

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

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Related Policies
<ul style="list-style-type: none"> <li>• <a href="#">Acquired Rare Disease Drug Therapy Exception Process</a></li> <li>• <a href="#">Experimental/Investigational Treatment for NJ Plans</a></li> <li>• <a href="#">Preterm Labor Management</a></li> </ul>

## INSTRUCTIONS FOR USE

This Clinical Policy provides assistance in interpreting Oxford benefit plans. Unless otherwise stated, Oxford policies do not apply to Medicare Advantage members. Oxford reserves the right, in its sole discretion, to modify its policies as necessary. This Clinical Policy is provided for informational purposes. It does not constitute medical advice. The term Oxford includes Oxford Health Plans, LLC and all of its subsidiaries as appropriate for these policies.

When deciding coverage, the member specific benefit plan document must be referenced. The terms of the member specific benefit plan document [e.g., Certificate of Coverage (COC), Schedule of Benefits (SOB), and/or Summary Plan Description (SPD)] may differ greatly from the standard benefit plan upon which this Clinical Policy is based. In the event of a conflict, the member specific benefit plan document supersedes this Clinical Policy. All reviewers must first identify member eligibility, any federal or state regulatory requirements, and the member specific benefit plan coverage prior to use of this Clinical Policy. Other Policies may apply.

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

## CONDITIONS OF COVERAGE

Applicable Lines of Business/Products	This policy applies to Oxford Commercial plan membership.
Benefit Type	General benefits package
Referral Required (Does not apply to non-gatekeeper products)	No
Authorization Required (Precertification always required for inpatient admission)	Yes
Precertification with Medical Director Review Required	No
Applicable Site(s) of Service (If site of service is not listed, Medical Director review is required)	Inpatient, Outpatient, Home, Office <sup>1</sup>
Special Considerations	<b><sup>1</sup>Participating Providers in the Office Setting:</b> Precertification is required for services performed in the office of a participating provider. <b>Non-Participating/Out-of-Network Providers in the Office Setting:</b> Precertification is not required, but is encouraged for

## BENEFIT CONSIDERATIONS

Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances. 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; refer to the [Acquired Rare Disease Drug Therapy Exception Process](#).

Oral and Intravaginal progesterone formulations are administered as a pharmacy benefit.

### **Essential Health Benefits for Individual and Small Group**

For plan years beginning on or after January 1, 2014, the Affordable Care Act of 2010 (ACA) requires fully insured non-grandfathered individual and small group plans (inside and outside of Exchanges) to provide coverage for ten categories of Essential Health Benefits ("EHBs"). Large group plans (both self-funded and fully insured), and small group ASO plans, are not subject to the requirement to offer coverage for EHBs. However, if such plans choose to provide coverage for benefits which are deemed EHBs, the ACA requires all dollar limits on those benefits to be removed on all Grandfathered and Non-Grandfathered plans. The determination of which benefits constitute EHBs is made on a state by state basis. As such, when using this policy, it is important to refer to the member specific benefit plan document to determine benefit coverage.

## COVERAGE RATIONALE

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 the 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 26 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 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 and not medically necessary.

**\*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).<sup>1</sup> The Pharmacy Compounding Accreditation Board will verify that the pharmacy is adhering to these standards.<sup>2</sup>

**\*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.

## 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 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
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

ICD-10 Diagnosis Code	Description
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.<sup>5,14</sup>

## CLINICAL EVIDENCE

### **Proven/Medically Necessary**

#### ***Singleton Pregnancy***

Saccone et al. (2015) conducted a meta-analysis 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).<sup>4</sup> 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, 1.46-3.51), 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.

### **Unproven/Not Medically Necessary**

#### ***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.<sup>13</sup> Randomised 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 (17OHP) prolongs gestation beyond 37 weeks of gestation (primary outcome) and reduces neonatal morbidity (secondary outcome) in twin pregnancy (PROGESTWIN).<sup>3</sup> Pregnant women received weekly injections of 250 mg 17OHP (n = 194) or placebo (n = 94), from 16-20 to 36 weeks of gestation. Intramuscular 17OHP therapy did not reduce PTB before 37 weeks of gestation in unselected twin pregnancies. However, 17OHP 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.<sup>12</sup> 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 (No.130, reaffirmed in 2016) Practice Bulletin makes the following recommendations based upon good and consistent scientific evidence (Level A):<sup>6</sup>

- 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 2014, ACOG published an additional practice bulletin (No. 144) regarding Multifetal Gestations that included the following statement on progesterone therapy:<sup>11</sup>

- 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)**

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.<sup>6</sup>

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.<sup>6</sup>

The FDA issued a statement dated March 30, 2011 regarding the availability of a compounded version of Makena. The FDA states that it does not intend to take enforcement action against pharmacies that compound hydroxyprogesterone caproate based on a valid prescription for an individually identified patient unless the compounded products are unsafe, of substandard quality, or are not being compounded in accordance with appropriate standards for compounding sterile products.<sup>7</sup>

In a statement dated November 8, 2011, the FDA reported that it was conducting an ongoing sampling and analysis of compounded hydroxyprogesterone caproate products and the bulk active pharmaceutical ingredients (APIs) used to make them. Physicians and patients were reminded that before approving the Makena new drug application, the FDA reviewed manufacturing information, such as the source of the API used by its manufacturer, proposed manufacturing processes, and the firm's adherence to current good manufacturing practice. Therefore, as with other approved drugs, greater assurance of safety and effectiveness is generally provided by the approved product than by a compounded product.<sup>8</sup>

On June 15, 2012, the FDA issued an update regarding compounded versions of hydroxyprogesterone caproate. Although their analysis of a limited sample of compounded hydroxyprogesterone caproate products and APIs did not identify any major safety problems, the FDA stated that approved drug products provide a greater assurance of safety and effectiveness than do compounded products. Therefore, when an FDA-approved drug is commercially available,

the FDA recommends that practitioners prescribe the FDA-approved drug rather than a compounded drug unless the prescribing practitioner has determined that a compounded product is necessary for the particular patient and would provide a significant difference for the patient as compared to the FDA-approved commercially available drug product. The FDA emphasized that it is applying its normal enforcement policies for compounded drugs to compounded hydroxyprogesterone caproate. The compounding of any drug, including hydroxyprogesterone caproate, should not exceed the scope of traditional pharmacy compounding. As the Agency has previously explained, the FDA generally prioritizes enforcement actions related to compounded drugs using a risk-based approach, giving the highest enforcement priority to pharmacies that compound products that are causing harm or that amount to health fraud.<sup>9</sup>

## REFERENCES

The foregoing Oxford policy has been adapted from an existing UnitedHealthcare Pharmacy Clinical Pharmacy Program that was researched, developed and approved by the UnitedHealth Group National Pharmacy & Therapeutics Committee. [2018D0040K]

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13. 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.
14. Robinson JN et al. Preterm birth: Risk factors and interventions for risk reduction. Uptodate. Accessed February 7, 2018.

## POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
12/01/2018	<ul style="list-style-type: none"> <li>• Updated conditions of coverage/special considerations; modified notation to clarify:               <ul style="list-style-type: none"> <li>○ For <b>participating providers in the office setting</b>: Precertification is required for services performed in the office of a participating provider</li> <li>○ For <b>non-participating/out-of-network providers in the office setting</b>: Precertification is not required, but is encouraged for out-of-network services performed in the office; if precertification is not obtained, Oxford will review for out-of-network benefits and medical necessity after the service is rendered</li> </ul> </li> <li>• Archived previous policy version PHARMACY 198.14 T2</li> </ul>