



**BlueCross BlueShield  
of Alabama**

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**Name of Blue Advantage Policy:**  
**Acute and Maintenance Tocolysis**

Policy #: 471  
Category: Pharmacology

Latest Review Date: April 2021  
Policy Grade: Effective 10/01/2018,  
Active policy but no longer  
scheduled for regular literature  
reviews or updates.

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**BACKGROUND:**

*Blue Advantage medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational\*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
  - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
  - *Furnished in a setting appropriate to the patient's medical needs and condition;*
  - *Ordered and furnished by qualified personnel;*
  - *One that meets, but does not exceed, the patient's medical need; and*
  - *At least as beneficial as an existing and available medically appropriate alternative.*

*\*Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill **Original Medicare** for covered services that are related to **clinical trials** that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

## **POLICY:**

**Blue Advantage** will treat **acute tocolytic therapy** with parenteral terbutaline, calcium channel blockers, magnesium sulfate, and prostaglandin inhibitors as a **covered benefit** for the induction of tocolysis in patients with preterm (<37 weeks' gestational age) labor.

**Blue Advantage** will treat **maintenance tocolytic therapy** (beyond 48-72 hours) with any medication as a **non-covered benefit** and as **investigational**.

**NOTE:** On February 17, 2011, the FDA issued a safety alert with notice of a label change for terbutaline. The safety alert can be found online at:  
<https://www.fda.gov/Drugs/DrugSafety/ucm243539.htm>

*Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.*

## **DESCRIPTION OF PROCEDURE OR SERVICE:**

Tocolysis refers to the suppression of preterm labor to delay delivery. A variety of medications are used as tocolytic agents; although none of the currently available options are approved by the U.S. Food and Drug Administration (FDA) for this indication. These medications have also been evaluated as maintenance therapy following successful tocolysis.

General indications for tocolysis, or the suppression of preterm labor, include continued regular uterine contractions associated with cervical changes in a pregnant woman at less than 37 weeks' gestation. Successful delay of preterm delivery allows further fetal development and precludes the complications of preterm delivery, especially neonatal respiratory distress syndrome. Even short-term delay of delivery is thought to be beneficial in that it allows treatment of the patient with corticosteroids, which has proved beneficial in ameliorating the effects of neonatal respiratory distress syndrome. In some cases, a short delay in delivery may also allow transport of the pregnant woman to a medical center better equipped to handle premature delivery and neonatal intensive care.

### **Treatment**

Several agents have been used for tocolysis. The calcium channel blocker, Nifedipine, is commonly used for tocolysis. Terbutaline has also been used and is a beta-sympathomimetic that can be administered subcutaneously. Terbutaline has also been administered by continuous subcutaneous infusion via a portable pump for maintenance tocolysis, but should not be used for more than 72 hours. Other tocolytic drugs include magnesium sulfate and nonsteroidal anti-inflammatory drugs.

Tocolytic agents have potential risks as well as potential benefits. A 2012 guideline issued (reaffirmed 2014) by the American College of Obstetricians and Gynecologists (ACOG) summarized the potential adverse effects of common classes of tocolytic agents:

### **Calcium Channel Blockers**

- Maternal side effects: Dizziness, flushing, and hypotension; suppression of heart rate, contractility, and left ventricular systolic pressure when used with magnesium sulfate; and elevation of hepatic transaminases.
- Fetal or newborn adverse effects: No known adverse effects.

### **Non-steroidal Anti-inflammatory Drugs (NSAIDs)**

- Maternal side effects: Nausea, esophageal reflux, gastritis, and emesis; platelet dysfunction is rarely of clinical significance in patients without underlying bleeding disorder.
- Fetal or newborn adverse effects: In utero constriction of ductus arteriosus\*, oligohydramnios\*, necrotizing enterocolitis in preterm newborns, and patent ductus arteriosus in newborn†.

\*Greatest risk associated with use for longer than 48 hours.

†Data are conflicting regarding this association.

### **Beta-adrenergic Receptor Agonists**

- Maternal side effects: Tachycardia, hypotension, tremor, palpitations, shortness of breath, chest discomfort, pulmonary edema, hypokalemia, and hyperglycemia.
- Fetal or newborn adverse effects: Fetal tachycardia.

### **Magnesium Sulfate**

- Maternal side effects: Causes flushing, diaphoresis, nausea, loss of deep tendon reflexes, respiratory depression, and cardiac arrest; suppresses heart rate, contractility and left ventricular systolic pressure when used with calcium channel blockers; and produces neuromuscular blockade when used with calcium channel blockers.
- Fetal or newborn adverse effects: Neonatal depression. (The use of magnesium sulfate in doses and duration for fetal neuroprotection alone does not appear to be associated with an increased risk of neonatal depression when correlated with cord blood magnesium levels.)

## **KEY POINTS:**

A literature search was conducted through April 28, 2021.

### **Summary of Evidence**

For individuals who preterm labor or threatened preterm labor who receive acute tocolytic therapy, the evidence includes multiple randomized controlled trials (RCTs) and systematic reviews. Relevant outcomes are overall survival, morbid events, functional outcomes, and

treatment-related morbidity. Overall, the body of evidence found that the commonly used tocolytic agents presented here are effective at inducing tocolysis in patients with preterm labor or threatened preterm labor. Data have suggested that oral terbutaline is associated with more adverse events than parenteral terbutaline for acute tocolysis. Each medication has a different risk/benefit profile, and there is no clear first-line tocolytic agent. The evidence is sufficient to determine quantitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals who have successful acute tocolysis for preterm labor who receive maintenance tocolytic therapy, the evidence includes RCTs and systematic reviews. Relevant outcomes are overall survival, morbid events, functional outcomes, and treatment-related morbidity. Studies have generally not found that maintenance tocolysis lowers the rate of preterm birth or perinatal mortality, or increases the birthweight. The evidence is insufficient to determine the effects of the technology on health outcomes.

### **Practice Guidelines, and Position Statements**

#### **American College of Obstetricians and Gynecologists (ACOG)**

The American College of Obstetricians and Gynecologists (2016) updated its practice bulletin on the management of preterm labor. The 2016 bulletin contained the following relevant recommendations based on “good and consistent” scientific evidence:

- “A single course of corticosteroids is recommended for pregnant women between 24 weeks of gestation and 34 weeks of gestation who are at risk of preterm delivery within seven days.
- Accumulated available evidence suggests that magnesium sulfate reduces the severity and risk of cerebral palsy in surviving infants if administered when birth is anticipated before 32 weeks of gestation. Hospitals that elect to use magnesium sulfate for fetal neuroprotection should develop uniform and specific guidelines for their departments regarding inclusion criteria, treatment regimens, concurrent tocolysis, and monitoring in accordance with one of the larger trials.
- The evidence supports the use of first-line tocolytic treatment with beta-adrenergic agonist therapy, calcium channel blockers, or non-steroidal anti-inflammatory drugs (NSAIDs) for short-term prolongation of pregnancy (up to 48 hours) to allow for the administration of antenatal steroids.
- Maintenance therapy with tocolytics is ineffective for preventing preterm birth and improving neonatal outcomes and is not recommended for this purpose.”

#### **National Institute for Health and Care Excellence**

A 2015 guidance from the National Institute for Health and Care Excellence on preterm labor and birth (updated August 2019) made the following recommendations on tocolysis:

- 1.8.2 “Consider nifedipine for tocolysis for women between 24+0 and 25+6 weeks of pregnancy who have intact membranes and are in suspected preterm labour.
- 1.8.3 Offer nifedipine for tocolysis to women between 26+0 and 33+6 weeks of pregnancy who have intact membranes and are in suspected or diagnosed preterm labour.
- 1.8.4 If nifedipine is contraindicated, offer oxytocin receptor antagonists for tocolysis.
- 1.8.5 Do not offer betamimetics for tocolysis.”

- 1.9.1 “For women between 23+0 and 23+6 weeks of pregnancy who are in suspected or established preterm labour, are having a planned preterm birth or have P-PROM [preterm prelabour rupture of membranes] ... discuss with the woman (and her family members or carers as appropriate) the use of maternal corticosteroids in the context of her individual circumstances.
- 1.9.2 Consider maternal corticosteroids for women between 24+0 and 25+6 weeks of pregnancy who are in suspected or established preterm labour, are having a planned preterm birth or have P-PROM.
- 1.9.3 Offer maternal corticosteroids to women between 26+0 and 33+6 weeks of pregnancy who are in suspected, diagnosed or established preterm labour, are having a planned preterm birth or have P-PROM.
- 1.9.4 Consider maternal corticosteroids for women between 34+0 and 35+6 weeks of pregnancy who are in suspected, diagnosed or established preterm labour, are having a planned preterm birth or have P-PROM.”
- 1.10.2 “Offer intravenous magnesium sulfate for neuroprotection of the baby to women between 24+0 and 29+6 weeks of pregnancy who are:
  - in established preterm labour or
  - having a planned preterm birth within 24 hours.
- 1.10.3 Consider intravenous magnesium sulfate for neuroprotection of the baby for women between 30+0 and 33+6 weeks of pregnancy who are:
  - in established preterm labour or
  - having a planned preterm birth within 24 hours.”

**U.S. Preventive Services Task Force Recommendations**

Not applicable

**KEY WORDS:**

Tocolytic, acute tocolytic therapy, maintenance tocolytic therapy, betamimetics, calcium channel blockers, magnesium sulfate, and prostaglandin inhibitors, terbutaline

**APPROVED BY GOVERNING BODIES:**

Ritodrine was approved by the FDA for use as a tocolytic agent, but was voluntarily withdrawn from the U.S. market in 1998.

Terbutaline sulfate is FDA-approved for the prevention and treatment of bronchospasm in patients with asthma and reversible bronchospasm associated with bronchitis and emphysema. Like other tocolytic agents, its use in tocolysis is off-label. In response to a citizen petition in June, 2008, the FDA reviewed safety data on terbutaline sulfate. They issued a safety announcement on February 17, 2011. Based on animal studies, the FDA reclassified terbutaline sulfate from pregnancy risk category B to pregnancy risk category C. In addition, the FDA required a boxed warning stating that injectable terbutaline should not be used for prevention or prolonged (beyond 2 to 3 days) treatment of preterm labor and oral terbutaline should not be

used for acute or maintenance tocolysis. The labeling change is based on a review of post-marketing safety reports submitted to the FDA’s Adverse Event Reporting System (AERS) of maternal death and serious maternal cardiovascular events associated with use of terbutaline.

**BENEFIT APPLICATION:**

Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.

**CURRENT CODING:**

**CPT Codes:**

96372	Therapeutic prophylactic or diagnostic injection (specify substance or drug); subcutaneous or intramuscular
96374	Therapeutic, prophylactic or diagnostic injection (specify substance or drug); intravenous push, single or initial substance/drug

**HCPCS Codes:**

J3105	Injection, terbutaline sulfate, up to 1 mg
J3475	Injection magnesium sulfate, per 500mg
S9349	Home infusion therapy, tocolytic infusion therapy; administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem

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## **POLICY HISTORY:**

Adopted for Blue Advantage, April 2011

Available for comment April 25 – June 13, 2011

Medical Policy Group, May 2013

Medical Policy Group, September 2013

Medical Policy Group, October 2014

Medical Policy Group, October 2015

Medical Policy Group, August 2017

Medical Policy Group, September 2018 **(4)**: Updates to Description, Policy, Key Points, and References. Removed coverage information prior to June 14, 2011 from policy section. No change in policy statements. Policy retired.

Medical Policy Group, April 2021

*This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.*

*This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plan contracts.*