Medical Drug Clinical Criteria

Subject:	**Hydroxyprogesterone caproate**		
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Overview

This document addresses the use of hydroxyprogesterone caproate.

Delalutin was indicated for use in non-pregnant women for the treatment of advanced adenocarcinoma, management of amenorrhea, and abnormal uterine bleeding. Initially, Delalutin was approved in 1956 for use in pregnant women for "habitual and threatened abortion". In 1977, the Food and Drug Administration (FDA) determined that studies had shown that the use of sex hormones early in pregnancy may damage the offspring; therefore, labeling for all progestational drug products were to include a contraindication and warning regarding the use of progestational agents during pregnancy. In 1999, FDA revoked its labeling requirements for progestational products, saying that such labeling for all progestogens was not warranted. Delalutin was voluntarily removed from the market due to the availability of other options for its labeled indications. FDA confirmed that Delalutin was not removed from the market due to safety or efficacy reasons. (FDA Federal Register, 2010). The ANDA for Delalutin was approved and hydroxyprogesterone caproate injection came available with the same labeled indications as Delalutin.

The FDA approval for Makena in the prevention of preterm births in those with a singleton pregnancy with a history of previous singleton pregnancy was based on the Meis 2003 study. As a condition of approval the sponsors of Makena were required to perform and submit data from a second confirmatory study. The second study took nine years to complete and publish (Blackwell 2020; PROLONG). The PROLONG study failed to provide evidence to support the use of Makena in the prevention of preterm birth or in the reduction of neonatal morbidity and mortality. April 5, 2023, the Food and Drug Administration (FDA) withdrew the approval for Makena and its generics for reducing the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. Makena and its generics were not shown to be effective for this use and cannot lawfully be distributed in interstate commerce. Additionally, the FDA notes that there are known risks associated with Makena, "based on its lack of effectiveness, no level of risk is justified". The announcement can be found at the following: https://www.fda.gov/news-events/press-announcements/fda-commissioner-and-chief-scientist-announce-decision-withdraw-approval-makena?utm_medium=email&utm_source=govdelivery

Injectable hydroxyprogesterone caproate is also compounded. The FDA states the following regarding whether compounders can use hydroxyprogesterone caproate for patients: " A health care practitioner considering whether to prescribe compounded drug products containing hydroxyprogesterone caproate should be aware of FDA's determination that Makena and its generics are not shown to be effective in reducing the risk of preterm birth in women with a prior spontaneous preterm birth. In addition, as a general matter, we note that compounded drugs, including compounded drugs containing hydroxyprogesterone caproate, do not undergo FDA premarket review for safety, effectiveness, or quality."

Additional information regarding Makena, its generics and the compounded hydroxyprogesterone caproate products can be found under the "Frequently Asked Questions" section of the following site: https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/makena-hydroxyprogesterone-caproate-injection-information#FAQs.

Due to the withdrawal of Makena, this product and its generics will not be covered for new users.

US specialty societies, American College of Obstetricians and Gynecologists (ACOG) and Society for Maternal Fetal Medicine (SMFM), support the withdrawal of Makena and discourage the use of hydroxyprogesterone caproate for

preterm birth. “On April 5, 2023, the US Food and Drug Administration (FDA) withdrew approval of 17-alpha hydroxyprogesterone caproate (17-OHPC), effective immediately, due to lack of evidence that it reduces the risk of recurrent spontaneous preterm birth (PTB). This decision withdraws approval for all formulations of 17-OHPC (both intramuscular and subcutaneous) and applies to both brand name (Makena) and generic versions of the medication. We agree with the FDA determination and discourage continued prescribing of 17-OHPC, including through compounding pharmacies. We do not recommend changing indications for cerclage, indications for vaginal progesterone in patients with short cervix, or recommendations against activity restriction based on the FDA withdrawal of 17-OHPC from the market. We recommend that discussion of the use of vaginal progesterone for primary prevention of recurrent PTB without input of cervical length or in those with a cervical length of 25 mm or greater include a shared decision-making process, especially if a progesterone formulation for PTB prevention was received in a prior pregnancy. The FDA determined that it would be inappropriate to delay the effective date of the withdrawal to allow patients currently receiving 17-OHPC to finish treatment. We agree with the FDA that there is no evidence of benefit with continued treatment. Patients currently receiving 17-OHPC can be counseled that the FDA’s Center for Drug Evaluation and Research (CDER) has not identified evidence of harm from discontinuation prior to 37 weeks of gestation.”

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.

Hydroxyprogesterone Caproate Injection

Requests for 17-hydroxyprogesterone caproate may be approved when the following criteria are met:

I. Individual is a non-pregnant woman; AND
II. Individual is using for one of the following:
    A. The treatment of advanced adenocarcinoma of the uterine corpus (Stage III or IV); OR
    B. 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); OR
    C. As a test for endogenous estrogen production and for the production of secretory endometrium and desquamation.

Requests for hydroxyprogesterone caproate may not be approved for the following:

I. For prevention of pre-term delivery or any subgroup of this population; OR
II. Hydroxyprogesterone caproate may not be approved when the above criteria are not met and for all other indications.

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.

HCPCS	
J1729	Injection, hydroxyprogesterone caproate, not otherwise specified, 10mg

ICD-10 Diagnosis	
N91.0	Primary Amenorrhea
N91.1	Secondary Amenorrhea
C54.9	Malignant neoplasm of corpus uteri, unspecified
D25.0	Submucous leomyoma of uterus
C55	Malignant neoplasm of the uterus, part unspecified

Document History

New: 05/10/2023
Document History:

- **05/10/2023 – Add new clinical criteria document for Hydroxyprogesterone caproate. Coding Reviewed: Added HCPCS J1729, ICD-10: N91.0, N91.1, C54.9, D25.0, C55.**

References

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3. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc. Updated periodically.
4. American College of Obstetricians and Gynecologists (ACOG) Practice Advisory. Updated Clinical Guidance for the Use of Progesterone Supplementation for the Prevention of Recurrent Preterm Birth. Available at https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2023/04/updated-guidance-use-of-progesterone-supplementation-for-prevention-of-recurrent-preterm-birth. Accessed April 12, 2023
5. Determination That DELALUTIN (hydroxyprogesterone caproate) Injection, 125 Milligrams/Milliliter and 250 Milligrams/Milliliter, Was Not Withdrawn From Sale for Reasons of Safety or Effectiveness. Department of Health and Human Services, Food and Drug Administration. Docket No. FDA-2006-P-0089 (formerly Docket No. 2006P-0144). Available from: https://www.gpo.gov/fdsys/pkg/FR-2010-06-25/pdf/2010-15416.pdf. Accessed April 11, 2023.
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9. SMFM Special Statement: Response to the Food and Drug Administration's withdrawal of 17-alpha hydroxyprogesterone caproate. Available at https://www.smfm.org/publications/467-smfm-special-statement-response-to-the-food-and-drug-administrations-withdrawal-of-17-alpha-hydroxyprogesterone-caproate. Accessed April 12, 2023.

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.