Tocolytics

Description

Tocolytics (terbutaline injection, magnesium sulfate injection)

Background
Terbutaline is a beta-adrenergic agonist with preferential effects on the beta-2 receptors resulting in smooth muscle relaxation. It is FDA-approved for the treatment or prophylaxis of bronchospasm associated with asthma, bronchitis and emphysema in patients 12 years old and older (1).

Magnesium sulfate plays an important role in neurochemical transmission and muscular excitability. It has shown some efficacy in the termination of premature labor although it is not FDA-approved for this indication.

The American Congress of Obstetricians and Gynecologists (ACOG) makes the following recommendations regarding the use of tocolytics in the management of preterm labor (Level A recommendation)(2): There are no clear "first-line" tocolytic drugs to manage preterm labor. Clinical circumstances and physician preferences should dictate treatment.

Neither maintenance treatment with tocolytic drugs, nor repeated acute tocolysis improve perinatal outcome; neither should be undertaken as a general practice.

Tocolytic drugs may prolong pregnancy for 2-7 days, which may allow for administration of steroids to improve fetal lung maturity and the consideration of maternal transport to a tertiary care facility.
Preterm labor is defined as contractions, prior to 37 weeks gestation, with sufficient intensity and frequency to induce progressive softening, effacement and/or dilatation of the cervix (2).

Other obstetric indications for consideration of the use of tocolytics include the following:

Multiple gestation may benefit from short term tocolysis for steroid administration but have a greater risk of pulmonary edema when exposed to terbutaline or magnesium sulfate (2,5).

In conjunction with certain intervention procedures during pregnancy such as external cephalic version, intrauterine transfusion, cerclage placement and management of intrapartum fetal heart rate abnormalities associated with uterine hyperstimulation (6,7).

In the setting of premature rupture of membranes, short term use of tocolytics has been demonstrated to prolong latency to onset of labor, to allow treatment of premature labor, and to permit antibiotic administration and the use of corticosteroids to support fetal lung maturity. There is no consensus on this use of tocolytics for preterm premature rupture of membranes between 24-31 completed weeks of gestation (8).

Magnesium sulfate remains the drug of choice for seizure prophylaxis in severe preeclampsia and for control of seizures in eclampsia (9). There is some evidence of the neuroprotective effect of magnesium sulfate as a neuroprotective agent in antenatally exposed premature infants. The use of magnesium sulfate for this purpose is only recommended as part of a protocol similar to those which demonstrated benefit in published reports (10,11).

Prior approval limits of 72 hours of terbutaline therapy is based on the FDA warning, released in February 2011, which said that injectable terbutaline should not be used in pregnant women for prevention or prolonged treatment (beyond 48-72 hours) of preterm labor in either the hospital or outpatient setting because of the potential for serious maternal heart problems and death. This led to the requirement of a boxed warning and contraindication on the medication label of terbutaline (12).

Calcium channel blockers and prostaglandin inhibitors are considered experimental / investigational after 72 hours of therapy for tocolysis as is the use of magnesium sulfate for neuroprotection. Magnesium sulfate is the standard of care for seizure prophylaxis in severe preeclampsia and the treatment of seizures in eclampsia (11).

Regulatory Status
FDA Approved Indications: Terbutaline is indicated for the prevention and reversal of bronchospasm in patients 12 years of age and older with asthma and reversible bronchospasm associated with bronchitis and emphysema (13).

Magnesium sulfate is indicated for:

**Convulsions** (treatment) - Intravenous Magnesium Sulfate is indicated for immediate control of life-threatening convulsions in the treatment of severe toxemias (pre-eclampsia and eclampsia) of pregnancy and in the treatment of acute nephritis in children.

**Hypomagnesemia** (prophylaxis and treatment) - Magnesium Sulfate is indicated for replacement therapy in magnesium deficiency, especially in acute hypomagnesemia accompanied by signs of tetany similar to those of hypocalcemia.

Magnesium Sulfate is also used to prevent or treat magnesium deficiency in patients receiving total parenteral nutrition.

**Tetany, uterine** (treatment) - Magnesium Sulfate is indicated in uterine tetany as a myometrial relaxant (14).

Terbutaline has a boxed warning regarding that terbutaline has not been approved for prolonged tocolysis and should not be used. In particular, do not use terbutaline for maintenance tocolysis in the outpatient or home setting. Serious adverse reactions, including death, have been reported after administration of terbutaline to pregnant women. In mothers, these adverse reactions include increased heart rate, transient hyperglycemia, hypokalemia, cardiac arrhythmias, pulmonary edema, and myocardial ischemia. Increased fetal heart rate and neonatal hypoglycemia may occur as a result of maternal administration (13).

Most common maternal adverse effects of terbutaline are headache, nausea, tachycardia and palpitations (1). However, more serious maternal adverse effects that can occur include cardiac or cardiopulmonary arrhythmias, pulmonary edema, myocardial ischemia, hypotension and tachycardia. Further, serious fetal adverse effects including fetal tachycardia, hyperinsulinemia, hyperglycemia, myocardial and septal hypertrophy and myocardial ischemia can also occur as result of terbutaline use in a pregnant woman (2).

Most common adverse effects of magnesium sulfate include flushing, lethargy, hypotension and muscle weakness. More serious maternal effects include pulmonary edema and cardiac arrest. Fetal adverse effects are similar to maternal effects and also includes respiratory depression and demineralization with prolonged use (2).
Related policies

Policy

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Terbutaline injection and magnesium sulfate may be considered medically necessary for 48-72 hours of tocolysis therapy and for indications other than preterm labor.

Terbutaline injection and magnesium sulfate may be considered investigational for tocolysis therapy in excess of 72 hours.

Prior-Approval Requirements

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<tr>
<th>Age</th>
<th>Terbutaline injection: 12 years of age or older</th>
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<td>Magnesium Sulfate: All ages</td>
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<tr>
<th>Diagnoses</th>
<th>Patient must have the following:</th>
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<td>Diagnosis other than preterm labor</td>
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Prior – Approval Renewal Requirements

<table>
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<td>Diagnosis other than preterm labor</td>
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Policy Guidelines

Pre - PA Allowance

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<tr>
<th>Quantity</th>
<th>Terbutaline</th>
<th>1mg/ml X 12 vials</th>
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<tbody>
<tr>
<td>Magnesium Sulfate</td>
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<td>40mg/ml X 100ml X 74 vials</td>
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Prior - Approval Limits

<table>
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<th>Quantity</th>
<th>Unlimited</th>
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<tr>
<td>Duration</td>
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Prior – Approval Renewal Limits

**Quantity**  
Unlimited

**Duration**  
12 months

**Rationale**

**Summary**
Terbutaline is a beta-adrenergic agonist with preferential effects on the beta-2 receptors resulting in smooth muscle relaxation. It is FDA-approved for the treatment or prophylaxis of bronchospasm associated with asthma, bronchitis and emphysema in patients 12 years old and older. Tocolysis with terbutaline has been shown to prevent labor for anywhere from 48 hours to 7 days. Magnesium sulfate plays an important role in neurochemical transmission and muscular excitability. It has shown some efficacy in the termination of premature labor although it is not FDA-approved for this indication.

Tocolytic drugs may prolong pregnancy for 2-7 days, which may allow for administration of steroids to improve fetal lung maturity and the consideration of maternal transport to a tertiary care facility.

Prior authorization is required for terbutaline injection and magnesium sulfate injection to ensure their safe, clinically appropriate and cost effective use of while maintaining optimal therapeutic outcomes.

**References**

1. Facts and Comparisons. [http://online.factsandcomparisons.com/MonoDisp.aspx](http://online.factsandcomparisons.com/MonoDisp.aspx)  
   Accessed 11/18/11
Section: Prescription Drugs  Effective Date: October 1, 2014
Subsection: Endocrine and Metabolic Drugs  Original Policy Date: January 13, 2012
Subject: Tocolytics  Page: 6 of 7


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Keywords
This policy was approved by the FEP® Pharmacy and Medical Policy Committee on September 11, 2014 and is effective October 1, 2014.

Signature on File
Deborah M. Smith, MD, MPH