hydroxyprogesterone caproate

EOCCO POLICY

Policy Type:PA/SP Pharmacy Coverage Policy: EOCCO175

Description

Hydroxyprogesterone caproate is an injectable synthetic progestin.

Length of Authorization

- Initial:
  - i. Endogenous estrogen measurement, diagnosis: 2 months
  - ii. All other indications: 12 months
- Renewal:
  - i. Endogenous estrogen measurement, diagnosis: No renewal allowed
  - ii. All other indications: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
hydroxyprogesterone caproate*	1250 mg/5mL (250mg/mL)	Advanced adenocarcinoma of the uterus Amenorrhea Endometrial disorder Endogenous estrogen measurement, diagnosis	1 vial/28 days

**As of April 6, 2023, there is only one NDC of hydroxyprogesterone caproate FDA-approved for interstate commerce (67457-0886-05). All other NDCs have been discontinued by the FDA.*

Initial Evaluation

I. **Hydroxyprogesterone caproate** may be considered medically necessary when the following criteria are met:
   A. Member is age 18 years or older; **AND**
   B. Member is NOT currently pregnant; **AND**
   C. A diagnosis of one of the following:
      1. Advanced adenocarcinoma of the uterus (stage III or IV); **OR**
      2. Amenorrhea; **OR**
      3. Endometrial disorder (production of secretory endometrium and desquamation); **OR**
      4. Endogenous estrogen measurement test

II. Hydroxyprogesterone caproate (Makena) is considered not medically necessary when criteria above are not met and/or when used for:
   A. Reducing the risk of recurrent preterm birth

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has a diagnosis of one of the following:
   a. Advanced adenocarcinoma of the uterus (stage III or IV); **AND**
      i. Member has exhibited disease response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread; **OR**
   b. Amenorrhea; **OR**
   c. Endometrial disorder (production of secretory endometrium and desquamation); **AND**
      i. Member has exhibited improvement or stability of disease symptoms [e.g., normal menstrual bleeding]

Supporting Evidence

I. Hydroxyprogesterone caproate was initially approved under the ANDA pathway as a therapeutic equivalent to the reference listed drug (RLD) Delalutin in 2015. The labeled indications approved are in non-pregnant adult women: for the treatment of advanced adenocarcinoma of the uterine corpus (Stage III or IV), in the management of amenorrhea (primary and secondary) and abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as submucous fibroids or uterine cancer, as a test for endogenous estrogen production and for the production of secretory endometrium and desquamation.
II. It should be noted that the RLD Delalutin has been discontinued and removed from the U.S. market in 2010. The U.S. Food and Drug Administration (FDA) noted in their approval letter for the generic equivalent that because the RLD Delalutin as not withdrawn from sale for reasons of safety or effectiveness, it allowed the agency to continue to approve applications that refer to Delalutin. The FDA concluded that adequate information had been presented to demonstrate hydroxyprogesterone caproate is safe and effective for use as recommended in the submitted labeling (noted above) and was subsequently approved.

III. As of June 2023, there is only one hydroxyprogesterone caproate generic that is marketed in the U.S.; this product is manufactured by McGuff Pharmaceuticals for Mylan Institutional Inc.

Not Medically Necessary Uses

I. Hydroxyprogesterone caproate has not demonstrated sufficient safety and efficacy for the conditions or settings listed below:
   A. Reducing the risk of recurrent preterm birth
      i. As of April 6, 2023, the FDA announced their final decision to withdraw approval of Makena from the U.S. market, indicating that Makena and its generics (hydroxyprogesterone caproate) are no longer approved and cannot lawfully be distributed in interstate commerce. This decision was issued jointly by the FDA Commissioner and Chief Scientist after finding that there is an insufficient demonstration of effectiveness to balance any level of risk.
      ii. Hydroxyprogesterone caproate (Makena) was initially approved via the accelerated approval pathway based on the data from the NICHD-MFMU Network trial. The NICHD-MFMU Network trial was acquired by a pharmaceutical company (Adeza, Sunnyvale, CA) and submitted as part of a new drug application (NDA) to the Food and Drug Administration (FDA) in April 2006. In August 2006, an FDA Advisory Committee voted unanimously that an additional confirmatory clinical trial was required to further assess safety and efficacy.
      iii. Based on the FDA ruling, the NDA sponsor initiated the confirmatory clinical trial (PROLONG), enrolling 5% of the overall subjects prior to FDA approval. The study was designed to have the power to show a direct clinical benefit (i.e., a reduction in a prespecified neonatal morbidity and mortality index).
      iv. PROLONG is a Phase 3B, randomized double-blind parallel group study with a 2:1 ratio of active drug: vehicle, assigned randomly by a global telephone-based interactive registration system. Key inclusion criteria: at least 18 years of age, pregnant with a singleton gestation, documented history (chart notations from previous pregnancy and not just oral history) of singleton spontaneous preterm birth (PTB) between 200/7 and 366/7 weeks, after spontaneous PTB, or premature rupture of membranes. The primary safety outcome was fetal/early infant death defined as any of the following: spontaneous abortion/miscarriage (delivery from 160/7–196/7 weeks of gestation), stillbirth delivering after 200/7 weeks through term, or early infant death. The results of the PROLONG trial: fetal/early infant death rates were lower than expected and not different between treatment groups (17-OHPC 1.7% vs. placebo 1.9%; RR 0.87 [95% CI: 0.4–1.81]). No statistically significant difference in the frequency of stillbirth (17-OHPC 1.1% vs placebo 0.5%; RR 2.07 [95% CI 0.59–7.29])

v. On October 5, 2020, The Center for Drug Evaluation and Research (CDER) proposed withdrawing accelerated approval of Makena (hydroxyprogesterone caproate) on the grounds that the confirmatory study failed to verify clinical benefit of the drug and the evidence does not establish that the drug is effective under its conditions of use. A hearing took place in October 2022 where the advisory committee discussed and voted on whether the findings from PROLONG verify the clinical benefit of Makena and if the available evidence demonstrates that Makena is effective for its approved indication. The advisory committee voted unanimously that the PROLONG trial does not verify the clinical benefit of Makena, and 13 advisory committee members voted that the available evidence does not demonstrate that Makena is effective for its approved indication, with one member voting 'yes' and one member 'abstained'. Finally, 14 advisory committee members voted that Makena should not remain on the market while an appropriate confirmatory study is designed and conducted, while one member voted 'yes'. Most advisory committee members agreed during discussion that there was not sufficient evidence that Makena is effective in any population.

vi. Given the lack of efficacy for reducing the risk of preterm birth and the subsequent decision by the FDA to withdraw the indication, treatment with hydroxyprogesterone caproate for risk reduction in recurrent preterm birth is not medically necessary.

References

1. Hydroxyprogesterone caproate [Prescribing Information]. Morgantown, WV: Mylan Institutional LLC. November 2021.
2. Food and Drug Administration, HHS. Final Decision on Withdrawal of Makena (hydroxyprogesterone caproate) and Eight Abbreviated New Drug Applications Following Public Hearing; Availability of Final Decision. Federal Register. 2023;88(93), 30986-87. Available at: https://www.regulations.gov/document/FDA-2020-N-2029-0386.
3. Food and Drug Administration. Memorandum; Termination of Separation of Functions and Process for Issuing a Final Decision; Makena. Updated April 5, 2023. Available at: https://www.regulations.gov/document/FDA-2020-N-2029-0384.
4. Food and Drug Administration. Final Decision on the Proposal to Withdraw Approval of Makena. Updated April 5, 2023. Available at: https://www.regulations.gov/document/FDA-2020-N-2029-0385.
5. Food and Drug Administration. FDA Commissioner and Chief Scientist Announce Decision to Withdraw Approval of Makena. Fda.gov. April 6, 2023. Accessed May 15, 2023. https://www.fda.gov/news-events/press-announcements/fda-commissioner-and-chief-scientist-announce-decision-withdraw-approval-makena.
6. Blackwell SC, Gyamfi-Bannerman C, Biggio JR Jr, et al. PROLONG Clinical Study Protocol: Hydroxyprogesterone Caproate to Reduce Recurrent Preterm Birth. Am J Perinatol. 2018;35(12):1228–1234. doi:10.1055/s-0038-1642062
7. Blackwell SC, Gyamfi-Bannerman C, Biggio JR Jr, et al. 17-OHPC to Prevent Recurrent Preterm Birth in Singleton Gestations (PROLONG Study): A Multicenter, International, Randomized Double-Blind Trial [published online ahead of print, 2019 Oct 25]. Am J Perinatol. 2019;10.1055/s-0039-3400227. doi:10.1055/s-0039-3400227

8. Meis PJ, Klebanoff M, Thom E, et al; National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. N Engl J Med 2003;348 (24):2379–2385

Policy Implementation/Update:

Action and Summary of Changes	Date
Criteria for medical necessity of hydroxyprogesterone caproate (Makena) removed; use of hydroxyprogesterone caproate (Makena) for reducing risk of recurrent preterm birth moved to not medically necessary section; criteria added for medical necessity of hydroxyprogesterone caproate (therapeutic equivalent of Delalutin); supporting evidence updated	06/2023
Policy created	02/2020