17-Alpha-Hydroxyprogesterone Caproate (Makena® and 17P)

Policy Number: CS2022D0040V
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Instructions for Use

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Commercial Policy

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Application

This Medical Benefit Drug Policy does not apply to the states listed below; refer to the state-specific policy/guideline, if noted:

State	Policy/Guideline
Florida	Refer to the state's Medicaid clinical policy
Indiana	Refer to the state's Medicaid clinical policy
Kansas	Refer to the state's Medicaid clinical policy
Louisiana	Refer to the state's Medicaid clinical policy
North Carolina	None
Pennsylvania	Refer to the state's Medicaid clinical policy
Texas	Refer to the state's Medicaid clinical policy
Washington	Refer to the state's Medicaid clinical policy

Coverage Rationale

This policy provides coverage information about the use of injectable (both intramuscular and subcutaneous) 17-alpha-hydroxyprogesterone caproate, commonly called 17P. It may also be referred to as 17-OHP, 17-OHPC, 17Pc, Makena®, 17-alpha hydroxyprogesterone, hydroxyprogesterone, hydroxy-progesterone, and hydroxy progesterone. Hereafter, it will be referred to as 17P.

Note: Oral and intravaginal formulations of progesterone are not addressed in this policy and should be obtained through the member's pharmacy benefit.

Intramuscular and subcutaneous injection of 17P is proven and medically necessary for prevention of spontaneous preterm birth when all of the following criteria are met:

- Current singleton pregnancy; and
- History of a prior spontaneous preterm birth of a singleton pregnancy; and

- Treatment is initiated between 16 weeks, 0 days of gestation and 20 weeks, 6 days of gestation; and
- Administration is to continue weekly until week 37 (through 36 weeks, 6 days) of gestation or delivery, whichever occurs first

Intramuscular and subcutaneous injection of 17P is unproven and not medically necessary for:
- Prevention of spontaneous preterm birth with any of the following:
  - Short cervix with or without cerclage and no prior preterm birth
  - Current multi-fetal pregnancy (twins or greater)
  - Previous medically indicated preterm birth
- Initiation of 17P after 20 weeks, 6 days of gestation

Although there are ongoing clinical trials to broaden the indications for the use of 17P, at this time uses as indicated above are considered unproven.

Additional Information Regarding Compounded 17P

The active ingredient in the compounded 17P and Makena is hydroxyprogesterone caproate. Both have castor oil as an inactive ingredient. The compounded version can be made with an alternate oil base in the event of patient hypersensitivity to castor oil. Makena has the additional inactive ingredients of benzyl benzoate (1 ml and 5 ml vials) and benzyl alcohol (a preservative, in the 5 ml vial only). Based on the active ingredient, compounded preservative-free 17P is considered clinically interchangeable with Makena.

Compounding pharmacies must comply with United States Pharmacopeia (USP) Chapter 797, which sets standards for the compounding, transportation, and storage of compounded sterile products (CSP).[1] The Pharmacy Compounding Accreditation Board will verify that the pharmacy is adhering to these standards.[2]

Note: The FDA has stated that approved drug products provide a greater assurance of safety and effectiveness than do compounded products. Refer to the U.S. Food and Drug Administration (FDA) section of this policy for additional information.

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by federal, state, or contractual requirements and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS Code	Description
J1726	Injection, hydroxyprogesterone caproate, (Makena), 10 mg
J1729	Injection, hydroxyprogesterone caproate, not otherwise specified, 10 mg
J2675	Injection, progesterone, per 50 mg

Diagnosis Code	Description
O09.211	Supervision of pregnancy with history of pre-term labor, first trimester
O09.212	Supervision of pregnancy with history of pre-term labor, second trimester
O09.213	Supervision of pregnancy with history of pre-term labor, third trimester
O09.219	Supervision of pregnancy with history of pre-term labor, unspecified trimester
O20.0	Threatened abortion
O20.8	Other hemorrhage in early pregnancy
O20.9	Hemorrhage in early pregnancy, unspecified
O47.00	False labor before 37 completed weeks of gestation, unspecified trimester
O47.02	False labor before 37 completed weeks of gestation, second trimester

Diagnosis Code	Description
O47.03	False labor before 37 completed weeks of gestation, third trimester
O47.1	False labor at or after 37 completed weeks of gestation
O47.9	False labor, unspecified
O60.00	Preterm labor without delivery, unspecified trimester
O60.02	Preterm labor without delivery, second trimester
O60.03	Preterm labor without delivery, third trimester
O60.10X0	Preterm labor with preterm delivery, unspecified trimester, not applicable or unspecified
O60.12X0	Preterm labor second trimester with preterm delivery second trimester, not applicable or unspecified
O60.13X0	Preterm labor second trimester with preterm delivery third trimester, not applicable or unspecified
O60.14X0	Preterm labor third trimester with preterm delivery third trimester, not applicable or unspecified
O60.20X0	Term delivery with preterm labor, unspecified trimester, not applicable or unspecified
O60.22X0	Term delivery with preterm labor, second trimester, not applicable or unspecified
O60.23X0	Term delivery with preterm labor, third trimester, not applicable or unspecified
Z3A.16	16 weeks gestation of pregnancy
Z3A.17	17 weeks gestation of pregnancy
Z3A.18	18 weeks gestation of pregnancy
Z3A.19	19 weeks gestation of pregnancy
Z3A.20	20 weeks gestation of pregnancy
Z3A.21	21 weeks gestation of pregnancy
Z3A.22	22 weeks gestation of pregnancy
Z3A.23	23 weeks gestation of pregnancy
Z3A.24	24 weeks gestation of pregnancy
Z3A.25	25 weeks gestation of pregnancy
Z3A.26	26 weeks gestation of pregnancy
Z3A.27	27 weeks gestation of pregnancy
Z3A.28	28 weeks gestation of pregnancy
Z3A.29	29 weeks gestation of pregnancy
Z3A.30	30 weeks gestation of pregnancy
Z3A.31	31 weeks gestation of pregnancy
Z3A.32	32 weeks gestation of pregnancy
Z3A.33	33 weeks gestation of pregnancy
Z3A.34	34 weeks gestation of pregnancy
Z3A.35	35 weeks gestation of pregnancy
Z3A.36	36 weeks gestation of pregnancy
Z87.51	Personal history of pre-term labor

Background

Preterm birth is defined as the birth of an infant between 20 weeks, 0 days and 36 weeks, 6 days of gestation. Deliveries that are early by five weeks or more are the leading cause of infant morbidity and mortality in the United States. Progesterone is known to have an inhibitory effect on uterine contractility and is thought to play a key role in the maintenance of pregnancy until term. Progesterone is administered during pregnancy either vaginally (suppository) or intramuscularly (injection) beginning in the second trimester of pregnancy in asymptomatic women at high risk of spontaneous preterm delivery. Asymptomatic women can be considered high risk due to various risk factors, including previous preterm delivery, preterm labor, multiple pregnancy,

or short cervix. The objective of progesterone administration is to prevent preterm birth, prolong gestation, and avoid associated infant mortality and morbidity.[5,11]

Clinical Evidence

Proven

Singleton Pregnancy

Saccone et al. (2015) conducted a metanalysis of electronic databases (1966 through July 2014) to assess the efficacy of maintenance tocolysis with 17-alpha-hydroxyprogesterone caproate (17P) compared to control (either placebo or no treatment) in singleton gestations with arrested preterm labor (PTL).[4] Primary outcome was preterm birth (PTB) < 37 weeks. Women (n = 426) with a singleton gestation who received 17P maintenance tocolysis for arrested PTL had a similar rate of PTB < 37 weeks [42% vs. 51%; relative risk (RR), 0.78; 95% confidence intervals (CI), 0.50-1.22] and PTB < 34 weeks (25% vs. 34%; RR, 0.60; 95% CI, 0.28-1.12) compared to controls. Women who received 17P had significantly later gestational age at delivery (mean difference, 2.28 weeks; 95% CI, 1.46-13.51), longer latency (mean difference, 8.36 days; 95% CI, 3.20-13.51), and higher birthweight (mean difference, 224.30 g; 95% CI, 70.81-377.74) as compared to controls. Other secondary outcomes were similar for both groups which included incidences of recurrent PTL, neonatal death, admission to neonatal intensive care unit, neonatal respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular hemorrhage, necrotizing enterocolitis, and neonatal sepsis. Intramuscular 17P for maintenance tocolysis is associated with a significant prolongation of pregnancy, and significantly higher birthweight, further research is suggested.

The Evaluating Progestogen for Prevention of Preterm birth International Collaborative (EPPPIC) group (2021) conducted a meta-analysis of randomized trials comparing vaginal progesterone, intramuscular 17- hydroxyprogesterone caproate (17-OHPC), or oral progesterone with control, or with each other, in asymptomatic women at risk of preterm birth.[12] The group identified published and unpublished trials that completed primary data collection before July 30, 2016 (12 months before data collection began) by searching MEDLINE, Embase, CINAHL, the Maternity and Infant Care Database, and relevant trial registers between inception and July 30, 2019. One-stage meta-analyses found that vaginal progesterone (RR 0·78, 95% CI 0·68-0·90) and 17-OHPC (RR 0·83, 95% CI 0·68-1.01) reduced the risk of early preterm birth before 34 weeks in singleton pregnancies compared to control, although, for 17-OHPC the confidence interval just crossed the line of no effect. Some heterogeneity between vaginal progesterone trials was evident (I^2 = 23%, 95% CI 0-59%) but there was less variation for 17-OHPC (I^2 = 0%, 95% CI 0-57%).

Unproven

Multiple Gestations

Intramuscular Administration

Schuit et al. (2015) conducted an individual participant data meta-analysis (IPDMA) to assess the effectiveness of progestogen treatment in the prevention of neonatal morbidity or preterm birth (PTB) in twin pregnancies.[10] Randomized clinical trials (RCTs) of 17-hydroxyprogesterone caproate (17Pc) or vaginally administered natural progesterone, compared with placebo or no treatment were included in the analysis. The primary outcome was a composite of perinatal mortality and severe neonatal morbidity. Thirteen trials included 3,768 women and their 7,536 babies. Researchers found neither 17Pc nor vaginal progesterone reduced the incidence of adverse perinatal outcome (17Pc relative risk, RR 1.1; 95% confidence interval, 95% CI 0.97-1.4, vaginal progesterone RR 0.97; 95% CI 0.77-1.2). Therefore, in unselected women with an uncomplicated twin gestation, treatment with progestogens (intramuscular 17Pc or vaginal natural progesterone) does not improve perinatal outcome.

Awwad et al. (2015) conducted a randomized, controlled, double-blind trial to assess whether alpha-hydroxyprogesterone caproate (17-OHPC) prolongs gestation beyond 37 weeks (primary outcome) and reduces neonatal morbidity (secondary outcome) in twin pregnancy (PROGESTWIN).[3] Pregnant women received weekly injections of 250 mg 17-OHPC (n = 194) or placebo (n = 94), from 16-20 to 36 weeks of gestation. Intramuscular 17-OHPC therapy did not reduce PTB before 37 weeks of gestation in unselected twin pregnancies. However, 17-OHPC treatment reduced neonatal morbidity parameters and increased birthweight.

Short Cervix

Winer et al. (2015) conducted an open-label, multicenter, randomized controlled trial in 105 women with asymptomatic singleton pregnancies from 20 (+0) through 31 (+6) weeks of gestation with a cervical length less than 25 mm and a history of preterm delivery or cervical surgery or uterine malformation or prenatal diethylstilbestrol (DES) exposure.[9] Randomization assigned them to receive (or not) 500 mg of intramuscular 17 alpha-hydroxyprogesterone caproate (17-OHPC) weekly until 36 weeks. The primary outcome was time from randomization to delivery. After an interim analysis demonstrated the lack of efficacy of 17-OHPC in prolonging pregnancy, the study was discontinued because of futility. 17-OHPC did not prolong pregnancy in women with singleton gestations, a sonographic short cervix, and other risk factors of preterm delivery (prior history, uterine malformations, cervical surgery, or prenatal DES exposure).

Professional Societies

American College of Obstetricians and Gynecologists (ACOG)

A 2012 Practice Bulletin (No.130, reaffirmed in 2016) makes the following recommendations based upon good and consistent scientific evidence (Level A):[6]

- A woman with a singleton gestation and a prior spontaneous preterm singleton birth should be offered progesterone supplementation starting at 16-24 weeks of gestation, regardless of transvaginal ultrasound cervical length, to reduce the risk of recurrent spontaneous preterm birth.
- Progesterone treatment does not reduce the incidence of preterm birth in women with twin or triplet gestations and, therefore, is not recommended as an intervention to prevent preterm birth in women with multiple gestations.

In 2016, ACOG published an additional practice bulletin (No. 169) regarding multifetal gestations that included the following statement on progesterone therapy:[7]

- Progesterone treatment does not reduce the incidence of spontaneous preterm birth in unselected women with twin or triplet gestations and, therefore, is not recommended.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Makena is a progestin indicated to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. The effectiveness of Makena is based on improvement in the proportion of women who delivered < 37 weeks of gestation. There are no controlled trials demonstrating a direct clinical benefit, such as improvement in neonatal mortality and morbidity. While there are many risk factors for preterm birth, safety and efficacy of Makena has been demonstrated only in women with a prior spontaneous singleton preterm birth. It is not intended for use in women with multiple gestations or other risk factors for preterm birth.[6]

Treatment is indicated to begin between 16 weeks, 0 days and 20 weeks, 6 days of gestation. Continue administration once weekly until week 37 (through 36 weeks, 6 days) of gestation or delivery, whichever occurs first.[6]

References

1. United States Pharmacopeia: 2008-2009 USP Pharmacists' Pharmacopeia. 2nd ed. 5th supplement. Chapter <797> Pharmaceutical Compounding-Sterile Preparations. Rockville, MD: United States Pharmacopeia Convention. April 21-24, 2010. Washington, DC.
2. PCAB Standards. Pharmacy Compounding Accreditation Board. Washington DC. Accessed March 26, 2014.
3. Awwad J, Usta IM, Ghazeeri G, et al. A randomised controlled double-blind clinical trial of 17-hydroxyprogesterone caproate for the prevention of preterm birth in twin gestation (PROGESTWIN): evidence for reduced neonatal morbidity. *BJOG*. 2015 Jan;122(1):71-9.
4. Saccone G, Suhag A, Berghella V. 17-alpha-hydroxyprogesterone caproate for maintenance tocolysis: a systematic review and metaanalysis of randomized trials. *Am J Obstet Gynecol.* 2015 Feb 4.

5. American College of Obstetricians and Gynecologists. Practice Bulletin No. 130. Prediction and prevention of preterm birth. *Obstet Gynecol*. 2012 Oct;120:964-73. Reaffirmed 2018.
6. Makena [prescribing information]. St. Louis, MO: Ther-Rx Corporation; February 2018.
7. American College of Obstetricians and Gynecologists. Practice Bulletin No. 169. Multifetal gestations: twin, triplet, and higher-order multifetal pregnancies. No. 169 Obstet Gynecol. 2016 Oct;128(4):e131-46.
8. Likis FE, Andrews JC, Woodworth AL, et al. Progestogens for Prevention of Preterm Birth. Comparative Effectiveness Review No. 74. (Prepared by the Vanderbilt Evidence-based Practice Center under Contract No. 290-2007-10065-I). Agency for Healthcare Research and Quality (AHRQ) Publication No. 12-EHC105-EF. Rockville, MD: Agency for Healthcare Research and Quality (AHRQ). September 2012.
9. Winer N, Bretelle F, Senat MV, et al. 17 alpha-hydroxyprogesterone caproate does not prolong pregnancy or reduce the rate of preterm birth in women at high risk for preterm delivery and a short cervix: a randomized controlled trial. Am J Obstet Gynecol. 2015 Apr;212(4):485.e1-485.
10. Schuit E, Stock S, Rode L, et al. Effectiveness of progestogens to improve perinatal outcome in twin pregnancies: an individual participant data meta-analysis. BJOG. 2015 Jan;122(1):27-37.
11. Robinson JN et al. Preterm birth: Risk factors and interventions for risk reduction. UpToDate. Accessed November 12, 2018.
12. EPPPIC Group. Evaluating Progestogens for Preventing Preterm birth International Collaborative (EPPPIC): meta-analysis of individual participant data from randomised controlled trials [published correction appears in Lancet. 2021 Apr 17;397(10283):1446]. Lancet. 2021;397(10280):1183-1194. doi:10.1016/S0140-6736(21)00217-8.

Policy History/Revision Information

Date	Summary of Changes
09/01/2022	Supporting Information • Updated *Clinical Evidence* and *References* sections to reflect the most current information • Archived previous policy version CS2021D0040U

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. The UnitedHealthcare Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.