Clinical Policy: Hydroxyprogesterone Caproate (Makena/compound)

Reference Number: IL.PHAR.14
Effective Date: 08.01.20
Last Review Date: 11.17.23
Line of Business: Medicaid

Coding Implications
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.

***The FDA withdrew its approval of Makena and its generics. Makena and its generics are no longer approved and cannot lawfully be distributed in interstate commerce (*see Appendix D*).**

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)**:***

**CP.PMN.22/HNCA.CP.PMN.22 Brand Name Override policy does not apply*

1. Request is for compounded hydroxyprogesterone caproate;
2. Current singleton pregnancy;
3. History of singleton spontaneous preterm birth (delivery at < 37 weeks of gestation following spontaneous preterm labor or premature rupture of membranes);
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 (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the (Medicaid), the no coverage criteria policy for the relevant line of business: CP.PMN.255 for Medicaid; or
   b. For drugs NOT on PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.PMN.53 for Medicaid
   .
3. Request is for Brand Makena®;

II. Continued Therapy

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

**CP.PMN.22/HNCA.CP.PMN.22 Brand Name Override policy does not apply*

1. Provider attestation acknowledging FDA's withdrawal of Makena and its generics as a result of failure to demonstrate clinical benefit in the confirmatory PROLONG trial;
   2. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B*

3. Member is responding positively to therapy;
4.
5. 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. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the (Medicaid), the no coverage criteria policy for the relevant line of business: CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: 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.PMN.53 for Medicaid 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): 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

- 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.
- The American College of Obstetricians and Gynecologists. Practice Bulletin No. 234 states that patients with a singleton pregnancy and a prior spontaneous preterm birth should be offered progesterone supplementation (either vaginal or intramuscular) in the

context of a shared decision-making process incorporating the available evidence and the patient's preferences.

- On October 19, 2022 the FDA's Obstetrics, Reproductive, and Urologic Drugs Advisory Committee (ORUDAC) voted 14 to 1 to recommend the withdrawal of Makena from the market. The committee concluded that the PROLONG trial failed to verify the clinical benefit of Makena and the drug has not been shown to be effective on neonatal outcomes or in preventing preterm birth, nor did it show any treatment effect in different subgroups, including those with known risk factors for preterm birth. The FDA announced the final decision to withdraw approval of Makena on April 6, 2023. Makena and its generics are no longer approved and cannot lawfully be distributed in interstate commerce.

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

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 15, 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. Manag Care. February 2010; 19(2): 46-52.
10. FDA News Release: FDA Commissioner and Chief Scientist Announce Decision to Withdraw Approval of Makena. April 6, 2023. Available at: https://www.fda.gov/news-events/press-announcements/fda-commissioner-and-chief-scientist-announce-decision-withdraw-approval-makena. Accessed April 6, 2023.
11. FDA.gov. Makena (hydroxyprogesterone caproate injection) Information. Updated April 6, 2023. Available at: https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/makena-hydroxyprogesterone-caproate-injection-information. Accessed April 6, 2023.

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
J1726	Injection, hydroxyprogesterone caproate, (Makena), 10 mg
J1729	Injection, hydroxyprogesterone caproate, Not Otherwise Specified, 10 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	

HCPCS Codes	Description		
	1Q 2019 annual review: no significant changes; references reviewed and updated.	10.30.18	02.19
	Line of business updated to include HIM-Medical Benefit; removed the following requirement per SDC: "Request is for Makena unless there is a contraindication or documented reason to use an alternative formulation."; added notation that CP.PMN.22 Brand Name Override does not apply.	10.02.19	
	1Q 2020 annual review: no significant changes; replaced HIM Medical benefit with HIM line of business; references reviewed and updated.	11.05.19	02.20
	Policy created, adapted from CP.PHAR.14 **Hydroxyprogesterone Caproate (Makena/compound)** for migration to HFS PDL	7.16.20	
	3Q 2021 annual review: review and updated references	7.6.21	
	1Q2022 Annual Review: Added criteria request is for Brand Makena® per HFS PDL; Updated *Appendix D: General Information.* Updated Product Availability.	3.14.22	
	Template changes applied to other diagnoses/indications and continued therapy section	11.1.22	
	4Q 2023 Annual Review: Added disclaimer about FDA withdrawal of Makena and its generics; added requirement for prescriber attestation of market withdrawal; for initial therapy added requirement that request is for compounded hydroxyprogesterone caproate as Makena and its generics are no longer approvable for patients initiating therapy; added information to Appendix D regarding FDA advisory committee vote to withdraw Makena from the market; references reviewed and updated.	11.17.23	

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.