

<b>Department:</b>	Pharmacy Management	<b>Original Approval:</b>	12/24/2015
<b>Policy #:</b>	PM101	<b>Last Approval:</b>	06/14/2018
<b>Title:</b>	Hydroxyprogesterone caproate (Makena®) injection for intramuscular use		
<b>Approved By:</b>	UM Committee		

## REQUIRED CLINICAL DOCUMENTATION FOR REVIEW

Documentation required to determine medical necessity for Hydroxyprogesterone caproate (Makena): History and/or physical examination notes and relevant specialty consultation notes that address the problem and need for the service: -Diagnosis -Pregnancy status -Dosing and duration requested - Initial/extended approval.

## BACKGROUND

Makena is a progestin indicated to reduce the risk of preterm birth in women with a singleton pregnancy that have a history of singleton spontaneous preterm birth (SPTB).<sup>1</sup> The effectiveness of Makena is based on improvement in the proportion of women who delivered < 37 weeks of gestation. There are no clinical trials demonstrating a direct clinical benefit, such as improvement in neonatal mortality and morbidity. Limitations of Use: 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. Makena is administered by intramuscular (IM) route or subcutaneously (SC) route once weekly by a healthcare provider. Makena is administered once weekly until Week 37 of gestation or delivery, whichever occur first.

Makena is supplied as a 5 mL multi-dose vial and a preservative-free 1 mL single-dose vial, each containing 250 mg/mL of hydroxyprogesterone caproate (17P) (for IM use), and as a 1.1 mL single-patient-use auto-injector containing 275 mg of 17P (for SC use).<sup>1</sup>

This policy involves the use of Makena for IM and SC injection. Prior authorization is recommended for medical benefit coverage of Makena. Coverage is recommended for those who meet the conditions of coverage in the **Criteria, Dosing, Initial/Extended Approval, Duration of Therapy, and Labs/Diagnostics** for the diagnosis provided. The requirement that the patient meet the Criteria and **Waste Management** applies for all covered conditions. **Conditions Not Recommended for Approval** are listed following the recommended authorization criteria and Waste Management section.

## DEFINITIONS

None.

## INDICATIONS/CRITERIA

<b>MediCAID Members</b>	<i>Continue to criteria for approval below. Makena is part of WA HCA Single Preferred Drug List. Criteria mandated is HCA Medical policy Progesterones – hydroxyprogesterone caproate (MAKENA®)no. 26.00.00-1</i>
<b>MediCARE Members</b>	<i>Step-utilization of Part D drugs not required.</i>

Coverage of Makena is recommended in those who meet the following criteria:

### **Food and Drug Administration (FDA)-Approved Indications**

#### **1. Reduce Risk of Preterm Birth.**

**Criteria.** *The patient must meet the following criteria (A, B, C, and D):*

- A)** Patient age is greater than or equal to 16 years; AND
- B)** Patient is pregnant with a singleton pregnancy; AND
- C)** Patient has a history of singleton spontaneous preterm birth (SPTB) prior to 37 weeks gestation due to one of the following reasons: 1) Spontaneous preterm labor, or 2) Premature rupture of membranes; AND
- D)** Treatment will begin in patients who are at least 16 weeks, 0 days of gestation, according to the prescribing physician or other prescriber.

Makena is not intended for use in women with multiple gestations or other risk factors for preterm birth. There are no adequate and well-controlled studies of the use of Makena in the first trimester of pregnancy.

#### **Dosing to Reduce Risk of Preterm Birth.**

Makena is administered either by IM, at a dose of 250 mg (1 mL), or by SC, at a dose of 275 mg (1.1 mL), once weekly by a healthcare provider.

According to the Makena prescribing information, treatment should begin between 16 weeks, 0 days and 20 weeks, 6 days gestation. Weekly administration of Makena should continue until Week 37 of gestation or delivery, whichever occurs first.

**Initial Approval/Extended Approval.** Initial approval is for up to 5 months of therapy (21 injections). In cases where there was an inaccuracy in dating of the pregnancy, a one-month authorization may be granted to patients who have already received 21 injections and are < 37 weeks pregnant.

**Duration of Therapy to Reduce Risk of Preterm Birth:** Continue treatment until Week 37 of gestation or delivery, whichever occurs first.

**Labs/Diagnostics.** None required.

#### **2. Other Uses with Supportive Evidence.** Exceptions are not recommended.

#### **Waste Management**

PM101\_CCC\_Hydroxyprogesterone caproate (Makena)

2 of 7

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Multi-dose vials (available for IM injection only) should be used within 5 weeks after first use. Single-dose vials (for IM injection) and single-patient-use auto-injectors (for SC injection) are available for one-time use.

#### **Conditions Not Recommended for Approval**

Makena (SC and IM) has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

- 1. History of a Threatened Preterm Birth.** Makena is not indicated in pregnant women who experienced a past threatened preterm birth but delivered a full-term infant after 36 completed weeks of gestation.<sup>1</sup>
- 2. Infertility.** Some studies have evaluated hydroxyprogesterone caproate as the progesterone used in *in vitro* fertilization.<sup>2-3</sup> However, progesterone in oil or vaginally administered progesterone are mentioned for use during the luteal phase and in early pregnancy in the treatment of infertility by an educational bulletin by the Practice Committee of the American Society of Reproductive Medicine.<sup>4</sup>
- 3. Patients Pregnant with Multiple Gestations.** Makena is not indicated in patients pregnant with multiple gestations (e.g., twins, triplets, or other multiples).<sup>1</sup> Hydroxyprogesterone caproate has failed to decrease preterm birth in women pregnant with twins and triplets.<sup>5-7</sup> In a randomized, double-blind, placebo-controlled study in 661 women, delivery or fetal death prior to Week 35 occurred in 41.5% of women pregnant with twins in the hydroxyprogesterone caproate group compared to 37.3% of those pregnant with twins in the placebo group (relative risk [RR]: 1.1; 95% CI: 0.9, 1.5).<sup>5</sup> In a randomized, double-blind, placebo-controlled study in women pregnant with triplets (n = 134), treatment with hydroxyprogesterone caproate did not affect the rate of delivery or fetal loss prior to Week 35 (RR: 1.0; 95% CI: 0.9, 1.1).<sup>6</sup> In another randomized, double-blind, placebo-controlled study, 56 women pregnant with triplets were assigned to treatment with hydroxyprogesterone caproate and 25 were assigned to placebo.<sup>7</sup> There was not a significant difference in delivery prior to Week 28, 32, or 35 in either treatment group; however, significantly more stillbirths/miscarriages occurred in the hydroxyprogesterone group (8%) compared to the placebo group (0%) (P = 0.01). In one randomized, double-blind, controlled trial in unselected women with twin pregnancies, IM 17P (not Makena; another marketed product in Europe) did not reduce preterm birth before 37 weeks of gestation; however, it did reduce neonatal morbidity parameters and also increased birthweight.<sup>12</sup> Other studies in women with multiple gestations (primarily twin gestations) have not shown a prolonged gestation or a reduction in neonatal morbidity with 17P compared to placebo.<sup>8-10</sup>
- 4. Pregnant Patient with Short Cervix Without a History of a Prior Singleton Spontaneous Preterm Birth.** Makena is not indicated for use in pregnant women with short cervix and no history of singleton SPTB prior to 37 weeks gestation. The Society for Maternal-Fetal Medicine (SMFM) guidelines (2012) for the use of progesterone in preterm birth prevention recommends the use of vaginal progesterone 90 mg gel or 200 mg suppository daily from diagnosis of short cervical length

( $\leq 20$  mm at  $\leq 24$  weeks) until 36 weeks.<sup>11</sup> There is no evidence that other preparations (e.g., IM 17P) or doses of progesterone would be efficacious, even within the specified cervical length range. IM 17P is only recommended for use in singleton pregnancies with prior spontaneous preterm birth (approved indication). An open-label, randomized study in women ( $n = 165$ ) with asymptomatic twin pregnancies with a short cervix demonstrated that twice-weekly injections of 17P did not prolong pregnancy significantly compared with a control group.<sup>10</sup> In fact, treatment with 17P was associated with a significant increase in the pre-term delivery rate before 32 weeks. In another open-label, randomized controlled trial in 105 women with asymptomatic singleton pregnancies, short cervical length  $< 25$  mm, and with other risk factors of preterm delivery (prior history, cervical surgery, uterine malformation, or prenatal diethylstilbestrol exposure), 17P did not prolong pregnancy.<sup>13</sup> The trial was discontinued after an interim analysis indicated that there was no difference between patients who were treated with 17P and those who were not treated with 17P. A SMFM statement, published March 2017, discusses that women with a prior SPTB who start 17P and then develop cervical shortening, it is unknown whether there is any benefit to change progesterone to vaginal progesterone (with or without cervical cerclage placement). Based on data regarding the lack of benefit of vaginal progesterone in women with a history of a prior SPTB, the SMFM recommends the continuation of 17P in women with a history of a prior SPTB throughout pregnancy despite the development of cervical shortening (with or without cervical cerclage placement).<sup>14</sup>

5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

## **SPECIAL CONSIDERATIONS**

None.

## **LIMITATIONS/EXCLUSIONS**

Please refer to a product line's certificate of coverage for benefit limitations and exclusions for these services:

PRODUCT LINE	LINK TO CERTIFICATE OF COVERAGE
MEDICARE ADVANTAGE	<a href="http://healthfirst.chpw.org/for-members/resource-library/handbooks-and-guides">http://healthfirst.chpw.org/for-members/resource-library/handbooks-and-guides</a>
WASHINGTON APPLE HEALTH	<a href="http://chpw.org/our-plans/apple-health/">http://chpw.org/our-plans/apple-health/</a>
INTEGRATED MANAGED CARE	<a href="http://chpw.org/our-plans/apple-health/">http://chpw.org/our-plans/apple-health/</a>

## Citations & References

References
<ol style="list-style-type: none"> <li>1. Makena for intramuscular or subcutaneous use [prescribing information]. Waltham, MA: AMAG Pharmaceuticals; February 2018.</li> <li>2. Rjosk HK, Abendstein BJ, Kreuzer E, Schwärzler P. Preliminary experience with steroidal ovarian suppression for prevention of severe ovarian hyperstimulation syndrome in IVF patients. <i>Hum Fertil (Camb)</i>. 2001;4(4):246-248.</li> <li>3. Costabile L, Gerli S, Manna C, et al. A prospective randomized study comparing intramuscular progesterone and 17alpha-hydroxyprogesterone caproate in patients undergoing <i>in vitro</i> fertilization-embryo transfer cycles. <i>Fertil Steril</i>. 2001;76(2):394-396.</li> <li>4. Fritz M, Adamson GD, Barnhart K, et al. Progesterone supplementation during the luteal phase and in early pregnancy in the treatment of infertility: an educational bulletin. <i>Fertil Steril</i>. 2008;89(4):789-792.</li> <li>5. Rouse DJ, Caritis SN, Peaceman AM, et al. A trial of 17 alpha-hydroxyprogesterone caproate to prevent prematurity in twins. <i>N Engl J Med</i>. 2007;357(5):454-461.</li> <li>6. Caritis SN, Rouse DJ, Peaceman AM, et al. Prevention of preterm birth in triplets using 17 alpha-hydroxyprogesterone caproate: a randomized controlled trial. <i>Obstet Gynecol</i>. 2009;113(2 Pt 1):285-292.</li> <li>7. Combs CA, Garite T, Maurel K, et al. Failure of 17-hydroxyprogesterone to reduce neonatal morbidity or prolong triplet pregnancy: a double-blind, randomized clinical trial. <i>Am J Obstet Gynecol</i>. 2010;203(3):248.e1-9.</li> <li>8. Combs CA, Garite T, Maurel K, et al. 17-hydroxyprogesterone caproate for twin pregnancy: a double-blind, randomized clinical trial. <i>Am J Obstet Gynecol</i>. 2011;204(3):221.e1-8.</li> <li>9. Lim AC, Schuit E, Bloemenkamp K, et al. 17<math>\alpha</math>-hydroxyprogesterone caproate for the prevention of adverse neonatal outcome in multiple pregnancies: a randomized controlled trial. <i>Obstet Gynecol</i>. 2011;118(3):513-520.</li> <li>10. Senat MV, Porcher R, Winer N, et al. Prevention of preterm delivery by 17 alpha-hydroxyprogesterone caproate in asymptomatic twin pregnancies with a short cervix: a randomized controlled trial. <i>Am J Obstet Gynecol</i>. 2013;208:194.e1-8.</li> <li>11. Society for Maternal Fetal Medicine Publications Committee, Berghella V. SMFM Clinical Guideline. Progesterone and preterm birth prevention: translating clinical trials data into clinical practice. <i>Am J Obstet Gynecol</i>.</li> </ol>



	<p>2012;206:376-386. Reaffirmed August 2014.</p> <p>12. Awwad J, Usta IM, Ghazeeri G, et al. A randomized controlled double-blind clinical trial of 17-hydroxyprogesterone caproate for the prevention of preterm birth in twin gestation (PROGESTWIN): evidence for reduced neonatal morbidity. <i>BJOG</i>. 2015;122:71-79.</p> <p>13. 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. <i>Am J Obstet Gynecol</i>. 2015;212:485.e1-e10.</p> <p>14. Society for Maternal-Fetal Medicine Publications Committee. The choice of progesterone for the prevention of preterm birth in women with singleton pregnancy and prior preterm birth. <i>Am J Obstet Gynecol</i>. 2017 Mar; 216(3): B11-B13.</p> <p><b>OTHER REFERENCES UTILIZED</b></p> <ul style="list-style-type: none"> <li>• Meis PJ, Klebanoff M, Thom E, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. <i>N Engl J Med</i>. 2003;348(24):2379-2385.</li> <li>• Data on file. Gestiva. NDA 21-945. Food and Drug Administration Web site. August 2, 2006. Received February 11, 2011.</li> <li>• Wesley B. Meeting of the Advisory Committee for Reproductive Health Drugs, Division of Reproductive and Urologic Products. FDA Web site. August 29, 2006.</li> <li>• Schuit E, Stock S, Groenwold RH, et al. Progestogens to prevent preterm birth in twin pregnancies: an individual participant data meta-analysis of randomized trials. <i>BMC Pregnancy Childbirth</i>. 2012;12:13.</li> <li>• González-Quintero VH, de la Torre L, Rhea DJ, et al. Impact of prior gestational age at preterm delivery on effectiveness of 17-alpha-hydroxyprogesterone caproate in practice. <i>Am J Obstet Gynecol</i>. 2010;203(3):257.e1-5.</li> <li>• Rebarber A, Fox NS, Klauser CK, et al. Using 17 <math>\alpha</math>-hydroxyprogesterone caproate to impact rates of recurrent preterm delivery in clinical practice. <i>J Matern Fetal Neonatal Med</i>. 2010;23(10):1139-1142.</li> <li>• Rode L, Langhoff-Roos J, Andersson C, et al. Systematic review of progesterone for the prevention of preterm birth in singleton pregnancies. <i>Acta Obstet Gynecol Scand</i>. 2009;88(11):1180-1189.</li> <li>• Swamy GK, Ostbye T, Skjaerven R. Association of preterm birth with long-term survival, reproduction, and next-generation preterm birth. <i>JAMA</i>. 2008;299(12):1429-1436.</li> <li>• Northen AT, Norman GS, Anderson K, et al. Follow-up of children exposed in utero to 17 alpha-hydroxyprogesterone caproate compared with placebo. <i>Obstet Gynecol</i>. 2007;110(4):865-872.</li> </ul> <p>15.</p>
<b>CFR</b>	
<b>WAC</b>	284-43-2050
<b>RCW</b>	
<b>Contract Citation</b>	<input type="checkbox"/> WAH <input type="checkbox"/> IMC <input type="checkbox"/> MA
<b>Other Requirements</b>	
<b>NCQA Elements</b>	

## Revision History

Revision Date	Revision Description	Revision Made By
12/23/2015	New	Kelly Force; Yusuf Rashid, RPh
12/24/2015	Approval	MMLT
11/29/2016	Background, Criteria, References	Sophia Yun, PharmD
12/06/2016	Approval	MMLT
07/24/2017	Criteria completely updated and revised	Michael Sporck, Pharmacy Intern Sophia Yun, PharmD
07/25/2017	Approved	MMLT
03/08/2018	Reassigned from UM to PM	Cindy Bush
04/25/2018	Transferred to new template	Cindy Bush
05/18/2018	Updated and removed Accredo requirement	Catherine Vu, PharmD
06/14/2018	Approval	UM Committee