Policy Statement

Acute tocolytic therapy with calcium channel blockers, magnesium sulfate, prostaglandin inhibitors, and parenteral terbutaline may be considered medically necessary for the induction of tocolysis in patients with preterm (less than 37 weeks of gestational age) labor.

Maintenance (beyond 48 to 72 hours) tocolytic therapy with any medication is considered investigational.

Policy Guidelines

Patient selection criteria for induction of tocolysis include regular uterine contractions associated with cervical changes. Induction of tocolysis typically requires hospitalization to monitor for incipient delivery.

Description

Tocolysis refers to the suppression of preterm labor to delay delivery. A variety of medications are proposed as tocolytic agents, and while none are currently approved by the U.S. Food and Drug Administration for the purpose of suppressing labor, the medications can be used as maintenance therapy following successful tocolysis.

Related Policies

- N/A

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates [e.g., Federal Employee Program (FEP)] prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

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 Ritodrine was voluntarily withdrawn from the U.S. market in 1998.

Terbutaline has been approved by the FDA 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 for tocolysis is off-label. In response to a 2008 citizen petition, the FDA reviewed safety data on terbutaline sulfate. The FDA issued a safety announcement on February 2011. Based on animal studies, The FDA reclassified terbutaline 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 was based on a review of postmarketing safety reports submitted to the FDA’s Adverse Event Reporting System of maternal death and serious maternal cardiovascular events associated with the use of terbutaline.

### Rationale

**Background**

**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 of gestation. Successful delay of preterm delivery allows further fetal development and precludes potential 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 only tocolytic drug approved by the U.S. Food and Drug Administration (FDA) has been ritodrine, a beta-sympathomimetic. Ritodrine is no longer available in the United States, and thus only off-label medications are available. Terbutaline sulfate, FDA-approved for several nontocolytic indications, is also a beta-sympathomimetic. Terbutaline is available as an oral or intravenous medication and, more recently, has been administered by continuous subcutaneous infusion via a portable pump for maintenance tocolysis. Other tocolytic drugs include calcium channel blockers (e.g., nifedipine), magnesium sulfate, oxytocin receptor antagonists (e.g., atosiban), prostaglandin inhibitors (e.g., indomethacin), and nitrates (e.g., nitroglycerin).

Tocolytic agents have potential risks and benefits. The 2012 guidelines (reaffirmed 2014) issued by the American College of Obstetricians and Gynecologists summarized the potential adverse events 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 events: no known adverse effects

**Nonsteroidal Anti-inflammatory Drugs**

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 events: in utero constriction of ductus arteriosus,* oligohydramnios,* necrotizing enterocolitis in preterm newborns, and patent ductus arteriosus in newborn†

* Greatest risk associated with use for more than 48 hours.
† Data are conflicting on 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 events: 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 events: neonatal depression (note: 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).

Literature Review
Acute Tocolysis
Studies have focused on the ability of tocolytic agents to prevent preterm delivery and thereby reduce associated maternal and neonatal risks. Numerous randomized controlled trials (RCTs) on acute tocolysis have been published and, in 2009, Haas et al conducted a comprehensive meta-analysis of RCTs. They included 58 studies that directly compared different tocolytic medications or compared 1 medication with placebo or usual care. Studies were selected if they compared 2 drugs in the same class but excluded if they included 2 doses of the same medication. Participants were women diagnosed with preterm labor or threatened preterm labor. The analysis was limited to studies with fetuses of mean gestational ages between 28 weeks and 32 weeks of gestation. Multiple gestations was not an exclusion criterion—but if trials stratified on this variable, only data on singleton pregnancies were used. Data were extracted for each outcome and combined by drug class to calculate a weighted mean and standard error for proportions of successful events; proportions were weighted based on the number of participants in each study. Primary efficacy and safety outcomes are as follows in Tables 1 and 2.

Table 1. Effect of Tocolytics on Delaying Birth (Weighted Percentage of Women Experiencing Outcome)

<table>
<thead>
<tr>
<th>Medication Class</th>
<th>48-Hour Delay</th>
<th>7-Day Delay</th>
<th>After 37 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Studies</td>
<td>Percent (95% CI)</td>
<td>No. of Studies</td>
</tr>
<tr>
<td>Placebo/control</td>
<td>9</td>
<td>53 (45 to 61)</td>
<td>8</td>
</tr>
<tr>
<td>Betamimetics</td>
<td>29</td>
<td>75 (65 to 85)</td>
<td>26</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>17</td>
<td>76 (57 to 95)</td>
<td>10</td>
</tr>
<tr>
<td>Magnesium sulfate</td>
<td>11</td>
<td>89 (85 to 93)</td>
<td>5</td>
</tr>
<tr>
<td>Oxytocin receptor antagonists</td>
<td>8</td>
<td>86 (80 to 91)</td>
<td>6</td>
</tr>
<tr>
<td>Prostaglandin inhibitors</td>
<td>8</td>
<td>93 (90 to 95)</td>
<td>3</td>
</tr>
</tbody>
</table>

CI: confidence interval.

Table 2. Adverse Maternal and Neonatal Events Associated with Tocolytics (Weighted Percentage of Women/Neonates Experiencing Outcome)

<table>
<thead>
<tr>
<th>Medication Class</th>
<th>Maternal Adverse Eventsa</th>
<th>Neonates with RDS</th>
<th>Neonatal Death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Studies</td>
<td>Percent (95% CI)</td>
<td>No. of Studies</td>
</tr>
<tr>
<td>Placebo/control</td>
<td>6</td>
<td>(0 to 2)</td>
<td>3</td>
</tr>
<tr>
<td>Betamimetics</td>
<td>32</td>
<td>14 (9 to 18)</td>
<td>17</td>
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<tr>
<td>Calcium channel blockers</td>
<td>16</td>
<td>1 (0 to 3)</td>
<td>11</td>
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<tr>
<td>Magnesium sulfate</td>
<td>16</td>
<td>3 (1 to 6)</td>
<td>9</td>
</tr>
<tr>
<td>Oxytocin receptor antagonists</td>
<td>6</td>
<td>2 (0 to 5)</td>
<td>5</td>
</tr>
<tr>
<td>Prostaglandin inhibitors</td>
<td>6</td>
<td>0 (0 to 2)</td>
<td>4</td>
</tr>
</tbody>
</table>

CI: confidence interval; RDS: respiratory distress syndrome.
a Maternal adverse events are those that required discontinuation of the medication.
All tocolytic agents were significantly better than placebo/control at delaying delivery for 48 hours and for 7 days; although none significantly improved delivery rates until after 37 weeks of gestation. The rate of discontinuation due to adverse effects was significantly higher for betamimetics than placebo/control but not for any of the other categories of medication.

Reviewers also conducted a decision analysis to determine the optimal medication based on the balance of benefits and risks. The decision analysis model found that prostaglandin inhibitors might be the superior agent up to 32 weeks of gestation due to a high effectiveness at delaying delivery by at least 7 days and offering a low rate of adverse events. Calcium channel blockers were the superior agent for delaying delivery until 37 weeks. Compared with other tocolytics, calcium channel blockers reduced the incidence of birth within 7 days of treatment (relative risk [RR], 0.76; 95% confidence interval [CI], 0.60 to 0.97) and before 34 weeks of gestation (RR=0.83; 95% CI, 0.69 to 0.99).

In an additional study published in 2012, Haas et al conducted a network meta-analysis in which direct and indirect evidence on relative impacts of tocolytics on health outcomes were pooled simultaneously. Consequently, the analysis was not limited to comparisons in head-to-head trials that the research team had addressed in 2009. The investigators identified 95 RCTs: 25 contained a placebo arm, 60 included betamimetics, 29 included magnesium sulfate, 29 included calcium channel blockers, 18 included prostaglandin inhibitors, 13 included oxytocin receptor blockers, 4 included nitrates, and 5 included “other” drugs. Reviewers assumed that all drugs in the same class had a similar effect.

Fifty-five studies were included in the network analysis for the primary efficacy outcome, delivery delayed by 48 hours. All active classes were found to be superior to placebo. The analysis also suggested that prostaglandin inhibitors had a greater beneficial effect than any other active class of medication, and calcium channel blockers and magnesium sulfate had a greater beneficial effect than oxytocin receptor blockers, nitrates, and betamimetics. Prostaglandin inhibitors had an 83% probability of being the “best” class of active medications. The probability of being ranked among the 3 most efficacious classes was 96% for prostaglandin inhibitors, 63% for magnesium sulfate, 57% for calcium channel blockers, 33% for betamimetics, 24% for nitrates, and 14% for oxytocin receptor blockers.

Forty trials were included in the network analysis for the outcome neonatal mortality. There was no clear evidence for any class of medication being superior to placebo. Calcium channel blockers were found to be the “best” class, but the probability was only 41%, which reflects the considerable uncertainty in the estimate. Prostaglandin inhibitors had a 28% chance of being the “best” class, which was the second highest probability of any class. Similarly, calcium channel blockers were the “best” class for reducing neonatal respiratory distress syndrome (RDS), but the probability was only 47%. Fifty-eight trials were included in the network analysis for the outcome all-cause maternal side effects. Other than placebo, prostaglandin inhibitors had a 79% chance of being the drug class with the fewest maternal side effects. This was followed by oxytocin receptor blockers, which had a 70% probability of the class with the lowest rate of maternal side effects. Calcium channel blockers had a 15% chance of being included in the top 3 drug classes for the fewest maternal side effects. Overall, prostaglandin inhibitors and calcium channel blockers had the highest probability of being the best classes of medication based on all 4 outcome measures: delivery delayed by 48 hours, neonatal mortality, neonatal RDS, and maternal side effects.

There are also meta-analyses focusing on a single tocolytic class or agent. In 2011, Conde-Agudelo et al reviewed trials on nifedipine, a calcium channel blocker. They identified 26 randomized trials (total N=2179 women) comparing nifedipine with placebo, no treatment, or a different tocolytic agent. Twenty-three trials evaluated acute tocolysis and three evaluated maintenance tocolysis (maintenance tocolysis is discussed later in the Rationale section). Findings were mixed. Pooled analyses of trials comparing nifedipine and beta-agonists found significantly lower rates of delivery within 7 days of treatment (10 trials; RR=0.82; 95% CI, 0.70 to
0.97) and preterm birth before 34 weeks of gestation (5 trials; RR=0.77; 95% CI, 0.66 to 0.91), but no significant difference in the rate of preterm delivery within 48 hours of treatment (13 trials; RR=0.84, 95% CI, 0.68 to 1.05) or preterm delivery before 37 weeks of gestation (9 trials; RR=0.97; 95% CI, 0.87 to 1.08). There were no significant differences in any of the preterm delivery variables when nifedipine was compared with magnesium sulfate, but the number of trials and total sample sizes were small, making it difficult to draw conclusions about comparative efficacy.

Several Cochrane reviews on a single tocolytic agent are available and are described briefly next.

A 2014 review identified 38 trials evaluating calcium channel blockers for tocolysis (total N=3550 women). The calcium channel blocker was nifedipine in 35 trials and nicardipine in the other 3. Thirty-five trials used other tocolytic agents as the comparator (19 used betamimetics), one compared doses of nifedipine, and the other two compared calcium channel blockers with placebo or no intervention. Only 1 trial was double-blinded. Reviewers evaluated several primary and secondary outcomes and conducted pooled analyses when sufficient data were available. Findings were mixed among primary outcomes, but several favored calcium channel blockers over betamimetics. There was a significantly lower rate of “very preterm birth” before 34 weeks of gestation with calcium channel blockers compared with betamimetics (6 trials; RR=0.78; 95% CI, 0.66 to 0.93) and a significantly lower rate of maternal adverse events (15 trials; RR=0.36; 95% CI, 0.24 to 0.53). The incidence of birth less than 48 hours after trial entry and the rate of perinatal mortality did not differ significantly between calcium channel blockers and other tocolytic agents. Among secondary outcome measures, there was a significantly lower rate of preterm birth before completion of 37 weeks of gestation with calcium channel blockers compared with betamimetics (13 trials; RR=0.89; 95% CI, 0.80 to 0.98), and there were too few studies to compare with other tocolytic agents. Reviewers noted that the quality of studies (eg, lack of blinding, limited placebo controls), limited the ability to draw firm conclusions about the efficacy of calcium channel blockers compared with other tocolytic agents.

A 2014 updated Cochrane review identified 14 trials on oxytocin inhibitors (total N=2485 women). The control intervention was placebo in 4 trials, betamimetics in 8 trials, and a calcium channel blocker in 2 studies. Pooled analyses did not demonstrate the superiority of oxytocin receptor antagonists over betamimetics or placebo in terms of reduction in preterm birth or adverse neonatal outcomes (note that oxytocin inhibitors are not approved by the Food and Drug Administration [FDA] for use in the United States).

Another 2014 Cochrane review identified 37 trials (total N=3571 women). Comparison interventions included other tocolytic drugs, predominantly betamimetics, nitroglycerine, human chorionic gonadotropin, saline, and dextrose. No placebo-controlled trials were identified. Pooled analyses found no statistically significant differences between magnesium sulfate and comparator interventions for outcomes including birth less than 48 hours after trial entry, serious infant adverse events, and preterm birth before 37 weeks of gestation.

A 2005 Cochrane review by King et al included 13 trials on cyclooxygenase (COX) inhibitors (total N=713 women); indomethacin was used in 10 of the trials. Only 1 trial compared COX inhibitors with placebo. Pooled analysis of studies comparing COX inhibitors with other tocolytics found a significant reduction in the incidence of birth before 37 weeks of gestation (RR=0.53; 54 women). Reviewers noted that sample sizes were small, and thus estimates were imprecise and not definitive.

In addition to these reviews of single agents, Vogel et al (2014) published a Cochrane review on combinations of tocolytic agents for preventing preterm labor. Reviewers searched for RCTs comparing any combination of tocolytic agents with any other treatment (including other combinations, single tocolytic agents, no intervention, or placebo). Eleven trials evaluating 7 different comparisons met reviewers’ inclusion criteria; two of these did not report relevant
outcome data. Thus, few studies with small combined sample sizes were available for analysis, and reviewers were unable to pool data or draw conclusions about the safety and efficacy of any combination of tocolytics vs any comparator intervention.

Section Summary: Acute Tocolysis
Multiple RCTs and meta-analyses have found tocolytics to be effective at decreasing rates of preterm birth in women with preterm labor (e.g., delaying delivery for 7 days and/or decreasing rates of delivery before 34 or 37 weeks of gestation). The optimal first-line medication is uncertain. A 2012 network meta-analysis suggested that prostaglandin inhibitors and calcium channel blockers may have greater efficacy and fewer adverse events than other classes of medication. However, there was considerable uncertainty in the estimates of which class of medication was “best” for each outcome. Cochrane reviews of various tocolytic agents have not found any single agent to be superior over the other.

Maintenance of Tocolysis
Several meta-analyses have been published. The 2011 Conde-Agudelo meta-analysis (described earlier) included 3 studies evaluating the calcium channel blocker nifedipine for maintenance tocolysis.5 A pooled analysis of these 3 trials (total N=215 patients) did not find a significant difference in the rate of preterm birth before 37 weeks of gestation with nifedipine compared with placebo or no treatment (RR=0.87; 97% CI, 0.69 to 1.08). There were insufficient data to conduct pooled analyses on other pregnancy outcome variables.

In 2009, a Health Technology Assessment from the U.K. addressed a wider range of maintenance tocolytic agents.11 However, for the outcomes prevention of preterm birth before 34 or 37 weeks of gestation, there were only a sufficient number of trials to conduct pooled analyses for 2 comparisons. Neither analysis found a statistically significant benefit of tocolysis. In a pooled analysis comparing magnesium maintenance therapy with other tocolytic agents, the combined RR was 0.98 (95% CI, 0.56 to 1.72). In addition, a pooled analysis of 4 trials (total N=384 patients) did not find a significant benefit of oral betamimetics compared with placebo or no treatment for preventing preterm birth before 37 weeks of gestation. The combined RR was 1.08 (95% CI, 0.88 to 1.22).

Several Cochrane reviews have addressed specific agents used for maintenance therapy and are described briefly next.

A 2013 Cochrane review of maintenance therapy with oxytocin antagonists identified only 1 trial.12 This trial, published in 2000 by Valenzuela et al, did not find that atosiban reduced the rate of preterm birth after threatened preterm birth compared with placebo.13

Another 2013 Cochrane review identified 6 RCTs on maintenance therapy with calcium channel blockers.14 Nifedipine was used in all trials, and a total of 794 women were included. The comparison intervention was placebo in 3 trials and no treatment in the other 3 trials. Pooled analyses did not find that calcium channel blockers significantly reduced the rate of preterm birth before 37 weeks (5 trials; RR=0.97; 95% CI, 0.87 to 1.09) or 34 weeks (3 trials; RR=1.07; 95% CI, 0.88 to 1.30). A pooled analysis of 2 trials did not find significant differences between calcium channel blockers and controls for the outcome birth within 48 hours of treatment. There were insufficient data to draw conclusions about other outcomes.

In 2016, follow-up data were published from an RCT evaluating maintenance tocolysis with nifedipine.15 Two-year outcomes data were available for 135 (52.5%) of 276 participants. Outcomes were mixed for infants of women in the nifedipine maintenance group compared with the placebo group. Those on nifedipine maintenance doses had a higher incidence of fine motor problems (22% vs 8%; odds ratio, 3.43; 95% CI, 1.29 to 9.14) and a lower incidence of poor problem-solving ability (22% vs 29%; odds ratio, 0.27; 95% CI, 0.08 to 0.95).
In 2012, Dodd et al published a Cochrane review on oral betamimetics for maintenance tocolysis after threatened preterm labor. They identified 13 RCTs, some of which had more than 2 arms. There were 10 comparisons of a betamimetic and placebo or no treatment, 1 comparison of a betamimetic and indomethacin, 1 comparison between 2 different betamimetics, and 3 comparisons between a betamimetic and magnesium. Data could not be pooled on any outcomes due to a shortage of studies on a particular comparison. In a pooled analysis of 6 studies, there was no statistically significant difference in the rate of preterm birth before 37 weeks in patients receiving a maintenance betamimetic vs placebo or no treatment (RR=1.11; 95% CI, 0.91 to 1.35). In other pooled analysis of findings from studies comparing maintenance betamimetics with placebo or no treatment, there were no statistically significant differences between groups in birth weight (7 studies; mean difference, 4.13; 95% CI, -91.89 to 100.16), risk of perinatal mortality (6 studies; RR=2.41; 95% CI, 0.86 to 6.74), or risk of RDS in infants (6 studies; RR=1.10; 95% CI, 0.61 to 1.98).

A 2010 review by Han et al evaluated magnesium maintenance therapy and did not find a statistically significant effect of that maintenance therapy on prevention of preterm birth before 37 weeks of gestation. A meta-analysis of 2 studies (n=99 patients) that compared magnesium therapy with placebo or no treatment found a combined RR of 1.05 (99% CI, 0.80 to 1.40). Two studies (n=100 patients) were also available for a meta-analysis of studies comparing magnesium therapy with an alternative treatment. In this analysis, the combined RR was 0.99 (95% CI, 0.57 to 1.72).

**Section Summary: Maintenance of Tocolysis**

There are fewer RCTs comparing maintenance tocolysis with acute tocolysis. RCTs and meta-analyses on maintenance tocolysis have not found that tocolytic agents significantly improve health outcomes. Moreover, there are insufficient data from placebo-controlled trials.

**Risks Associated with Terbutaline**

An FDA-conducted search of its Adverse Event Reporting System (AERS) identified reports of 16 maternal deaths associated with terbutaline between 1976 and 2009. Documents from the FDA indicate that, in 3 cases, it was specified that terbutaline was administered by a subcutaneous pump; and in 9 cases oral terbutaline was used instead of or in addition to injectable or subcutaneous terbutaline (presumably, in the remaining cases, the mode of administration was not reported). Moreover, between 1998 and July 2009, 12 cases of serious maternal cardiovascular events associated with terbutaline were submitted to AERS; in 3 cases, subcutaneous terbutaline was specified and, in 5 cases, oral terbutaline was used alone or in addition to subcutaneous terbutaline.

A 2011 editorial examined the human and animal evidence on risks of autism spectrum disorders associated with terbutaline. The commentators concluded that the literature did not support the hypothesis that β2-adrenergic agonists (including terbutaline) are associated with autism spectrum disorders in offspring.

**Summary of Evidence**

For individuals who have preterm labor or threatened preterm labor who receive acute tocolytic therapy, the evidence includes multiple randomized controlled trials and meta-analyses. Relevant outcomes are overall survival, morbidity events, functional outcomes, and treatment-related morbidity. Overall, the body of evidence has shown that the commonly used tocolytic agents presented herein 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 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 randomized controlled trials and meta-analyses.
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 birth weight. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information
Clinical Input from Physician Specialty Societies and Academic Medical Centers
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests from Blue Cross Blue Shield Association, input was received from 2 physician specialty societies and 4 academic medical centers in 2012. There was consensus that acute tocolysis may be considered medically necessary for the induction of tocolysis in patients with preterm labor and near consensus that preterm should be defined as “<37 weeks” gestational age. There was mixed input on the investigational policy statement on maintenance tocolysis (beyond 48-72 hours).

Practice Guidelines and Position Statements
American College of Obstetricians and Gynecologists
In 2016, the American College of Obstetricians and Gynecologists published a practice bulletin on the management of preterm labor, which replaced previous bulletins on this topic. 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 7 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 NSAIDs [non-steroidal anti-inflammatory drugs] 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. Antibiotics should not be used to prolong gestation or improve neonatal outcomes in women with pre-term labor and intact membranes.”

National Institute for Health and Care Excellence
A 2015 guidance from the National Institute for Health and Care Excellence on preterm labor and birth has stated the following recommendations relevant to 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.”
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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.

1.10.1 “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.

1.10.2 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.”

Royal College of Obstetricians and Gynecologists

The Royal College of Obstetricians and Gynecologists’ evidence-based guidelines (updated in 2011, now archived) on the use of tocolysis for women in preterm labor included the following conclusions relevant to this evidence review:

“There is no clear evidence that tocolytic drugs improve outcome and therefore it is reasonable not to use them. However, tocolysis should be considered if the few days gained would be put to good use, such as completing a course of corticosteroids or in utero transfer.”

“Nifedipine and atosiban have comparable effectiveness in delaying birth for up to seven days.”

“Compared with beta-agonists, nifedipine is associated with improvement in neonatal outcome, although there are no long-term data.”

“Beta-agonists have a high frequency of adverse effects. Nifedipine, atosiban and the COX inhibitors have fewer types of adverse effects, and they occur less frequently than for beta-agonists but how they compare with each other is unclear.”

“There is insufficient evidence for any firm conclusions about whether or not tocolysis leads to benefit in preterm labor in multiple pregnancy.”

“There is insufficient evidence for any firm conclusion about whether or not maintenance tocolytic therapy following threatened preterm labor is worthwhile. Thus, maintenance therapy is not recommended.”

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in September 2015 did not identify any ongoing or unpublished trials that would likely influence this review.

References


Documentation for Clinical Review

Please provide the following documentation (if/when requested):

- History and physical and/or consultation notes including:
  - Reason for tocolysis
  - Gestational age
  - Type of medication and duration of use

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.

MN/IE

The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

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<td>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</td>
</tr>
<tr>
<td>ICD-10 Procedure</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>ICD-10 Diagnosis</td>
<td>All Diagnoses</td>
<td></td>
</tr>
</tbody>
</table>

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>09/13/1989</td>
<td>BCBSA Medical Policy adoption</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>10/07/1992</td>
<td>Administrative Review</td>
<td>Medical Policy Committee</td>
</tr>
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<td>01/12/2002</td>
<td>Administrative Review</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>07/12/2002</td>
<td>Administrative Review Policy statement unchanged</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>09/25/2009</td>
<td>Policy Title Revision, criteria revised</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>10/01/2010</td>
<td>Criteria Revised</td>
<td>Medical Policy Committee</td>
</tr>
</tbody>
</table>
### Definitions of Decision Determinations

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

### Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.