Clinical Policy: Hydroxyprogesterone Caproate (Makena/compound)

Reference Number: PA.CP.PHAR.14
Effective Date: 01/18
Last Review Date: 01/19

Coding Implications
Revision Log

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
It is the policy of Pennsylvania Health and Wellness ® that hydroxyprogesterone caproate is **medically necessary** for members meeting the following criteria:

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 PA.CP.PMN.53 if diagnosis is NOT specifically listed

II. Continued Therapy

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

1. Currently receiving medication via Pennsylvania Health and Wellness benefit or member has previously met initial approval criteria or the Continuity of Care policy (PA.LTSS.PHAR.01) applies;
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 Pennsylvania Health and Wellness benefit or member has previously met initial approval criteria or the Continuity of Care policy (PA.LTSS.PHAR.01) applies;

Approval duration: Duration of request or 6 months (whichever is less); or

2. Refer to PA.CP.PMN.53 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:

1. Refer to PA.CP.PMN.53 if diagnosis is NOT specifically listed
2.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/Boxed Warnings

- Contraindication(s): Makena should not be used in women with any 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
- Boxed warning(s): none reported

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 hydroxyprogesterone-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 (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 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.

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. Begin treatment between 16 weeks, 0 days and 27 weeks, 6 days of gestation. Dose should be administered by a healthcare professional.	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/5 mL
- Single-dose vial: 240 mg/1 mL

Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J1725	Injection, hydroxyprogesterone caproate, 1 mg

Reviews, Revisions, and Approvals	Date	Approval Date
References reviewed and approved	2.18	
1Q 2019 annual review: references reviewed and updated.	1.19	

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 October 30, 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, et al. Effects of a pregnancy management program on birth outcomes in managed Medicaid. Manag Care. April 2011; 20(4): 39-46.
4. 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. Manag Care. February 2010; 19(2): 46-52.
5. Romero R, 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.
6. Society for Maternal-Fetal Medicine (SMFM) 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. doi: 10.1016/j.ajog.2017.01.022.
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