Clinical Policy: Hydroxyprogesterone Caproate (Makena/compound)

Reference Number: CP.PHAR.14
Effective Date: 11.20.17
Last Review Date: 02.18 Coding Implications
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.

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 Centene Corporation® 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 the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial and CP.PMN.53 for Medicaid.

II. Continued Therapy

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

1. Currently receiving medication via Centene benefit 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 Centene benefit and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial and CP.PMN.53 for Medicaid.

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 policies – CP.CPA.09 for commercial and CP.PMN.53 for Medicaid 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. 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, 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.

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	P&T Approval Date
1Q18 annual review: - Combined policies for Medicaid and commercial - Medicaid: removed contraindications following the safety guidance - No significant changes from previous corporate approved policy - References reviewed and approved	11.20.17	02.18
No significant change; added new subcutaneous dosage form.	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. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. 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. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.