hydroxyprogesterone caproate (Makena®)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO175

Description

Hydroxyprogesterone caproate (Makena) is an injectable synthetic progestin with unknown mechanism in reducing the risk of recurrent preterm birth.

Length of Authorization

- Initial: Five or six months depending on gestational age of therapy initiation
- Renewal: no renewal

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
hydroxyprogesterone caproate (Makena, hydroxyprogesterone caproate)	Intramuscular solution: 250 mg/mL, 1250 mg/5mL Subcutaneous auto-injector: 275 mg/1.1mL	Preterm birth	Intramuscular solution: 250 mg/mL (5 vials/28 days), 1250 mg/5 mL (1 vial/28 days) Subcutaneous auto-injector*: 4 auto-injectors/28 days

Initial Evaluation

I. Hydroxyprogesterone caproate (Makena) may be considered medically necessary when the following criteria are met:
   A. Member is 16 years of age or older; **AND**
   B. A diagnosis of **preterm birth** when the following are met:
      1. Member has a singleton pregnancy; **AND**
      2. Ultrasound confirming gestational age between 16 weeks, 0 days and 20 weeks, 6 days; **AND**
      3. Member will start dose **AT** as early as 16 weeks, 0 days of gestation; **AND**
      4. Member has a history of singleton spontaneous preterm birth or singleton premature rupture of membranes at less than 37 weeks of gestation; **AND**
   C. The request is for generic hydroxyprogesterone caproate vials; **OR**
      1. Documentation of treatment with generic hydroxyprogesterone caproate vial has been ineffective, contraindicated, or not tolerated; **AND**
   D. Provider attest that member's pharmacy benefit will be billed.

II. Hydroxyprogesterone caproate (Makena) is considered not medically necessary when criteria above are not met and/or when used for:
   A. Multifetal gestation
   B. Major fetal anomalies
   C. Maternal complications (current or planned cerclage, hypertension requiring medication, or seizure disorder)
   D. Uterine anomalies
   E. Pediatric population (< 16 years of age)
   F. Therapy initiated after 21 weeks of gestation
   G. Breast cancer
   H. Adenocarcinoma of uterus
   I. Amenorrhea
   J. Endometrial disorder (production of secretory endometrium and desquamation)

Supporting Evidence

I. Hydroxyprogesterone caproate (Makena) was initially approved 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. An FDA Advisory Committee in August 2006 voted unanimously that an additional confirmatory clinical trial was required to further assess safety and efficacy.

II. 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).

III. 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. The inclusion criteria was: at least 18 years of age, pregnant with a singleton gestation, has a documented history (chart notations from previous pregnancy and not just oral history) of singleton spontaneous 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%; RR¼0.87 [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])

IV. In a clinical trial, the effectiveness of 17 alpha -hydroxyprogesterone caproate (17P) was demonstrated in patients as young as 16 years of age. Treatment with 17P significantly reduced the risk of delivery at less than 37 weeks of gestation (incidence, 36.3 percent in the progesterone group vs. 54.9 percent in the placebo group; relative risk, 0.66 [95 percent confidence interval, 0.54 to 0.81]), delivery at less than 35 weeks of gestation (incidence, 20.6 percent vs. 30.7 percent; relative risk, 0.67 [95 percent confidence interval, 0.48 to 0.93]), and delivery at less than 32 weeks of gestation (11.4 percent vs. 19.6 percent; relative risk, 0.58 [95 percent confidence interval, 0.37 to 0.91]).

V. In order to assess for medical versus pharmacy billing, the criterion for provider attestation that member's pharmacy benefit will be billed. Since we do not carry member's medical benefit, this criterion is to ensure that the provider will not be double billing, medical and pharmacy.

Not Medically Necessary Uses

I. Hydroxyprogesterone caproate (Makena) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. There is limited clinical evidence to suggest that hydroxyprogesterone caproate (Makena) is safe and efficacious in the setting of: multifetal gestation, major fetal anomalies, maternal complications (current or planned cerclage, hypertension requiring medication, or seizure disorder), uterine anomalies, pediatric population (< 16 years of age), and therapy initiated after 21 weeks of gestation
   B. Although there may be a role for generic hydroxyprogesterone caproate in the setting of breast cancer, adenocarcinoma of uterus, amenorrhea and endometrial disorder (production of secretory endometrium and desquamation); for the purpose of this hydroxyprogesterone caproate (Makena) policy, only the indication of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth/premature rupture of membranes at less than 37 weeks would be considered medically necessary.

References

1. Makena [Prescribing Information]. Waltham, MA: AMAG Pharmaceuticals, Inc. February 2018.
2. 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
3. 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

4. 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
Policy created	02/2020