

## Corporate Medical Policy

### Progesterone Therapy in High Risk Pregnancies

**File Name:** progesterone\_therapy\_in\_high\_risk\_pregnancies

**Origination:** 01/2005

**Last Review:** 3/2023

#### 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 10% according to the Centers for Disease Control and Prevention. 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.

Progesterone dependent regulation of myometrial contractility and local inflammatory responses are thought to be the physiologic basis for the therapeutic use of progesterone and progestins to prevent preterm labor and birth. Progesterone and progestins can be administered by intramuscular or subcutaneous injection. Compounded vaginal suppositories or intravaginal administration of other formulations such as gels or tablets are also in use.

#### Regulatory Status

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.

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 approval by the FDA to reduce the risk for preterm birth in singleton pregnancies in women with a history of previous singleton preterm birth under its Accelerated Approval Program. The product also has an Orphan Drug Designation. The accelerated approval was based on results of an RCT, that reported that Makena® significantly reduced the risk of preterm birth before 37 weeks of gestational age. The study was not planned or conducted for drug approval and was not powered for neonatal morbidity or mortality outcomes. A confirmatory trial to assess efficacy and safety was required. In 2019, the FDA Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC) considered the results of the post-approval study (NCT01004029, Progestin's Role in Optimizing Neonatal Gestation study [PROLONG]). In PROLONG, Makena® did not significantly reduce the risk of preterm birth or neonatal mortality or morbidity. BRUDAC briefing materials prepared by AMAG Pharmaceuticals, Makena's manufacturer, are publicly

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available, as are minutes from this meeting. The BRUDAC voted 9 to 7 in favor of recommending that FDA withdraw its conditional approval of Makena. On October 5, 2020, the FDA Center for Drug Evaluation and Research (CDER) proposed that Makena (hydroxyprogesterone caproate injection) be withdrawn from the market. On October 14, 2020, AMAG Pharmaceuticals, Inc and Covis Pharma Group, requested a public hearing regarding this matter. On December 14, 2020, the manufacturer submitted supporting documentation detailing the basis for Makena remaining available for use in women who are at risk for preterm birth, including clinical study results that highlight the evidence of the effectiveness of Makena among minority women. In August 2021, the FDA announced that a public hearing would be held in 2022 to address the administration's decision. While the FDA reviews the submission of supporting documentation, Makena remains available.

In 2018, the FDA approved the first generic version of hydroxyprogesterone caproate as well as the Makena (hydroxyprogesterone caproate injection) Subcutaneous Auto-Injector.

This policy does not address procedures or treatments related to transgender services. Please see the policy “Gender Affirmation 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.***

## 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 in High Risk Pregnancies

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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The American College of Obstetricians and Gynecologists (ACOG) (2021) published an updated Practice Bulletin on the prediction and prevention of preterm birth. The Bulletin includes the following level A evidence recommendations related to progesterone therapy:

- "Vaginal progesterone is recommended for asymptomatic individuals without a history of preterm birth with a singleton pregnancy and a short cervix."
- "Intramuscular 17-OHPC is not recommended for prevention of preterm birth in patients who do not have a history of spontaneous preterm delivery."
- "Patients with a singleton pregnancy and a prior spontaneous preterm birth should be offered progesterone supplementation (either vaginal or intramuscular) in the context of a shared decision-making process incorporating the available evidence and the patient's preferences."

The Bulletin includes the following level B evidence recommendations related to progesterone therapy:

- "Intramuscular 17-OHPC is not recommended for prevention of preterm birth based solely on the indication of multiple gestation."
- "Routine prophylactic use of vaginal progesterone to prevent preterm birth in twin pregnancies is not recommended."

The Bulletin includes the following level C evidence recommendations related to progesterone therapy:

- "Patients with a singleton gestation, a prior spontaneous preterm birth, and a short cervix in the second trimester who are not on progesterone supplementation should be informed of their increased risk of preterm birth, the two treatment options available (vaginal progesterone and cerclage), and the uncertainty about which management course is best in the context of a shared decision-making process."
- "Patients with a singleton gestation, prior spontaneous preterm birth, and a short second-trimester cervix who are on progesterone supplementation should be informed of their increased risk of preterm birth, and cerclage may be offered in addition to continuation of progesterone."

ACOG (2021) updated and replaced its practice bulletin on multifetal gestations. The updated Practice Bulletin on multifetal gestations includes the following level A evidence recommendation related to 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."

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. The RCTs varied in baseline risk for preterm birth, the formulation of vaginal progesterone comparator used, the gestational age length of pregnancy at treatment initiation, and the duration of treatment. Two RCTs have compared IM progesterone to placebo in individuals who have a singleton pregnancy and prior spontaneous preterm birth. The RCT

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with a population most relevant to US women demonstrated a benefit for IM progesterone versus placebo with a significantly reduced risk of the primary outcome of preterm delivery at <37 weeks gestation as well as <35 and <32 weeks gestation. The RCT was used to support U.S. Food and Drug Administration accelerated approval. Gestational outcomes are considered surrogate outcomes expected to predict clinical benefit. Infants of women treated with 17P had significantly lower rates of necrotizing enterocolitis, intraventricular hemorrhage, and need for supplemental oxygen. There were no differences in any other neonatal mortality or morbidity outcomes. There were no significant differences between the 2 groups for maternal health related complications such as the rates of hospital visits for preterm labor, use of tocolytic drugs, corticosteroid use, cesarean delivery, or chorioamnionitis. The study was not planned or conducted for drug approval and was not powered for all neonatal morbidity or mortality outcomes. The confirmatory RCT (Progestin's Role in Optimizing Neonatal Gestation study [PROLONG]) found no significant benefit for IM progesterone for the primary outcome of preterm birth < 35 weeks as well as a defined neonatal composite outcome. A lower than predicted event rate resulted in the study being underpowered to assess the primary outcomes. A high proportion of patients enrolled from non-US regions further limited the clinical relevancy of the overall findings to US high-risk women. In the planned prespecified subgroup analysis of the treatment effects for the US subgroup versus non-US subgroups, there were nonsignificant trends of benefit for IM progesterone efficacy for preterm birth at < 32 weeks and < 35 weeks, but not <37 weeks gestation. The meta-analysis with the most relevant pooled population found significantly lower rates of preterm birth < 34 weeks with vaginal versus IM progesterone, but no differences at < 28 or < 37 weeks. No review pooled data on neonatal mortality or morbidity outcomes was reported and a single RCT demonstrated no differences. Conducting a new confirmatory placebo-controlled trial would be ideal but is unlikely because IM progesterone has been widely used for many years and continues to be guideline-recommended. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have a singleton pregnancy and prior spontaneous preterm birth before 37 weeks of gestation who receive vaginal progesterone, the evidence includes several RCTs and systematic reviews. Relevant outcomes are OS, morbid events, and treatment-related morbidity. Placebo-controlled RCTs are heterogenous in baseline risk, the formulation of vaginal progesterone used, and the control treatment (e.g., placebo, no treatment). Statistically significant reductions in preterm delivery rates varied across RCTs for vaginal progesterone based on these sources of heterogeneity. Pooled analyses of RCT data have found statistically significant reductions in preterm birth rates with progesterone compared with placebo, but interpretation of their findings is limited by their inclusion of study populations with a wider range of risk factors than the intended population. The evidence is sufficient to determine 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 IM injections of progesterone, the evidence includes 1 RCT. Relevant outcomes are OS, morbid events, and treatment-related morbidity. The placebo-controlled randomized trial did not find that IM progesterone significantly decreased the rate of preterm birth. 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 RCTs and meta-analyses of individual patient data from the RCTs. Relevant outcomes are OS, morbid events, and treatment-related morbidity. Several RCTs have evaluated vaginal progesterone compared to placebo and compared to IM progesterone for preventing preterm birth in women with short cervical length. These trials have tended to be underpowered for meaningful clinical outcomes. Multiple meta-analyses found that vaginal progesterone significantly reduced the rate of preterm delivery in women with a short cervical length. In addition, there was a benefit in a subgroup of women with singleton pregnancies and no prior preterm birth. The evidence is sufficient to determine the effects of the technology on health outcomes.

For individuals who are pregnant with twins who receive IM injections of progesterone or vaginal progesterone, the evidence includes RCTs and systematic reviews. Relevant outcomes are OS, 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

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delivery or other perinatal outcomes in pregnant women with twins. Two RCTs of high doses of vaginal progesterone (400 to 600 mg) in women pregnant with twins demonstrated inconsistent benefits depending on preterm birth outcome definition (e.g., before 32 or 34 weeks; between 24-33 weeks) and proportion of women 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 IM injections of progesterone or vaginal progesterone, the evidence includes RCTs and a meta-analysis. Relevant outcomes are OS, morbid events, and treatment-related morbidity. Two RCTs and a meta-analysis of data from these 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 IM injections of progesterone or vaginal progesterone, the evidence includes 2 published RCTs and a systematic review of 6 RCTs. Relevant outcomes are OS, morbid events, and treatment-related morbidity. The 2 published RCTs identified did not find improved pregnancy and neonatal outcomes in women who received progesterone vs placebo. A 2018 systematic review identified 6 RCTs that compared IM progesterone with placebo or no treatment in singleton pregnancies with preterm premature rupture of fetal membranes (PPROM); no significant differences between the groups were found. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with a singleton pregnancy following successful tocolysis of a prior episode of preterm labor in the current pregnancy who receive IM injections of progesterone or vaginal progesterone, the evidence includes RCTs and meta-analyses. Relevant outcomes are OS, morbid events, and treatment-related morbidity. These RCTs demonstrated inconsistent benefits for progesterone. Heterogeneity in preterm birth outcome definitions (e.g., birth at < 32, 34, or 37 weeks or mean/median gestational age) and methodologic limitations (e.g., lack of blinding, inadequate handling of missing data) make it difficult to draw conclusions about the source of the variation. Meta-analyses of RCTs have not definitively found that IM progesterone or vaginal progesterone used as maintenance tocolysis reduces the rate of preterm birth or improves other outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

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## Billing/Coding/Physician Documentation Information

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.bcbsnc.com](http://www.bcbsnc.com). They are listed in the Category Search on the Medical Policy search page.

*Applicable service codes: J1726, J1729, 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.

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## Scientific Background and Reference Sources

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

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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.

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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.

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Specialty Matched Consultant Advisory Panel – 9/2014

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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> .

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BCBSA Medical Policy Reference Manual [Electronic Version]. 4.01.16, 10/15/2015

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## 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)



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- 6/22/10 Policy Number(s) removed (amw)
- 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)

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- 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 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)
- 4/16/19 Description and Policy Guidelines sections updated. References added. Specialty Matched Consultant Advisory Panel review 3/20/2019. No change to policy statement. (an)
- 3/31/20 Description, Policy Guidelines, Coding and Reference sections updated. Specialty Matched Consultant Advisory Panel review 3/18/2020. No change to policy statement. (eel)
- 3/31/21 Description, Policy Guidelines, and Reference sections updated. Specialty Matched Consultant Advisory Panel review 3/9/2021. No change to policy statement. (bb)
- 3/31/22 References sections updated. Specialty Matched Consultant Advisory Panel review 3/2022. Medical Director review 3/2022. No change to policy statement. (tt)
- 3/31/23 Description, Regulatory Status, Policy Guidelines, and Reference sections updated. Specialty Matched Consultant Advisory Panel review 3/2023. Medical Director review 3/2023. No change to policy statement. (tt)

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