization approval of hydroxyprogesterone caproate (Makena) prior to coverage. Hydroxyprogesterone caproate (Makena) may be considered medically necessary for the prevention of preterm birth in women when criteria A and B are met.

   A. There is a confirmed singleton pregnancy with gestational age between 16 weeks 0 days and 20 weeks 6 days.

   AND

   B. There is a history of singleton spontaneous preterm birth. Preterm birth is defined as birth that occurs before 37 weeks of gestation.

II. Administration, Quantity Limitations, and Authorization Period

   A. OmedaRx does not consider hydroxyprogesterone caproate (Makena) to be a self-administered medication.

   B. When prior authorization is approved, hydroxyprogesterone caproate (Makena) may be authorized in quantities of up to one 250-mg injection administered once weekly. Coverage for injections must begin when the gestational age is between 16 weeks 0 days and 20 weeks 6 days and may continue until 36 weeks 6 days of gestation or delivery, whichever occurs first.

III. Hydroxyprogesterone caproate (Makena) is considered not medically necessary when used for the following conditions:

   A. When therapy is initiated after 21 weeks of gestation

   B. Abnormal uterine bleeding

   C. Amenorrhea

   D. Female infertility

   E. Contraception

   F. Endometrial hyperplasia

   G. Endometrial cancer

   H. Breast cancer

   I. Polycystic ovary syndrome

IV. Hydroxyprogesterone caproate (Makena) is considered investigational when used for all other conditions, including, but not limited to the prevention of preterm labor in women with other risk factors such as:

   A. Abnormal cervix or uterus

   B. Cigarette or cocaine use

   C. History of miscarriage

   D. Hypertension requiring medication
E. Infection during pregnancy  
F. Known fetal anomaly  
G. Lack of prenatal care  
H. Multiple gestations

Position Statement  
- Progesterone is a hormone that inhibits the uterus from contracting and is involved in maintaining pregnancy. Hydroxyprogesterone caproate is a metabolite of progesterone.  
- Hydroxyprogesterone caproate was originally approved in 1956; although, the commercially manufactured product was later discontinued for reasons other than safety. Following discontinuation of the commercially manufactured product, a compounded version of hydroxyprogesterone continued to be widely used to prevent preterm birth.  
- Hydroxyprogesterone caproate is again commercially available under the trade name, Makena. The FDA approval of Makena was based on one pivotal trial funded by the National Institute of Health. Intramuscular administration of hydroxyprogesterone caproate has been reported to reduce the risk of singleton preterm birth before 37 weeks of gestation in women with history of spontaneous singleton preterm birth.

Clinical Efficacy  
- Preterm birth (< 37 weeks of gestation) affects 12% of all births in the United States and is the leading cause of newborn death. [1] According to Centers for Disease Control and Prevention (CDC), one in eight infants in the United States are born prematurely each year. [2]  
- Infant mortality increases with decreasing gestational age. Women with a previous preterm delivery have an increased risk for preterm delivery with subsequent pregnancies. [3]  
- There are no controlled trials demonstrating a direct clinical benefit of hydroxyprogesterone caproate (Makena) in improving neonatal mortality and morbidity. The efficacy of hydroxyprogesterone caproate was evaluated based on a surrogate endpoint of reducing the rate of preterm birth before 37 weeks of gestation. [3]  
- In one published randomized, double-blind, vehicle-controlled clinical trial, hydroxyprogesterone caproate (Makena) was found to reduce the rate of recurrent preterm delivery among women (ages 16 – 43 years) who were at high risk for preterm delivery. Specifically, the frequency of delivery at < 37 weeks of gestation was 36.3% in the treatment group compared to 54.9% in the placebo group (P < 0.001). The incidence of delivery at < 35 weeks of gestation was also less frequent in the treatment group than in the placebo group (20.6% vs 30.7%; P = 0.02). [3]
- A recently published cohort study determined there was no significant difference in the recurrence of preterm birth ≤35 weeks in women treated with hydroxyprogesterone caproate (Makena) who were at high risk for preterm delivery compared to historical control. However, the single-center, open-label study design has high potential for bias. [4]

- Hydroxyprogesterone caproate (Makena) has not been shown to be effective in women pregnant with more than one fetus (multiple gestations) or other risk factors for preterm birth. [5]

- Due to the FDA labeled indication, and data limited to retrospective studies, the initiation of hydroxyprogesterone caproate (Makena) after 21 weeks of gestation is considered not medically necessary. [6-8]

- Other conditions considered not medically necessary include abnormal uterine bleeding, amenorrhea, female infertility, contraception, and endometrial hyperplasia due to the availability of other treatment options that provide better value.

**Safety**

- The most common side effects reported with hydroxyprogesterone caproate (Makena) included pain, swelling or itching at the injection site, hives, nausea, and diarrhea. Serious adverse reactions were rare and included a single report each of pulmonary embolism and an infection at the injection site. [9]

- Four-year follow up of the hydroxyprogesterone caproate (Makena) randomized controlled trial found no adverse health outcomes of surviving children. However, long-term safety outcomes remain uncertain due to high loss to follow-up (35%). [10]

- In a cohort study with historical control, the rate of gestational diabetes was found to be significantly higher in women treated with hydroxyprogesterone caproate (Makena) compared to case-matched controls. [4]

### Appendix 1: Other Progesterone Medications*

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose Commonly Prescribed for Prevention of Preterm Birth</th>
<th>FDA Approved for Prevention of Preterm Birth?</th>
<th>FDA Approved Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progesterone suppository</td>
<td>100 mg vaginally daily</td>
<td>No</td>
<td>- Assisted Reproductive Technology (ART)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Amenorrhea and abnormal uterine bleeding</td>
</tr>
<tr>
<td>Progesterone micronized</td>
<td>400 mg oral daily</td>
<td>No</td>
<td>- Prevention of endometrial hyperplasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Secondary amenorrhea</td>
</tr>
</tbody>
</table>

* OmedaRx does not endorse the use of these medications due to a lack of reliable evidence. However, these medications may be used off-label for the prevention of preterm delivery, and are therefore listed for reference. Providers are expected to exercise their medical judgment in providing the most appropriate care.
Cross References

<table>
<thead>
<tr>
<th>Compounded Medications, Medication Policy Manual, Policy No.135</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progesterone Therapy as a Technique to Reduce Preterm Delivery in High Risk Pregnancies, BlueCross BlueShield Association Medical Policy, #4.01.16, Issue 10/2009.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Codes</th>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>96372</td>
<td>Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular.</td>
</tr>
<tr>
<td>ICD-9</td>
<td>V23.41</td>
<td>Pregnancy with history of preterm labor</td>
</tr>
</tbody>
</table>

References

**Revision History**

<table>
<thead>
<tr>
<th>Revision Date</th>
<th>Revision Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>08/11/2017</td>
<td>No criteria changes with this annual update</td>
</tr>
<tr>
<td>09/09/2016</td>
<td>No criteria changes with this annual update</td>
</tr>
</tbody>
</table>