

## Corporate Medical Policy

### Progesterone Therapy in High Risk Pregnancies

**File Name:** progesterone\_therapy\_in\_high\_risk\_pregnancies  
**Origination:** 01/2005  
**Last CAP Review:** 3/2018  
**Next CAP Review:** 3/2019  
**Last Review:** 3/2018

#### Description of Procedure or Service

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Preterm labor and delivery are major determinants of neonatal morbidity and mortality. In the U.S., the rate of preterm birth is 12%. A variety of diagnostic and prophylactic measures to prevent preterm labor and delivery have been investigated, including home uterine activity monitoring, subcutaneous terbutaline tocolytic therapy, and routine culture and antibiotic treatment of subclinical bacterial vaginosis. To date, none of these have made a significant demonstrable impact on the incidence rate of preterm delivery.

Delalutin® (hydroxyprogesterone caproate) injection was approved in 1956 for a variety of gynecologic and obstetric conditions including the treatment or prevention of threatened spontaneous abortion and habitual abortion. The original approval was based on safety as defined by existing U.S. Food and Drug Administration (FDA) regulations. In 1971, an additional review under the Drug Efficacy Implementation program determined that the drug was probably effective for those indications. In 1973, FDA modified the effectiveness finding and, along with a review of recent data on the potential association of prenatal hormone exposure and fetal cardiac malformations, withdrew labeled indications for progestin use in pregnancy. In 2010, after a series of interactions between Bristol Myers Squibb (the sponsor of the original new drug application) and FDA, the Administration announced that the manufacturer's removal of the product from the market was not due to safety and efficacy reasons. Progesterone in compounded form continued to be used for pregnancy-related second and third-trimester indications.

#### Regulatory Status

In 2007, the synthetic progestin, hydroxyprogesterone caproate, was granted an orphan designation. In February 2011, Makena®, an injectable formulation of 17 $\alpha$ -progesterone caproate, was granted a new drug approval by FDA to reduce the risk for preterm birth in singleton pregnancies in women with a history of previous singleton preterm birth. On June 26, 2017, the current manufacturer (AMAG Pharmaceuticals) announced that FDA had accepted a supplemental new drug approval for a Makena® subcutaneous autoinjector for review.

#### Related Policies

Acute and Maintenance Tocolysis

This policy does not address procedures or treatments related to transgender services. Please see the policy "Gender Confirmation Surgery and Hormone Therapy" for information regarding transgender services.

**\*\*\*Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

# Progesterone Therapy in High Risk Pregnancies

## Policy

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**BCBSNC will provide coverage for progesterone therapy to reduce preterm birth in high risk pregnancies when the medical criteria and guidelines shown below are met.**

## Benefits Application

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This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

The Healthy Outcomes Maternity program is available to most members who are pregnant. This program gives mothers-to-be helpful tools and information so they can make healthy choices throughout their pregnancy.

## When Progesterone Therapy is covered in High Risk Pregnancies

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For individuals with a singleton pregnancy and prior history of spontaneous preterm birth before 37 weeks of gestation, the following may be considered medically necessary:

- Weekly injections of 17 alpha-hydroxyprogesterone caproate, performed in the office setting, initiated between 16 and 20 weeks of gestation and continued until 36 weeks 6 days.
- Daily vaginal progesterone between 24 and 34 weeks of gestation.

For individuals with a singleton pregnancy and a short cervix (less than 20 mm), the following may be considered medically necessary:

- Daily vaginal progesterone initiated between 20 and 23 weeks 6 days of gestation and continued until 36 weeks 6 days.

## When Progesterone Therapy is not covered in High Risk Pregnancies

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Progesterone therapy as a technique to prevent preterm labor is considered investigational in pregnant individuals with other risk factors for preterm delivery, including, but not limited to:

- Twin or multiple gestation;
- Prior episode of preterm labor in current pregnancy (i.e., progesterone therapy in conjunction with tocolysis or following successful tocolysis);
- Positive tests for cervicovaginal fetal fibronectin
- In conjunction with or following cervical cerclage; and/or
- Uterine anomaly.

Administration of 17 alpha-hydroxyprogesterone caproate or vaginal suppositories in the home setting by a health professional is considered not medically necessary.

## Policy Guidelines

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In May 2014 (reaffirmed 2016), the American College of Obstetricians and Gynecologists (ACOG) published a Practice Bulletin on multifetal gestations that included the following statement on progesterone therapy:

---Progesterone treatment does not reduce the incidence of spontaneous preterm birth in unselected women with twin or triplet gestations and, therefore, is not recommended as an intervention to prevent preterm birth in women with multiple gestations.

# Progesterone Therapy in High Risk Pregnancies

Previously, in October 2012, ACOG published a Practice Bulletin on prediction and prevention of preterm birth. The bulletin includes the following recommendations related to progesterone therapy in women with singleton pregnancies:

---A woman with a singleton pregnancy and a prior spontaneous 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.

---Vaginal progesterone is recommended as a management option to reduce the risk of preterm birth in asymptomatic women with a singleton gestation without a prior preterm birth with an incidentally identified very short cervical length less than or equal to 20mm before or at 24 weeks of gestation.

For individuals who have a singleton pregnancy and prior spontaneous preterm birth before 37 weeks of gestation who receive intramuscular injections of progesterone or vaginal progesterone, the evidence includes randomized controlled trials (RCTs) and a meta-analysis. Relevant outcomes are overall survival, morbid events, and treatment-related morbidity. Pooled analyses of RCT data found statistically significant reductions in term birth rates with progesterone compared with placebo. Findings were similar in studies that used injectable or vaginal progesterone but there are clinical opinions on the preferred agent for this indication. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals who have a singleton pregnancy and a short cervix (<20 mm) who receive intramuscular injections of progesterone, the evidence includes 2 RCTs. Relevant outcomes are overall survival, morbid events, and treatment-related morbidity. A placebo-controlled RCT did not find that intramuscular progesterone significantly decreased the rate of preterm birth. An RCT comparing intramuscular and vaginal progesterone did not find a significant difference in preterm delivery in the subgroup of women with a short cervix; however, the ability to draw conclusions from this trial is limited because it was not powered for a subgroup analysis. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have a singleton pregnancy and a short cervix (<20 mm) who receive vaginal progesterone, the evidence includes several RCTs and a meta-analysis of individual patient data from the RCTs. Relevant outcomes are overall survival, morbid events, and treatment-related morbidity. A meta-analysis of RCTs found that vaginal progesterone significantly reduced the rate of preterm delivery. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals who are pregnant with twins who receive intramuscular injections of progesterone or vaginal progesterone, the evidence includes RCTs and systematic reviews. Relevant outcomes are overall survival, morbid events, and treatment-related morbidity. The RCTs and several meta-analyses of these studies have consistently found that progesterone is not significantly associated with decreased rates of preterm delivery or other perinatal outcomes in pregnant women with twins. One RCT found that a high dose of vaginal progesterone was associated with a lower rate of preterm delivery in women pregnant with twins who also had a short cervix; additional studies in this population are needed to confirm findings and optimal dose of medication. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are pregnant with triplets who receive intramuscular injections of progesterone or vaginal progesterone, the evidence includes RCTs and a meta-analysis. Relevant outcomes are overall survival, morbid events, and treatment-related morbidity. Two RCTs and a meta-analysis of data from these 2 trials did not find that progesterone was associated with improved outcomes in women pregnant with triplets. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with a singleton pregnancy and preterm premature rupture of the membranes who receive intramuscular injections of progesterone or vaginal progesterone, the evidence includes 1 RCT. Relevant outcomes are overall survival, morbid events, and treatment-related morbidity. The RCT did not find a lower rate of preterm delivery or neonatal outcomes (e.g., birthweight, neonatal mortality) in women treated with progesterone versus placebo. The evidence is insufficient to determine the effects of the technology on health outcomes.

# Progesterone Therapy in High Risk Pregnancies

For individuals with a singleton pregnancy and prior episode of preterm labor in the current pregnancy who receive intramuscular injections of progesterone or vaginal progesterone, the evidence includes RCTs and meta-analyses. Relevant outcomes are overall survival, morbid events, and treatment-related morbidity. A meta-analysis of RCTs on intramuscular progesterone did not find significantly better outcomes compared with control interventions. A meta-analysis of RCTs on vaginal progesterone had mixed findings. The evidence is insufficient to determine the effects of the technology on health outcomes.

## Billing/Coding/Physician Documentation Information

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This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at [www.bcsnc.com](http://www.bcsnc.com). They are listed in the Category Search on the Medical Policy search page.

*Applicable service codes: J1726, S9208*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

## Scientific Background and Reference Sources

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### **From policy titled: Preventing Premature Labor and Delivery**

Meis PJ, Klebanoff M, Thom E et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. *N Eng J Med* 2003;348(24):2379-85.

da Fonseca EB, Bittar RE, Carvalho MH et al. Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: a randomized placebo- controlled double-blind study. *Am J Obstet Gynecol* 2003;188(2):419-24.

American College of Obstetricians and Gynecologists. ACOG Committee Opinion No. 291. Use of Progesterone to Reduce Preterm Birth. *Obstet Gynecol* 2003;102:1115-6

Specialty Matched Consultant Advisory Panel - 12/2004.

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.03, 12/14/05.

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.11, 3/7/06.

BCBSA Medical Policy Reference Manual [Electronic Version]. 4.01.09, 12/14/05.

BCBSA Medical Policy Reference Manual [Electronic Version]. 4.04.16, 12/14/05.

Specialty Matched Consultant Advisory Panel - 12/13/2006

### **For policy titled: Progesterone Therapy in High Risk Pregnancies**

BCBSA Medical Policy Reference Manual [Electronic Version]. 4.04.16, 12/12/06.

BCBSA Medical Policy Reference Manual [Electronic Version]. 4.04.16, 4/9/08.

17-Alpha hydroxyprogesterone caproate for prevention of preterm birth: overview of FDA background document. Rockville, MD: Food and Drug Administration. 2006 Available at: <http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4227B1-02-01-FDA-Background.pdf>.

Specialty Matched Consultant Advisory Panel - 12/2008

American College of Obstetricians and Gynecologists' Committee on Obstetric Practice and the Society for Maternal Fetal Medicine. Use of Progesterone to Reduce Preterm Birth. ACOG Committee Opinion Number 419 (replaces No. 291. November 2003). *Obstet Gynecol* 2008; 112(4):963-5.

# Progesterone Therapy in High Risk Pregnancies

- BCBSA Medical Policy Reference Manual [Electronic Version]. 4.04.16, 10/06/09  
Senior Medical Director review 9/2010
- BCBSA Medical Policy Reference Manual [Electronic Version]. 4.04.16, 7/14/2011
- BCBSA Medical Policy Reference Manual [Electronic Version]. 4.01.16, 11/10/2011  
Specialty Matched Consultant Advisory Panel – 9/2012
- BCBSA Medical Policy Reference Manual [Electronic Version]. 4.01.16, 9/13/2012
- Committee on Practice Bulletins-The American College of Obstetricians and Gynecologists. Practice bulletin no. 130: prediction and prevention of preterm birth. *Obstet Gynecol* 2012; 120(4):964-73.
- Specialty Matched Consultant Advisory Panel – 9/2013
- BCBSA Medical Policy Reference Manual [Electronic Version]. 4.01.16, 9/12/2013
- Specialty Matched Consultant Advisory Panel – 9/2014
- BCBSA Medical Policy Reference Manual [Electronic Version]. 4.01.16, 10/9/2014
- American College of Obstetricians and Gynecologists (ACOG). Multifetal gestations: twin, triplet, and higher-order multifetal pregnancies. Washington (DC): American College of Obstetricians and Gynecologists (ACOG); 2014 May. 15 p. (ACOG practice bulletin; no. 144). Last accessed December 2014 at <http://www.guideline.gov/content.aspx?id=48025&search=multifetal+gestations>.
- Specialty Matched Consultant Advisory Panel – 9/2015
- BCBSA Medical Policy Reference Manual [Electronic Version]. 4.01.16, 10/15/2015
- BCBSA Medical Policy Reference Manual [Electronic Version]. 4.01.16, 8/11/2016
- BCBSA Medical Policy Reference Manual [Electronic Version]. 4.01.16, 8/10/2017

## Policy Implementation/Update Information

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### **From policy titled: Preventing Premature Labor and Delivery**

- 1/6/2005 Specialty Matched Consultant Advisory Panel review - 12/9/04. Added Section re: Progesterone Therapy in High Risk Pregnancies. Reference sources added.
- 1/17/07 Specialty Matched Consultant Advisory Panel review - 12/13/06. Under Section II - Progesterone Therapy in High Risk Pregnancies, second paragraph, added "by a health care professional" to the following sentence: " Administration of 17 alpha-hydroxyprogesterone caproate or vaginal suppositories in the home setting *by a health professional* is considered not medically necessary." Reference sources added. Added CPT code 90772 to the "Billing /Coding" section. Deleted CPT code 90782 from "Billing /Coding" section. No other changes. (pmo)

### **For policy titled: Progesterone Therapy in High Risk Pregnancies**

- 1/12/09 Section II: Progesterone Therapy in High Risk Pregnancies removed from policy entitled: "Preventing Premature Labor and Delivery". Separate policy issued entitled "Progesterone Therapy in High Risk Pregnancies". Separate policy has no changes to policy criteria (What is covered and What is not covered), only added policy guidelines and reference sources. (pmo)
- 6/22/10 Policy Number(s) removed (amw)

# Progesterone Therapy in High Risk Pregnancies

- 10/26/10 Description section revised. When Progesterone Therapy is Covered section revised to read: “Weekly injections of 17 alpha-hydroxyprogesterone caproate, performed in the office setting, between 16 and 36 weeks of gestation may be considered **medically necessary** for women with a singleton pregnancy and a prior history of spontaneous preterm birth before 37 weeks’ gestation. Daily vaginal progesterone between 24 and 34 weeks of gestation may be considered **medically necessary** for women with a singleton pregnancy and a prior history of spontaneous preterm birth before 37 weeks’ gestation.” The When Progesterone Therapy is Not Covered section revised to read: “In the absence of a prior history of spontaneous preterm birth, progesterone therapy as a technique to prevent preterm labor is considered **investigational** in pregnant women with other risk factors for preterm delivery, including, but not limited to multiple gestations, short cervical length, or positive tests for cervicovaginal fetal fibronectin, cervical cerclage, or a uterine anomaly.” Policy Guidelines updated. References updated. (adn)
- 1/18/2011 Specialty Matched Consultant Advisory Panel review 12/16/2010. Policy accepted as written. (adn)
- 10/11/11 Description section updated. When Covered section was changed to read: “For women with a singleton pregnancy and prior history of spontaneous preterm birth before 37 weeks’ gestation, the following may be considered medically necessary: Weekly injections of 17 alpha-hydroxyprogesterone caproate, performed in the office setting, initiated between 16 and 20 weeks of gestation and continued until 36 weeks 6 days, Daily vaginal progesterone between 24 and 34 weeks of gestation. For women with a singleton pregnancy and a short cervix (less than 20 mm), the following may be considered medically necessary: Daily vaginal progesterone initiated between 20 and 23 weeks 6 days of gestation and continue until 36 weeks 6 days.” The first statement in the When Not Covered section was revised to read: “Progesterone therapy as a technique to prevent preterm labor is considered investigational in pregnant women with other risk factors for preterm delivery, including, but not limited to multiple gestations, or positive tests for cervicovaginal fetal fibronectin, cervical cerclage, or a uterine anomaly.” Deleted CPT codes 90772 and 99506 from the Billing/Coding section and added code Q2042. Specialty Matched Consultant Advisory Panel review 9/28/11. (adn)
- 1/1/12 Code Q2042 deleted and replaced with code J1725 in Billing/Coding section. (adn)
- 11/13/12 Specialty Matched Consultant Advisory Panel review 9/19/12. No change to policy statement. (sk)
- 10/15/13 References added. Specialty Matched Consultant Advisory Panel review 9/18/13. Policy Guidelines updated. No change to policy statement. (sk)
- 4/1/14 Removed Home Uterine Activity Monitoring from the list of Related Policies. (sk)
- 10/14/14 Specialty Matched Consultant Advisory Panel review 9/30/14. No change to Policy statement. (sk)
- 12/30/14 References added. (sk)
- 10/30/15 Specialty Matched Consultant Advisory Panel review 9/30/15. (sk)
- 11/24/15 Reference added. Policy Guidelines updated. (sk)
- 11/22/16 Policy Guidelines section updated. Specialty Matched Consultant Advisory Panel. No change to policy statement. (an)
- 4/28/17 Specialty Matched Consultant Advisory Panel review 3/29/2017. No change to policy statement. (an)
- 6/30/17 Added new codes effective 7/1/2017: Q9985, Q9986. (an)
- 9/29/17 Description section updated. In the NonCovered section, wording revised to read: progesterone therapy in conjunction with or following cervical cerclage is considered

# Progesterone Therapy in High Risk Pregnancies

investigational. Policy Guidelines updated. Reference added. Codes Q9985, Q9986 added to Billing/Coding section. (an)

12/15/17 Effective 1/1/2018 new code J1726. Codes J1725, Q9985, Q9986 deleted. (an)

4/27/18 Specialty Matched Consultant Advisory Panel review 3/28/2018. No change to policy statement. (an)

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Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.