

Clinical Policy: Hydroxyprogesterone Caproate (Makena/compound)

Reference Number: CP.PHAR.14

Effective Date: 11.20.17

Last Review Date: 12.20

Line of Business: Commercial, HIM, 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.

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. 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 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, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid.

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. 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, HIM.PHAR.21 for health insurance marketplace, 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, HIM.PHAR.21 for health insurance marketplace, and 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):
 - 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. 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. 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: 250 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 November 5, 2019.
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 17 α -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.
7. Blackwell SC, Gyamfi-Bannerman C, Biggio JR, et al. 17-OHPC to Prevent Recurrent Preterm Birth in Singleton Gestations (PROLONG Study): A Multicenter, International, Randomized Double-Blind Trial. *American Journal of Perinatology.* 2019 October; DOI <https://doi.org/10.1055/s-0039-3400227>.
8. Clinical guidance for integration of the findings of the PROLONG study: progestin’s role in optimizing neonatal gestation. Practice Advisory, October 2019. American College of Obstetricians and Gynecologists (ACOG). 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 July 22, 2020.
9. SMFM Statement: Use of 17-alpha hydroxyprogesterone caproate for prevention of recurrent preterm birth. Society for Maternal-Fetal Medicine (SMFM) Publications Committee. July 2020. Available at <https://www.smfm.org/publications/280-smfm-statement-use-of-17-alpha-hydroxyprogesterone-caproate-for-prevention-of-recurrent-preterm-birth>. Accessed July 22, 2020.

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

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	
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
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
Aligning WCG medical drug policies (aka, Clinical Coverage Guidelines – CCGs) with CNC.	12.16.20	

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.

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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.

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