hydroxyprogesterone caproate Injection (Makena®, generics)

Policy # 00302
Original Effective Date: 07/20/2011
Current Effective Date: 03/09/2020

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider the use of brand and generic hydroxyprogesterone caproate injection (Makena®)‡ to reduce the risk of preterm birth in women to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for the use of brand and generic hydroxyprogesterone caproate injection (Makena) to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth (SPTB) will be considered when all of the following patient selection criteria are met:

- Patient has a history of singleton spontaneous preterm birth defined as delivery at less than 37 weeks, 0 days gestation); AND
- Patient is currently pregnant with a singleton pregnancy and dosed as follows:
    - Begin administration between 16 weeks, 0 days and 20 weeks, 6 days of gestation; AND
    - Continue administration once weekly until 36 weeks, 6 days of gestation or delivery, whichever occurs first.

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When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of brand and generic hydroxyprogesterone caproate injection (Makena) when patient selection criteria are not met to be **investigational.***

Background/Overview

Makena, or hydroxyprogesterone caproate injection, is a progestin indicated to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton SPTB. It is not intended for use in women with multiple gestations or other risk factors for preterm birth. Makena has two dosage forms: an autoinjector (for subcutaneous use, 275 mg) and vials (for intramuscular administration, 250 mg). The vial form is available as a generic. Makena is administered once weekly by a healthcare provider beginning between 16 weeks, 0 days and 20 weeks, 6 days gestation. It is not intended to stop active preterm labor, and effects in active labor are unknown. Makena is a synthetic progestin. The mechanism by which hydroxyprogesterone caproate reduces the risk of recurrent preterm birth is not known.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

On February 3, 2011, the FDA approved the drug Makena for the reduction of the risk of certain preterm births in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, Blue Cross and Blue Shield Association technology assessment program (TEC) and other non-affiliated technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

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The efficacy and safety of hydroxyprogesterone caproate injection were established in a randomized, double-blind, multicenter, vehicle-controlled, pivotal study in women between the ages of 16 and 43 years. Women were pregnant with a singleton pregnancy with a documented history of singleton SPTB, defined as delivery < 37 weeks gestation following spontaneous preterm labor or premature rupture of membranes (PROM). Major exclusion criteria included: pregnancy with multiple gestations, known fetal anomaly, progesterone or heparin treatment during the current pregnancy, current or planned cervical cerclage, hypertension requiring medication, or seizure disorder. Patients were randomized between 16 weeks, 0 days gestation and 20 weeks, 6 days gestation; ultrasound examination was used to confirm gestational age and the absence of congenital abnormality. The primary endpoint was the proportion of women in each treatment arm who delivered at < 37 weeks gestation.

The study took place in the United States and was conducted with an investigational formulation of hydroxyprogesterone caproate identical to Makena. Women were randomized to receive weekly intramuscular (IM) injections from a study nurse. Patients were assigned to treatment with hydroxyprogesterone caproate, 250 mg in 1 mL (n = 310), or vehicle (castor oil) (n = 153) in a 2:1 ratio. All women also received standard medical care appropriate for their level of risk of preterm delivery. The characteristics of the women qualifying for the study were similar between the two treatment groups: approximately 59% Black, 25.5% Caucasian, 13.9% Hispanic, and 0.6% Asian; mean age (approximately 26 years); mean body mass index (BMI) (26.9 kg/m^2); and duration of gestation at the time of qualifying delivery (30.6 weeks and 31.3 weeks for the hydroxyprogesterone caproate and vehicle groups, respectively). However, the number of previous preterm deliveries was significantly higher in the vehicle group (1.4 ± 0.7 and 1.6 ± 0.9 deliveries for the hydroxyprogesterone caproate and vehicle groups, respectively; P = 0.007).

Noncompliance, defined as a gap of ≥ 10 days between any two injections, was assessed for all of the women in the study. Over 91% of the women were compliant with all of the injections with no difference between patients receiving hydroxyprogesterone caproate and vehicle. The study planned to enroll 500 women, but after 463 women had undergone randomization, the trial was discontinued early because statistical significance of the primary endpoint had been reached. There was a statistically significant reduction in the rate of delivery before 37 weeks gestation with patients treated with hydroxyprogesterone caproate compared to vehicle with the rates of delivery prior to Week 37 similar for Black and non-Black women. Among women of similar risk, the number needed

to treat (NNT) was 5 to 6 women (95% confidence interval [CI]: 3.6, 11.1) to prevent one preterm delivery prior to 37 weeks gestation. Patients treated with hydroxyprogesterone caproate also had statistically significant reductions in the rates of delivery prior to 35 weeks and 32 weeks gestation. A small increase in the rate of miscarriage occurred in the hydroxyprogesterone caproate group compared to patients taking vehicle; however, this difference was not statistically significant. There was not a statistically significant difference in the rate of hospital visits for preterm labor, use of tocolytic therapy, administration of corticosteroids for fetal lung maturity, cesarean delivery, or chorioamnionitis between the hydroxyprogesterone caproate and vehicle treatment groups.

Refer to Table 1 for additional details of pregnancy outcomes.

Table 1. Pregnancy Outcomes from Study 1.

	Hydroxyprogesterone Caproate Group (n = 306)	**Vehicle Group (n = 153)**	**Relative Risk***
Delivery before 37 weeks gestation[a]	**111 (36.3%)**	**84 (54.9%)**	**0.66 (0.54, 0.81)^**
Spontaneous	90 (29.4%)	69 (45.1%)	0.65 (0.51, 0.83)
Indicated because of complications	21 (6.9%)	15 (9.8%)	0.70 (0.37, 1.32)
Delivery before 35 weeks gestation	**63 (20.6%)**	**47 (30.7%)**	**0.67 (0.48, 0.93)#**
Delivery before 32 weeks gestation	**35 (11.4%)**	**30 (19.6%)**	**0.58 (0.37, 0.91)φ**
Miscarriage at < 20 weeks gestation	5 (1.6%)	0	N/A

*With 95% confidence interval; ^P = 0.001; #P = 0.0165; φP = 0.0180; [a]Primary outcome.

Study 1 was not adequately powered to assess infant morbidity and mortality. The incidence of certain outcomes, including infant birth weight < 1,500 grams, neonatal death, transient tachypnea, respiratory distress syndrome, bronchopulmonary dysplasia, ventilator support, grade 3 or 4 intraventricular hemorrhage, necrotizing enterocolitis, patent ductus arteriosus, retinopathy, and proven sepsis did not differ significantly between treatment groups. However, a significant

improvement was noted in the birth weight < 2,500 grams, supplemental oxygen use, and any grade of intraventricular hemorrhage in patients treated with hydroxyprogesterone caproate. A small increase in the rate of stillbirth occurred in the hydroxyprogesterone caproate group compared to patients taking vehicle; however, this difference was not statistically significant.

Refer to Table 2 for additional details of fetal and neonatal outcomes.

Table 2 Fetal and Neonatal Outcomes from Study 1

Outcome	Hydroxyprogesterone Caproate Group (n = 306)	Vehicle Group (n = 153)	Relative Risk*
Stillbirth (antepartum or intrapartum)	6/306 (2%)	2/153 (1.3%)	1.50 (0.31, 7.34)
Birth weight < 2,500 g	82/301 (27.2%)	62/151 (41.1%)	0.66 (0.51, 0.87)
Supplemental oxygen	45/303 (14.9%)	36/151 (23.8%)	0.62 (0.42, 0.92)
Intraventricular hemorrhage (any grade)	4/305 (1.3%)	8/153 (5.2%)	0.25 (0.8, 0.82)

*With 95% confidence interval; ^Data expressed as number/total number with data.

Figure 1 Proportion of Enrolled Patients Pregnant by Gestational Age (hydroxyprogesterone caproate [17 OHP] and Vehicle [Placebo])

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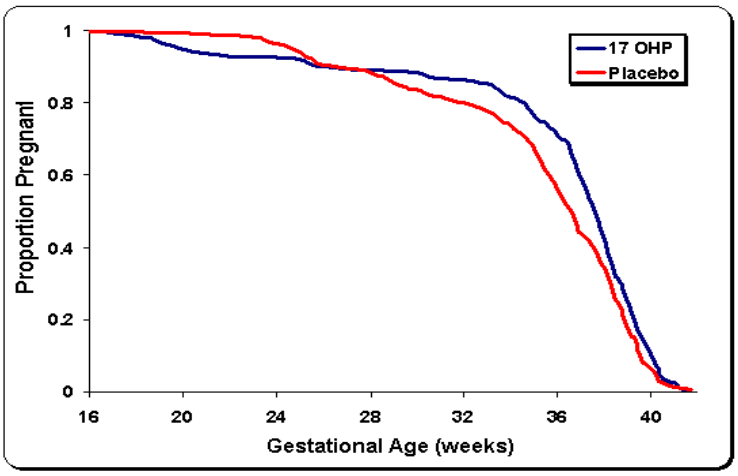

There have also been randomized, double-blind, vehicle-controlled controlled studies that showed no benefit of weekly 17P injections in women pregnant with multiple gestations.

The American College of Obstetricians and Gynecologists (ACOG) has published a Committee opinion (updated in 2008) on the use of progesterone to reduce preterm birth. The Committee notes that progesterone supplementation should be offered to women with a singleton pregnancy and a prior SPTB due to spontaneous preterm labor or PROM. The Committee does not recommend cervical length screening; however, progesterone supplementation may be considered in asymptomatic women with a short cervix (< 15 mm). Hydroxyprogesterone caproate and vaginal progesterone are mentioned as forms of progesterone that have shown evidence in certain populations to reduce preterm birth.

In a single-dose, open-label, randomized, parallel design bioavailability study in 120 healthy postmenopausal women, comparable systemic exposure of hydroxyprogesterone caproate was seen when hydroxyprogesterone caproate was administered subcutaneously with the auto-injector (1.1 mL) in the back of the upper arm and when hydroxyprogesterone caproate was dosed intramuscularly (1 mL) in the upper outer quadrant of the gluteus maximus.

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References

1. Makena injection [package insert]. St. Louis, MO: Ther-Rx Corporation; Revised February, 2018.
2. Meis PJ, Klebanoff M, Thom E, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. *N Engl J Med*. 2003;348(24):2379-2385.
3. Data on file. Gestiva. NDA 21-945. Food and Drug Administration Web site. August 2, 2006.
4. Society for Maternal Fetal Medicine Publications Committee. ACOG Committee Opinion number 419 (replaces no. 291, November 2003). Use of progesterone to reduce preterm birth. *Obstet Gynecol*. 2008;112(4):963-965.
5. Wesley B. Meeting of the Advisory Committee for Reproductive Health Drugs, Division of Reproductive and Urologic Products. FDA Web site. August 29, 2006. Available at: http://www.fda.gov/default.htm
6. Rouse DJ, Caritis SN, Peaceman AM, et al. A trial of 17 alpha-hydroxyprogesterone caproate to prevent prematurity in twins. *N Engl J Med*. 2007;357(5):454-461.
7. Caritis SN, Rouse DJ, Peaceman AM, et al. Prevention of preterm birth in triplets using 17 alpha-hydroxyprogesterone caproate: a randomized controlled trial. *Obstet Gynecol*. 2009;113(2 Pt 1):285-292.
8. 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. *Am J Obstet Gynecol*. 2010;203(3):248.e1-9.
9. Rjosk HK, Abendstein BJ, Kreuzer E, Schwärzler P. Preliminary experience with steroidal ovarian suppression for prevention of severe ovarian hyperstimulation syndrome in IVF patients. *Hum Fertil (Camb).* 2001;4(4):246-248.
10. Costabile L, Gerli S, Manna C, et al. A prospective randomized study comparing intramuscular progesterone and 17alpha-hydroxyprogesterone caproate in patients undergoing *in vitro* fertilization-embryo transfer cycles. *Fertil Steril.* 2001;76(2):394-396.
11. 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. *Fertil Steril.* 2008;89(4):789-792.
12. FDA label information Makena 2011.
13. Express Scripts Makena (hydroxyprogesterone caproate injection). 2011.

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07/07/2011	Medical Policy Committee review
07/20/2011	Medical Policy Implementation Committee approval. New policy.
06/28/2012	Medical Policy Committee review
07/27/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/27/2013	Medical Policy Committee review
07/17/2013	Medical Policy Implementation Committee approval. Added "injection (Makena)" to the first sentence of the patient selection criteria and added "and dosed as follows" to the second bullet of the patient selection criteria. Coverage eligibility unchanged.
07/10/2014	Medical Policy Committee review
07/16/2014	Medical Policy Implementation Committee approval. No change to coverage.
06/25/2015	Medical Policy Committee review
07/15/2015	Medical Policy Implementation Committee approval. No change to coverage.
06/30/2016	Medical Policy Committee review
07/20/2016	Medical Policy Implementation Committee approval. No change to coverage.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
07/06/2017	Medical Policy Committee review
07/19/2017	Medical Policy Implementation Committee approval. No change to coverage.
05/03/2018	Medical Policy Committee review
05/16/2018	Medical Policy Implementation Committee approval. Updated dosage form information to include the subcutaneous form.
02/07/2019	Medical Policy Committee review
02/20/2019	Medical Policy Implementation Committee approval. Updated to reflect the availability of generic Makena. Added "generics" to the title.
02/06/2020	Medical Policy Committee review
02/12/2020	Medical Policy Implementation Committee approval. Updated to reflect the availability of generic Makena. Added "generics" to the title.

Next Scheduled Review Date: 02/2021

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Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2019 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes
HCPCS	J1726, J1729
ICD-10 Diagnosis	O09.211-O09.219, O47.00-470.3, O47.1-047.9, O60.10X0-O60.10X9, O60.12X0-O60.12X9, O60.13X0-O60.13X9, O60.14X0-O60.14X9, O60.20X0-O60.20X9, O60.22X0-O60.22X9, O60.23X0-O60.23X9, Z87.51

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*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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‡ Indicated trademarks are the registered trademarks of their respective owners.

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