Clinical Policy: Hydroxyprogesterone Caproate (Makena/compound)

Reference Number: ERX.SPA.198
Effective Date: 01.11.17
Last Review Date: 02.22
Line of Business: Commercial, Medicaid

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. 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(s) of use: While there are many risk factors for preterm birth, safety and efficacy of Makena 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.

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.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

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. Makena is not prescribed concurrently with Crinone® or Endometrin®;
4. Therapy to begin between 16 weeks, 0 days and 27 weeks, 6 days of gestation;
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. 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/Boxed Warnings
- Contraindication(s):
  - 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
- Boxed warning(s): none reported

Appendix D: General Information
- Data are inconclusive on the benefits of initiating hydroxyprogesterone therapy after 20 weeks, 6 days of gestation. However, 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 neonatal 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.
- In response to the 2019 PROLONG confirmatory trial showing 17-alpha-hydroxyprogesterone caproate provided no benefit in preventing preterm birth, the American College of Obstetricians and Gynecologists and Society for Maternal-Fetal Medicine advise more research is needed before substantively changing practice guidance.

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.	IM: 250 mg/week, SC: 275 mg/week until week 37 of gestation or

Indication	Dosing Regimen	Maximum Dose
	Begin treatment between 16 weeks, 0 days and 27 weeks, 6 days of gestation. Dose should be administered by a healthcare professional.	delivery, whichever occurs first

VI. Product Availability

Drug Name	Availability
Makena	Multi-dose vial: 250 mg/mL Single-dose vial (preservative free): 250 mg/mL Prefilled syringe (preservative free): 250 mg/mL
Hydroxyprogesterone caproate	Multi-dose vial: 250 mg/mL Single-dose vial (preservative free): 250 mg/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 November 10, 2021.
2. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc. Updated periodically. Accessed November 10, 2021.
3. Society for Maternal-Fetal Medicine Publications Committee. SMFM Statement: Use of 17-alpha hydroxyprogesterone caproate for prevention of recurrent preterm birth. Am J Obstet Gynecol. 2020 Jul;223(1):B16-B18.
4. Society for Maternal-Fetal Medicine Publications Committee. The choice of progestogen for the prevention of preterm birth in women with singleton pregnancy and prior preterm birth. Am J Obstet Gynecol. 2017 Mar;216(3):B11-B13.
5. Society for Maternal-Fetal Medicine Publications Committee, with assistance of Vincenzo Berghella. Progesterone and preterm birth prevention: translating clinical trials data into clinical practice. Am J Obstet Gynecol 2012;206:376-86.
6. Clinical Guidance for Integration of the Findings of the PROLONG Study: Progestin's Role in Optimizing Neonatal Gestation. The American College of Obstetricians and Gynecologists Practice Advisory. October 2019. Available at https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2019/10/clinical-guidance-for-integration-of-the-findings-of-the-prolong-study. Accessed September 21, 2020.
7. Committee on Practice Bulletins—Obstetrics. The American College of Obstetricians and Gynecologists. Practice Bulletin No. 130: Prediction and prevention of preterm birth. Obstet Gynecol 2012 [reaffirmed 2016];120:964–73.
8. Mason MV, Poole-Yaeger A, Lucas B, et al. Effects of a pregnancy management program on birth outcomes in managed Medicaid. Managed Care. April 2011; 20(4): 39-46.
9. Mason MV, Poole-Yaeger A, Krueger C, et al.. Impact of 17P usage on NICU admissions in a managed Medicaid population – a five-year review. Managed Care. February 2010; 19(2): 46-52.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created.	12.16	01.17
1Q18 annual review: 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	
1Q 2019 annual review: no significant changes; references reviewed and updated.	10.30.18	02.19
1Q 2020 annual review: removed the following requirement: "Request is for Makena unless there is a contraindication or documented reason to use an alternative formulation." as brand Makena is non-preferred relative to generic; references reviewed and updated.	11.05.19	02.20

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Added requirement precluding concurrent therapy with Crinone or Endometrin; PROLONG confirmatory trial synopsis added to general information appendix - related ACOG/SMFM citations added to reference section.	05.12.20	08.20
1Q 2021 annual review: no significant changes; generic formulation availability added for single- and multi-dose vials for information; references reviewed and updated.	10.21.20	02.21
1Q 2022 annual review: no significant changes; references reviewed and updated.	11.16.21	02.22

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.

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