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

Policy Number: CS2023D0040W
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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	None
Louisiana	Refer to the state's Medicaid clinical policy
North Carolina	None
Ohio	17-Alpha-Hydroxyprogesterone Caproate (Makena® and 17P) (for Ohio Only)
Pennsylvania	None
Texas	Refer to the state's Medicaid clinical policy
Washington	Refer to the state's Medicaid clinical policy

Coverage Rationale

On April 6, 2023, the FDA announced the final decision to withdraw approval of Makena because Makena and its generics (i.e., generic versions of Makena) are not shown to be effective for reducing the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth.[15,16] Makena and its generics are no longer approved and cannot lawfully be distributed in interstate commerce. Lack of adequate data supporting effectiveness implicates compounded products as well.

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.

Intramuscular and subcutaneous injection of 17P, including but not limited to compounded 17P, are not proven nor medically necessary for prevention of spontaneous preterm birth due to the approval for the drug being withdrawn by the FDA.

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

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
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

Diagnosis Code	Description
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. Asymptomatic women can be considered to be at high risk of spontaneous preterm delivery due to various risk factors, including previous preterm delivery, preterm labor, multiple pregnancy, or short cervix. 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. The active pharmaceutical ingredient in Makena is hydroxyprogesterone caproate, a synthetic progestin.

Clinical Evidence

Unproven

Singleton Pregnancy

Center for Drug Evaluation and Research (CDER)

Based on the available evidence, Makena is no longer shown to be effective for its approved use—either for its indicated population or any subset of that population.[13] The randomized, placebo-controlled trials specifically designed to evaluate Makena's approved use in the intended population—Trials 002 and 003—provide the most rigorous and relevant evidence to evaluate Makena's efficacy for its approved use. Makena's accelerated approval was based on one adequate and well-controlled trial (Trial 002). The treatment effect shown in Trial 002 on the intermediate clinical endpoint of delivery < 37 weeks gestation appeared independent of race, number of prior preterm deliveries, and gestational age of the prior preterm birth (PTB). Trial 003, which was almost four times larger than Trial 002, failed to show that Makena reduced the proportion of women delivering prior to 37-, 35-, or 32-weeks' gestation. Furthermore, exploratory subgroup analyses of Trial 003 did not provide evidence of a treatment effect in any identified subgroup analyzed, including those with risk factors that differed between Trials 002 and 003. There was no consistent evidence of treatment effect within an identified subpopulation across Trials 002 and 003 [e.g., by race, number of prior spontaneous preterb birth (sPTB)]. The FDA's Center for Drug Evaluation and Research (CDER) has generally interpreted the substantial evidence of effectiveness standard as requiring clinically and statistically significant findings from at least two adequate and well-controlled trials. A single positive trial, even if well-

conducted, may have biases or may reflect a chance finding. If the collective findings of Trials 002 and 003 were submitted at the same time in an NDA seeking approval, CDER would conclude that there is not substantial evidence of effectiveness of Makena for reducing the risk of recurrent PTB—for either the overall population of women with a singleton pregnancy and a history of singleton sPTB, or for any identified subset of that population. Lastly, review of published evidence potentially relevant to the efficacy of Makena did not demonstrate Makena was effective in reducing the risk of PTB. CDER thoroughly explored all available evidence of effectiveness. CDER's analysis included other available data, in addition to Trials 002 and 003, on the effect of HPC (the active ingredient in Makena) on singleton sPTB. These data included CDER's review of (a) the EPPPIC metaanalysis,[12] (b) five observational studies with HPC in Makena's indicated population, (c) three randomized, placebo-controlled trials described by the manufacturer Covis as supporting safety of HPC in other groups at high risk for PTB, and (d) three additional studies Covis points to as supporting the Trial 002 results. After review, CDER concluded these studies do not support a finding that Makena is effective in reducing PTB, as enumerated below.

EPPPIC (Evaluating Progestogens for Preventing Preterm birth International Collaborative) is an individual participant data meta-analysis of RCTs that evaluated the effect of various progestogens (vaginal progesterone, oral progesterone, and injectable HPC) compared to control (placebo or no-intervention) or to each other administered during pregnancy in preventing PTB (first occurrence or recurrent PTB). EPPPIC included a total of 31 RCTs, consisting of 11,644 women with singleton or multifetal gestations, with or without a history of prior PTB, and with or without a short mid-trimester cervical length.[12] Among EPPPIC's 31 clinical trials, CDER focused on the five trials (two of which were Trials 002 and 003) in the EPPPIC meta-analysis that have some relevance to Makena, because these trials evaluated HPC in singleton pregnancies and were placebo-controlled. Other than Trials 002 and 003, two of the five trials included non-Makena indicated patients, such as pregnant women with a shortened cervix in the current pregnancy but no prior birth or dosing different than that of Makena (HPC 500 mg rather than the HPC 250 mg in Makena). The remaining trial had known drug quality issues potentially impacting drug potency and efficacy. In addition, CDER's review identified important issues in data analysis and results interpretation of the EPPPIC study. Specifically, the investigator's conclusion of beneficial effect in reducing PTB < 34 weeks was based on an effect estimate that was not statistically significant (HR = 0.83, 95% CI = 0.68-1.01). Second, the claim of treatment effect among "high-risk" women (those with short cervix) is not evident because the analyses were based on a small subset (n = 81, 2.7%) of total study populations in five trials, with 70% of them treated with an HPC dose regimen twice that of the approved Makena dose, and without suitable statistical adjustment for multiplicity after assessing multiple subgroup analyses. Even given these caveats, the meta-analysis of these five HPC trials did not show a statistically significant finding on the main outcomes of delivery prior to 37-, 34-, or 28-weeks' gestation, perinatal deaths, or serious neonatal complications. CDER also identified five observational studies that provided exploratory evidence about HPC's effect for its approved use using keyword searches132 of the PubMed database. Although noting that observational studies have limitations in drawing causal inferences, CDER resolved that the lack of evidence of effectiveness across these 5 studies provides further support for the conclusion that Makena is not effective in the indicated population.

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)

In April 2023, the American College of Obstetricians and Gynecologists (ACOG) published a Practice Advisory to serve as an update to Practice Bulletin No. 234, Prediction and Prevention of Spontaneous Preterm Birth, originally published in 2021.[14] This Practice Advisory was provided to address the April 6, 2023, decision by the FDA to withdraw approval of Makena and its generics (17-alpha hydroxyprogesterone caproate [17-OHPC]). Additionally, the Practice Advisory served to update the current evidence and recommendations for the use of progesterone for the prevention of recurrent preterm birth. The ACOG guidance regarding the use of progesterone for the prevention of preterm birth is included in ACOG Practice Bulletin No. 234, "Prediction and Prevention of Spontaneous Preterm Birth". Updated recommendations are:

- Vaginal progesterone may be considered as a treatment option for patients with a history of preterm birth, singleton gestation, and a shortened cervix. However, vaginal progesterone has not been proven effective in the absence of a shortened cervix and should not be considered as an alternative to 17-OHPC.
- Intramuscular 17-OHPC is not recommended for the primary prevention of preterm birth in patients with a history of spontaneous preterm birth.
- Dependent upon cervical length measurement, prior pregnancy history, and past treatment, a discussion of the range of interventions available to prevent a recurrent preterm birth should occur and a collaborative action plan should be developed.

In 2016, ACOG published a 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 was approved under an accelerated approval pathway in 2011.[13] As a condition of this approval, the sponsor was required to conduct a confirmatory clinical trial to demonstrate the predicted clinical benefit to newborns. On April 6, 2023, the FDA announced the final decision to withdraw approval of Makena.[13,15,16] Makena and its generics are not shown to be effective for reducing the risk of preterm birth in women with singleton pregnancy who have a history of singleton spontaneous preterm birth. Additionally, Makena and its generics have not been shown to be effective for any subgroup of this population, including in women at high risk of preterm birth. The benefits of Makena do not outweigh the risks.

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Policy History/Revision Information

Date	Summary of Changes

08/01/2023	**Application**
	Kansas and ***Pennsylvania***
	• Removed reference to the state's Medicaid clinical policy
	Coverage Rationale
	• Changed coverage status for intramuscular and subcutaneous injection of 17P from "proven and medically necessary when [listed] criteria are met" to "unproven and not medically necessary"
	  ○ Added language to indicate:
	  ▪ On April 6, 2023, the FDA announced the final decision to withdraw approval of Makena because Makena and its generics (i.e., generic versions of Makena) are not shown to be

Date	Summary of Changes
	effective 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 are no longer approved and cannot lawfully be distributed in interstate commerce; lack of adequate data supporting effectiveness implicates compounded products as well ▪ Intramuscular and subcutaneous injection of 17P, including but not limited to compounded 17P, is not proven nor medically necessary for prevention of spontaneous preterm birth due to the approval for the drug being withdrawn by the FDA ○ Removed language pertaining to: ▪ Coverage criteria and limitations for intramuscular and subcutaneous injection of 17P ▪ Additional information regarding compounded 17P **Supporting Information** • Updated *Background*, *Clinical Evidence*, *FDA*, and *References* sections to reflect the most current information • Archived previous policy version CS2022D0040V

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.