09-J1000-33

Original Effective Date: 05/15/11

Reviewed: 06/14/23

Revised: 07/15/23

Subject: Hydroxyprogesterone Caproate

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Progesterone is a progestinic hormone secreted mainly from the corpus luteum of the ovary during the latter half of the menstrual cycle. Progesterone is formed from steroid precursors in the ovary, testis, adrenal cortex, and placenta. Luteinizing hormone (LH) stimulates the synthesis and secretion of progesterone from the corpus luteum. Progesterone is necessary for nidation (implantation) of the ovum and for maintenance of pregnancy. Although the hormone is secreted mainly during the luteal phase of the menstrual cycle, small amounts of progesterone are also secreted during the follicular phase. High concentrations of the hormone are secreted during the latter part of pregnancy. Amounts comparable to those secreted in women during the follicular phase have been shown to be secreted in males.

Progesterone shares the pharmacologic actions of the progestins. In women with adequate endogenous estrogen, progesterone transforms a proliferative endometrium into a secretory one. The abrupt decline in the secretion of progesterone at the end of the menstrual cycle is principally responsible for the onset of menstruation. Progesterone also stimulates the growth of mammary alveolar tissue and relaxes uterine smooth muscle. Progesterone has minimal estrogenic and androgenic activity.

Hydroxyprogesterone Caproate Injection is indicated in non-pregnant 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.

Hydroxyprogesterone caproate (Makena®) was previously FDA approved via an accelerated approval pathway (requiring confirmatory clinical trials) to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. The FDA withdrew the

approval of Makena due to lack of efficacy in a confirmatory trial that was nearly four times larger than the trial that supported the initial approval. The trial did not show improvement in the health of the babies born to mothers who were treated with Makena and failed to show a reduction in risk of preterm birth. For more information see the following information provided by the FDA: Makena (hydroxyprogesterone caproate injection) Information | FDA.

POSITION STATEMENT:

I. Hydroxyprogesterone caproate injection (generic for Delalutin), **meets the definition of medical necessity** when the dose does not exceed the FDA labeled dosing for **ONE** of the following indications:

   a. Advanced adenocarcinoma of the uterine corpus (Stage III or IV)

   b. Amenorrhea (primary or secondary)

   c. Abnormal uterine bleeding in the absence of organic pathology

   d. As a test for endogenous estrogen production

   e. For production of secretory endometrium and desquamation

II. Hydroxyprogesterone caproate injection is **does not meet the definition of medical necessity** for the following conditions due to the lack of clinical data to support the effects of better health outcomes:

   - To reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth

Approval duration: 180 days

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

Hydroxyprogesterone Caproate Injection (generic for Delalutin): see prescribing information for indication specific dosing

PRECAUTIONS:

Contraindications

- Current thrombosis or thromboembolic disorders or history of these conditions
- Known or suspected breast cancer, other hormone-sensitive cancer, or history of these conditions
- Undiagnosed abnormal vaginal bleeding
- Cholestatic jaundice of pregnancy
- Liver tumors (benign or malignant) or active liver disease

- Uncontrolled hypertension
- Hypersensitivity to the medication
- Use as a diagnostic test for pregnancy

Warnings:

- **Thromboembolic disorders:** Hydroxyprogesterone caproate should be discontinued if an arterial or deep venous thrombotic or thromboembolic event occurs.
- **Sensitivity Reactions:** Allergic reactions, including urticaria, pruritus, and angioedema, have been reported with hydroxyprogesterone caproate and other products containing castor oil. Discontinuance of hydroxyprogesterone caproate should be considered if such reactions occur.
- **Decreased Glucose Tolerance:** Decreased glucose tolerance has been observed in some persons receiving progestin therapy. Members with prediabetes or diabetes should be carefully monitored during hydroxyprogesterone caproate therapy.
- **Fluid Retention:** Because progestational agents may cause some degree of fluid retention, members with conditions that may be aggravated by fluid retention (e.g., preeclampsia, epilepsy, migraine, asthma, cardiac or renal dysfunction) should be carefully monitored.
- **Depression:** Members with a history of clinical depression should be monitored during therapy with hydroxyprogesterone caproate. Hydroxyprogesterone caproate should be discontinued if clinical depression recurs.
- **Jaundice**: Monitor women who develop jaundice and consider if the benefit of use warrants continuation.
- **Hypertension:** Monitor women who develop hypertension and consider if the benefit of use warrants continuation.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding, Hydroxyprogesterone Caproate Injection

J3490	Unclassified drugs [for compounded hydroxyprogesterone caproate ONLY]
J1729	Injection, hydroxyprogesterone caproate, not otherwise specified, 10 mg

ICD-10 Diagnosis Codes That Support Medical Necessity, Hydroxyprogesterone caproate injection in non-pregnant members (J1729 only)

C54.0 – C54.9	Neoplasm of uterine corpus
N91.0	Primary amenorrhea
N91.1	Secondary amenorrhea
N91.2	Amenorrhea, unspecified

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage Products: No National Coverage Determination (NCD) or Local Coverage Determination (LCD) was found at the time of the last guideline revised date.

DEFINITIONS:

Singleton: a person that is not a twin or other multiple births.

RELATED GUIDELINES:

Unclassified Codes and Compounded Drug Products, 09-J0000-58

OTHER:

None applicable.

REFERENCES:

1. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.;2023. URL www.clinicalpharmacilogy-ip.com. Accessed 5/25/23.
2. Committee on Practice Bulletins - Obstetrics, The American College of Obstetricians and Gynecologists. Practice bulletin no. 130: prediction and prevention of preterm birth. Obstet Gynecol. 2012 Oct;120(4):964-73.
3. da Fonseca EB, Bittar RE, Carvalho MH, et al. Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: a randomized placebo-controlled double-blind study. Am J Obstet Gynecol. 2003; 188(2):419-424.
4. Dodd JM, Jones L, Flenady V, et al. Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth. Cochrane Database Syst Rev. 2013 Jul 31;7:CD004947. doi: 10.1002/14651858.CD004947.pub3.
5. Makena (hydroxyprogesterone caproate injection) Information | FDA website. Accessed April 27, 2023.
6. Hydroxyprogesterone caproate. In: McEvoy GK, editor. AHFS drug information 2017 [monograph on the Internet]. Bethesda (MD): American Society of Health-System Pharmacists; 2017 [cited 2017 March 21]. Available from: http://online.statref.com. Subscription required to view.
7. Hydroxyprogesterone caproate [package insert]. ANI Pharmaceuticals. Baudette, MN: February 2018.
8. Information Update on 17a-Hydroxyprogesterone Caproate (17P) from The American College of Obstetricians and Gynecologists and The Society for Maternal-Fetal Medicine. October 13, 2011. Accessed March 17, 2015, at: http://www.acog.org/-/media/Announcements/20111013MakenaLtr.pdf?dmc=1&ts=20150317T0901361042.
9. Makena (hydroxyprogesterone caproate) [package insert]. Lumara Health. Chesterfield (MO): December 2022.

10. Meis PJ, Klebanoff M, Thom E et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. N Engl J Med. 2003; 348:2379-85.
11. Micromedex Healthcare Series [Internet Database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed 5/25/23.
12. Northen AT, Norman GS, Anderson K et al. Follow-up of children exposed in utero to 17 alpha-hydroxyprogesterone caproate compared with placebo. Obstet Gynecol. 2007; 110:865-72.
13. Society for Maternal-Fetal Medicine Publications Committee, with assistance of Vincenzo Berghella. Progesterone and preterm birth prevention: translating clinical trials data into clinical practice. Am J Obstet Gynecol. 2012 May;206(5):376-86. doi: 10.1016/j.ajog.2012.03.010.
14. Society for Maternal-Fetal Medicine 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

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Medical Policy and Coverage Committee on 06/14/23.

GUIDELINE UPDATE INFORMATION:

05/15/11	New Medical Coverage Guideline.
07/01/11	Revision to guideline; consisting of updating coding.
01/01/12	Revision to guideline; consisting of updating coding.
05/15/12	Review and revision to guideline; consisting of updating references.
05/15/13	Review and revision to guideline; consisting of updating description section, position statement, coding, references and exceptions.
05/15/14	Review and revision to guideline; consisting of reformatting the position statement and updating precautions and references.
05/15/15	Review and revision to guideline; consisting of updating description, updating and reformatting the position statement, reformatting and updating coding, and adding and updating references.
07/01/15	Revision to guideline; consisting of updating coding.
11/01/15	Revision: ICD-9 Codes deleted.
01/01/16	Annual HCPCS coding update: added code J7999 and deleted code Q9977.
05/15/16	Review and revision to guideline; consisting of updating position statement, warnings, and references.
01/15/17	Revision to guideline consisting of updating position statement.
02/15/17	Review and revision to guideline; consisting of updating position statement, dosing, precautions, coding and references.
05/15/17	Review and revision to guideline; consisting of updating references.
07/01/17	Addition of HCPCS codes Q9985 and Q9986 that replaces HCPCS code J1725.
01/01/18	Annual HCPCS coding update: added HCPCS codes J1726 and J1729, and deleted codes Q9985 and Q9986.
05/15/18	Review and revision to guideline; consisting of updating position statement, coding and references.

07/15/19	Review and revision to guideline; consisting of updating position statement and references.
07/15/23	Removal of indication to reduce the risk of preterm birth following FDA withdrawal of Makena.