17-ALPHA-HYDROXYPROGESTERONE CAPROATE (MAKENA™ AND 17P)

Policy Number: 2019D0040M **Effective Date**: March 1, 2019

Instructions for Use

Table of Contents **Page**

Related Commercial Policy

- Preterm Labor Management

COVERAGE RATIONALE

See Benefit Considerations

This policy provides coverage information about the use of injectable (both intramuscular and subcutaneous) 17-alpha-hydroxyprogesterone caproate, commonly called 17P, 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:

I. Current singleton pregnancy; **and**
II. History of a prior spontaneous preterm birth of a singleton pregnancy; **and**
III. Treatment is initiated between 16 weeks, 0 days of gestation and 26 weeks, 6 days of gestation; **and**
IV. Administration is to continue weekly until week 37 (through 36 weeks, 6 days) of gestation or delivery, whichever occurs first.

Intramuscular and subcutanous injection of 17P is unproven and not medically necessary for:

I. Prevention of spontaneous preterm birth with **any** of the following:
   A. Short cervix with or without cerclage and no prior preterm birth.
   B. Current multi-fetal pregnancy (twins or greater).
   C. Previous medically indicated preterm birth.
II. Initiation of 17P after 26 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 (1ml and 5ml vials) and benzyl alcohol (a preservative, in the 5ml 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. Please refer to the U.S. Food and Drug Administration (FDA) section of this policy for additional information.

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

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]

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]

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 the member specific benefit plan document 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 Coverage Determination 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

ICD-10 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
O47.03	False labor before 37 completed weeks of gestation, third trimester
O47.1	False labor at or after 37 completed weeks of gestation

ICD-10 Diagnosis Code	Description
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

BENEFIT CONSIDERATIONS

The UnitedHealthcare standard Certificate of Coverage excludes coverage for non-injectable medications administered in a physician's office. Oral and intravaginal progesterone formulations are administered as a pharmacy benefit.

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The member specific benefit plan document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy. Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met. See the Policy and Procedure addressing the treatment of serious rare diseases.

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. Intramusulcar 17P for maintenance tocolysis is associated with a significant prolongation of pregnancy, and significantly higher birthweight, further research is suggested.

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 3768 women and their 7536 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 (17OHPC) prolongs gestation beyond 37 weeks of gestation (primary outcome) and reduces neonatal morbidity (secondary outcome) in twin pregnancy (PROGESTWIN).[3] Pregnant women received weekly injections of 250 mg 17OHPC (n = 194) or placebo (n = 94), from 16-20 to 36 weeks of gestation. Intramuscular 17OHPC therapy did not reduce PTB before 37 weeks of gestation in unselected twin pregnancies. However, 17OHPC 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 (17OHP-C) weekly until 36 weeks. The primary outcome was time from randomization to delivery. After an interim analysis demonstrated the lack of efficacy of 17OHP-C in prolonging pregnancy, the study was discontinued because of futility. 17OHP-C 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

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 recommened 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.

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Medicare does not have a National Coverage Determination (NCD) for Makena® (hydroxyprogesterone caproate injection). Local Coverage Determinations (LCDs) do not exist at this time.

In general, Medicare covers outpatient (Part B) drugs that are furnished "incident to" a physician's service provided that the drugs are not usually self-administered by the patients who take them. Refer to the Medicare Benefit Policy Manual, Chapter 15, §50 - Drugs and Biologicals. (Accessed November 13, 2018)

REFERENCES

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POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
03/01/2019	Reorganized policy template; simplified and relocated *Instructions for Use* and *Benefit Considerations* section. Archived previous policy version 2019D0040L.
02/01/2019	Annual review with no changes to clinical criteria. Updated FDA section, clinical evidence, CMS statement, & references. Policy 8201D0040K archived.
04/01/2018	Annual review with no changes to clinical criteria. Updated background, clinical evidence, and references. Approved by the National Pharmacy and Therapeutics Committee on 03/21/2018. Policy 2016D0040J archived.
01/01/2018	Added J1726 & J1729. Removed J1725, Q9985 & Q9986. Policy 2016D0040I archived.
07/01/2017	Annual review with minor revision to clinical evidence, applicable codes, and references. Approved by the National Pharmacy and Therapeutics Committee on 06/28/2017. Policy 2016D0040H archived.
09/01/2016	Annual review with minor revision to clinical overage, clinical evidence and references. Approved by the National Pharmacy and Therapeutics Committee on

Date	Action/Description
	06/22/2016. Policy 2015D0040G archived.
10/01/2015	Annual review with no changes to the clinical criteria. Updated Benefit Considerations, Background, Clinical Evidence, Applicable Codes and References. Approved by the National Pharmacy and Therapeutics Committee on 08/19/2015. Policy 2014D0040F archived.
08/01/2014	Annual policy review. Removed medical necessity heading such that criteria applies to all requests for 17P. Clinical evidence and references updated. Added ICD-10 codes. Approved by the National Pharmacy & Therapeutics Committee on 05/21/2014. Policy 2013D0040E archived.
07/01/2103	Annual policy review. Added medical necessity criteria. Clinical evidence and references updated. Updated ICD-10 codes. Approved by the National Pharmacy & Therapeutics Committee on 05/21/2013. Policy 2013D0040D archived.
01/01/2013	Policy updated. Parenthetical reference in policy title changed from "(17P and Makena)" to "(Makena and 17P)." Added Updated FDA Statements on Makena and Compounded Versions of Hydroxyprogesterone Caproate. Approved by the National Pharmacy & Therapeutics Committee on 11/13/2012. Policy 2012D0040C archived.
09/01/2012	Added list of applicable ICD-10 codes (preview draft) in preparation for the transition from ICD-9 to ICD-10 medical coding on 10/01/2014.
07/01/2012	Annual policy review. Removed clinical evidence regarding intravaginal and oral administration of progesterone. Updated Hayes Technology Directory added. Approved by the National Pharmacy & Therapeutics Committee on 05/15/2012. Policy 2012D0040B archived.
01/01/2012	Removed Q2042 which becomes inactive on 01/01/2012. Added J1725 which becomes effective on 01/01/2012. Policy 2011D0040A archived.
10/01/2011	New policy 2011D0040A. Approved by the National Pharmacy & Therapeutics Committee on 05/10/2011.

INSTRUCTIONS FOR USE

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard benefit plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. 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.

This Medical Benefit Drug Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. UnitedHealthcare 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.