Medical Drug Clinical Criteria

Subject:	Injectable Hydroxyprogesterone for Prevention of Preterm Birth		
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Overview

This document addresses the use of Makena (17 alpha-hydroxyprogesterone caproate) subcutaneous and intramuscular injections as well as compounded 17 alpha-hydroxyprogesterone for prevention of preterm birth.

Preterm labor and delivery is a major cause of neonatal morbidity and mortality; in the United States the rate of preterm delivery (PTD) is 9.85% in 2016 (Centers for Disease Control and Prevention [CDC], 2018). In the past, intramuscular injections (IM) of 17 alpha-hydroxyprogesterone, (that is, Delalutin) were used to prevent the onset of premature labor. However, the progesterone agents were thought to have teratogenic properties, and the Food and Drug Administration (FDA) gave the drug a Category D pregnancy status meaning studies had demonstrated fetal risk, but use of the drug may outweigh the potential benefits. Delalutin is no longer on the market but a generic was approved and is currently available on the market.

Research interest was renewed in 17 alpha-hydroxyprogesterone caproate (17P) during the second trimester when the teratogenic risk is minimized. 17P is a weakly acting, naturally occurring, progesterone metabolite, which, when coupled with caproate dextran, works as a long-acting progestin. 17P is administered by IM or subcutaneous injection.

Use of 17 alpha-hydroxyprogesterone caproate are recommended by both The American College of Obstetrics and Gynecology (ACOG) and the Society for Maternal-Fetal Medicine (SMFM) in women with a single gestation and history of prior spontaneous preterm birth between 20 and 36 weeks 6 days gestation. Weekly injections starting between 16 and 20 weeks of gestation until 36 weeks of gestation or delivery. (ACOG 2012, SMFM 2012, SMFM 2017)

The completion of the PROLONG study provided the results of a required post-marketing trial to determine efficacy of 17P in prevention of preterm birth. In the study population in the PROLONG trial, 17P did not decrease the risk of recurrent preterm birth. (Blackwell 2020) As a result of this trial, the FDA advisory committee in 2019 voted 9-7 to recommend the FDA pursue withdrawal of approval of 17P for prevention of preterm birth. ACOG and SMFM released statements shortly thereafter supporting continued use of 17P. ACOG indicated that their current guidance will remain in effect and indicated that the PROLONG authors suggested that the study was underpowered to assess treatment efficacy and that due to previous treatment guidelines, there may have been unintentional selection bias. (ACOG 2019) SMFM advised that they believe the differences in the PROLONG study and the Meis, et al trial used for approval may be partially explained by differences in study population. According to SMFM, the use of 17P may still be appropriate in women with a profile more representative of the very high risk population reported in the Meis trial and use in all women at risk of recurrent spontaneous preterm birth should be done after incorporating the risk/benefit and taking into account the lack of short-term safety concerns but uncertainty regarding benefit. (SMFM 2020) On 10/5/2020, the FDA Center for Drug Evaluation and Research (CDER) proposed that Makena and generics be removed from the market because the postmarket study failed to verify clinical benefit. Per the FDA:

> In the interim, we recommend that health care professionals discuss Makena's benefits, risks and uncertainties with their patients to decide whether to use Makena while a final decision is being made about the drug's marketing status. We intend to hold a meeting with experts in obstetrics, neonatal care, and clinical trial design to discuss how to facilitate development of effective and safe therapies to treat preterm birth.(FDA 10/5/2020)

Clinical Criteria

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

17 alpha-hydroxyprogesterone caproate Injection for the prevention of preterm birth

Requests for weekly 17 alpha-hydroxyprogesterone caproate injection for the prevention of preterm birth may be approved if the following criteria are met:

I. Individual is between 16 weeks, 0 days and 36 weeks, 6 days of gestation; **AND**
II. Therapy is initiated between 16 weeks, 0 days and 20 weeks, 6 days of gestation; **AND**
III. Individual has a singleton pregnancy; **AND**
IV. Individual has absence of preterm labor within the current pregnancy; **AND**
V. Individual has a prior history of a preterm singleton delivery before 37 weeks gestation due to either of the following:
    A. Spontaneous preterm labor; **OR**
    B. Premature rupture of membranes.

Requests for Makena (17 alpha-hydroxyprogesterone caproate) Injection may not be approved for the following criteria:

I. All other indications not included above; **OR**
II. Individual has other risk factors for preterm *in the current pregnancy*, including, but not limited to the following:
    A. Multiple gestation pregnancy; **OR**
    B. Cervical cerclage; **OR**
    C. A uterine anomaly; **OR**
    D. Positive tests for cervicovaginal fetal fibronectin; **OR**
    E. Preterm labor.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT

96372	Therapeutic, prophylactic, or diagnostic injection; subcutaneous or intramuscular

HCPCS

J1726	Injection, hydroxyprogesterone caproate, (Makena), 10 mg
J1729	Injection, hydroxyprogesterone caproate, not otherwise specified, 10 mg

ICD-10 Diagnosis

Z33.3	Pregnant State
Z3A.16-Z3A.36	Weeks of gestation 16 TO 36 weeks
O09.211-O09.219	Supervision of pregnancy with history of pre-term labor [includes codes O09.211, O09.212, O09.213, O09.219]

Document History

12/12/2022
Document History:

- 12/12/2022 – Annual Review: No changes. Coding reviewed: No changes.
- 12/13/2021 – Annual Review: No change. Coding reviewed: Added HCPCS J1729 back into the policy.
- 11/20/2020 – Annual Review: Minor wording update; Removed may not be approved criteria in home health setting. Coding Reviewed: Added CPT 96372, Removed CPT 99506, Removed HCPCS J1729, J7999, S9560. Removed ICD-10-CM O09.291-O09.299.
- 11/15/2019 – Annual Review: Minor wording and formatting changes. Coding reviewed: Z33.3, Z3A.16-Z3A.36 . Removed wording from coding description on S9560.
- 11/16/2018 – Annual Review: First Review of Progesterone Therapy as a Technique to Prevent Preterm Delivery in High-Risk Women. Separated injectable progesterone (17 alpha-hydroxyprogesterone caproate) and vaginal progesterone into different clinical guidelines. Proposed update to prior authorization to clarify initiation of therapy was to be between 16 weeks, 0 days and 20 weeks, 6 days gestation per label and individual can continue through 36 weeks, 6 days gestation per label; updated to note that individual should have prior history of singleton birth; Proposed new step therapy for Makena subcutaneous injection. Coding Review: No changes.

References

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Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.