# Clinical Policy: Hydroxyprogesterone Caproate (Makena/compound)

Reference Number: ERX.SPA.198
Effective Date: 01.11.17
Last Review Date: 02.18 Revision Log

**See Important Reminder at the end of this policy for important regulatory and legal information.**

**Description**
Hydroxyprogesterone caproate (Makena®/compound) is a progestin.

**FDA Approved Indication(s)**
Makena is indicated to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth.

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

**Policy/Criteria**
*Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.*

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Makena/compounded Hydroxyprogesterone caproate is **medically necessary** when the following criteria are met:

**I. Initial Approval Criteria**

**A. Prevention of Preterm Birth** (must meet all)**:**

1. Current singleton pregnancy;
2. History of singleton spontaneous preterm birth (delivery at < 37 weeks of gestation following spontaneous preterm labor or premature rupture of membranes);
3. Therapy to begin between 16 weeks, 0 days and 27 weeks, 6 days of gestation;
4. Request is for Makena unless there is a contraindication or documented reason to use an alternative formulation;
5. Dose does not exceed 250 mg (1 mL) IM or 275 mg (1.1 mL) SC once weekly.

**Approval duration**: **up to a total of 21 doses to reach week 37 (through 36 weeks, 6 days) of gestation, or delivery, whichever occurs first**

**B. Other diagnoses/indications**

1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

**II. Continued Therapy**

**A. Prevention of Preterm Birth** (must meet all)**:**

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Member is responding positively to therapy;
3. If request is for a dose increase, new dose does not exceed 250 mg (1 mL) IM or 275 mg (1.1 mL) SC once weekly.

**Approval duration**: **up to a total of 21 doses to reach week 37 (through 36 weeks, 6 days) of gestation, or delivery, whichever occurs first**

**B. Other diagnoses/indications** (must meet 1 or 2)**:**

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   **Approval duration: Duration of request or 6 months (whichever is less)**; or

2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

**III. Diagnoses/Indications for which coverage is NOT authorized:**

**A.** Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or evidence of coverage documents;

**B.** For use in women with multiple gestations.

**IV. Appendices/General Information**

*Appendix A: Abbreviation/Acronym Key*
FDA: Food and Drug Administration

*Appendix B: Therapeutic Alternatives*
Not applicable

*Appendix C: Contraindications*

- Makena should not be used in women with nay of the following conditions:
  - 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

*Appendix D: General Information*

- The FDA-approved indication has a limitation of use: Makena is not intended for use in women with multiple gestations or other risk factors for preterm birth. Studies of hydroxyprogesterone for multi-fetal gestations found no benefit to support its use with 41.5% of 17P treated patients experiencing delivery or fetal death before 35 weeks vs. 37.3% of placebo treated patients.
- The hydroxyprogesterone caproate product distributed by ANI Pharmaceuticals, Inc. is not a generic for Makena and is not indicated for prevention of preterm birth in pregnant women.
- Data are inconclusive on the benefits of initiating hydroxyprogesterone therapy after 20 weeks, 6 days of gestation.
- In a study by Durnwald et al., administration of Makena did not reduce preterm birth in women with twin gestations before 35 weeks among those with either a short cervix (64.3 vs. 45.8%, p=0.18) or a long cervix and 38.1 vs. 35.5%, p=0.85).
- In a trial by Grobman WA, et al. in nulliparous women with a midtrimester CL<30 mm. Delivery <37 weeks of gestation occurred in 25.1% of women in the Makena group and 24.2% of women in the placebo group (relative risk, 1.03; 95% confidence interval, 0.79 –1.35).
- In a trial by Combs CA, et al. Mothers carrying dichorionic-diamniotic twins were randomly assigned to weekly injections of 250 mg of Makena or placebo, starting at 16-24 weeks and continued until 34 weeks. Mean gestational age at delivery was not affected by Makena (35.3 vs. 35.9 weeks, p=0.10).
- A prospective cohort study by Centene Corporate evaluated whether providing 17 alpha-hydroxyprogesterone caproate (17P) to high-risk pregnant women (n=193) who have a history of pre-term delivery in a Medicaid managed care population reduces the rate of recurrent preterm delivery and neo natal intensive care unit (NICU) admissions. The findings were that offering 17P as a benefit does have a statistically significantly different, positive effect on reducing the rate of recurrent pre-term delivery and rate of NICU admission in a managed Medicaid population. There was no decrease in effectiveness with delay in initiation of 17P as long as it was started by 28 weeks of gestation.

**V. Dosage and Administration**

| Indication | Dosing Regimen | Maximum Dose |
|---|---|---|
| Prevention of preterm birth | Inject 250 mg (1 mL) IM or 275 mg (1.1 mL) SC once weekly (every 7 days) until week 37 of gestation or delivery, whichever occurs first.<br><br>Begin treatment between 16 weeks, 0 days and 27 weeks, 6 days of gestation. | IM: 250 mg/week, SC: 275 mg/week. until week 37 of gestation or delivery, whichever occurs first |

## VI. Product Availability

- Auto-injector: 275 mg/1.1 mL
- Multi-dose vial: 1,250 mg/ 5mL
- Single-dose vial: 240 mg/1 mL

## VII. References

1. Makena Prescribing Information. Waltham, MA: AMAG Pharmaceuticals, Inc.; February 2018. Available at https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=a1998c1d-8337-4f00-8dcb-af3b54d39b77. Accessed April 10, 2018.
2. Clinical management guidelines for obstetrician-gynecologists – practice bulletin 130: prediction and prevention of preterm birth. The American College of Obstetricians and Gynecologists. *Obstet Gynecol.* October 2012; 120(4): 964-973.
3. Mason MV, Poole-Yaeger A, Lucas B, Krueger C, Ahmed T, Duncan I. Effects of a pregnancy management program on birth outcomes in managed Medicaid. Managed Care April 2011.
4. Mason MV, Poole-Yaeger A, Krueger C, House K, Lucas B. Impact of 17P usage on NICU admissions in a managed medicaid population – a five-year review. Managed Care February 2010.
5. Romero R and Stanczyk FZ. Progesterone is not the same as 17α-hydroxyprogesterone caproate: implications for obstetrical practice. Am J Obstet Gynecol. June 2013; 208(6): 421-426.

| Reviews, Revisions, and Approvals | Date | P&T Approval Date |
|---|---|---|
| Policy created. | 12.16 | 01.17 |
| 1Q18 annual review:<br>No significant changes. References updated and reviewed. | 11.20.17 | 02.18 |
| No significant changes; added new subcutaneous dosage form and compound formulation. | 04.10.18 | |

**Important Reminder**

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.