I. POLICY

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 (<37 weeks’ gestational age) labor.

Maintenance (beyond 48-72 hours) tocolytic therapy with any medication is considered investigational, as there is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

NOTE: Terbutaline should only be administered in a hospital setting and is not to be administered in an outpatient or home setting. Oral terbutaline is contraindicated for the treatment or prevention of preterm labor.

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.

Cross-reference:
MP-7.025 Progesterone Therapy as a Technique to Reduce Preterm Delivery in High Risk Pregnancies

II. PRODUCT VARIATIONS

[N] = No product variation, policy applies as stated
[Y] = Standard product coverage varies from application of this policy, see below
**III. DESCRIPTION/BACKGROUND**

Tocolysis refers to the suppression of preterm labor to delay delivery. A variety of medications are proposed as tocolytic agents; none of the currently available options are approved by the U.S. Food and Drug Administration (FDA) for this indication. The same medications could also be used 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 (RDS). 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. If successful acute tocolysis is achieved, patients may continue to receive pharmacologic therapy for maintenance.

A variety of agents have been used for tocolysis. The only FDA-approved tocolytic drug is ritodrine, a beta-sympathomimetic. Ritodrine is no longer available in the United States and thus only off-label medications are available. Terbutaline sulfate, also a beta-sympathomimetic, is an alternative to ritodrine, for acute and maintenance tocolysis. Terbutaline is available as an oral or intravenous medication and, more recently, terbutaline 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 as well as potential benefits. A 2012 guideline issued by the American College of Obstetricians and Gynecologists (ACOG) summarized the potential adverse effects of common classes of tocolytic agents (1):

**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.)

**Regulatory Status**

Ritodrine was approved by the U.S. Food and Drug Administration (FDA) for use as a tocolytic agent. Ritodrine was voluntarily withdrawn from the U.S. market in 1998.

Terbutaline 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. (2) 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 2-3 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.

IV. RATIONALE

Acute tocolysis

Studies have focused on the ability of tocolytic agents to prevent preterm delivery and thereby reduce associated maternal and neonatal risks. A comprehensive meta-analysis of randomized controlled trials (RCTs) on acute tocolysis was published by Haas et al. in 2009. (3) Haas and colleagues included 58 studies that directly compared different tocolytic medications or compared 1 medication to placebo or usual care. Studies were included if they compared 2 drugs in the same class but excluded if they included 2 doses of the same medication. Participants were women who were diagnosed with preterm labor or had threatened preterm labor. The analysis was limited to studies with fetuses of mean gestational ages between 28 and 32 weeks’ gestation. Multiple gestation 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:

*Effect of tocolytics on delaying birth (weighted % of women experiencing outcome)*

<table>
<thead>
<tr>
<th></th>
<th>48-hour delay</th>
<th>7-day delay</th>
<th>After 37 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. Studies</td>
<td>% (95% CI)</td>
<td>No. Studies</td>
</tr>
<tr>
<td>Placebo/control</td>
<td>9</td>
<td>53 (45-61)</td>
<td>8</td>
</tr>
<tr>
<td>Betamimetics</td>
<td>29</td>
<td>75 (65-85)</td>
<td>26</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>17</td>
<td>76 (57-95)</td>
<td>10</td>
</tr>
<tr>
<td>Magnesium sulfate</td>
<td>11</td>
<td>89 (85-93)</td>
<td>5</td>
</tr>
</tbody>
</table>
### Acute and Maintenance Tocolysis

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

CI = confidence interval

**Adverse maternal and neonatal effects associated with tocolytics (weighted % of women/neonates experiencing outcome)**

RDS, respiratory distress syndrome

Maternal adverse effects are those that required discontinuation of the medication.

All tocolytic agents were significantly better than placebo/control at delaying delivery for 48 hours and delaying delivery for 7 days. None were significantly better than placebo/control at delaying delivery until after 37 weeks’ gestation. The rate of discontinuation due to adverse effects was significantly higher for betamimetics compared to placebo/control but not for any of the other categories of medication. As part of their review, the investigators 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’ gestation due to a high effectiveness at delaying delivery by at least 7 days and a low rate of adverse effects. Calcium channel blockers were the superior agent for delaying delivery until 37 weeks. Compared to other tocolytics, calcium channel blockers reduced the incidence of birth within 7 days of treatment (relative risk [RR]: 0.76, 95% CI).
confidence interval [CI]: 0.60-0.97) and before 34 weeks’ gestation (RR: 0.83, 95% CI: 0.69-0.99).

In an additional study published in 2012, Haas and colleagues conducted a network meta-analysis in which direct and indirect evidence on relative impacts of tocolytics on health outcomes were pooled simultaneously. (4) Consequently, the analysis was not limited to the comparisons in head-to-head trials that the research team had addressed in 2009. The investigators identified a total of 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. The authors 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 of this 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 was the “best” class for reducing neonatal respiratory distress syndrome (RDS), but the probability of being the best 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 respiratory distress syndrome and maternal side effects.

There are also meta-analyses on tocolysis focusing on a single tocolytic agent. In 2011, Conde-Agudelo and colleagues reviewed trials on nifedipine, a calcium channel blocker. (5) The investigators identified 26 randomized trials with a total of 2,179 women comparing nifedipine to placebo, no treatment, or a different tocolytic agent. Twenty-three of the trials evaluated acute tocolysis and 3 evaluated maintenance tocolysis (maintenance tocolysis is
discussed in a later section of the Rationale). 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’ gestation (5 trials, RR: 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’ 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 individual agents are available. A 2003 review identified 12 trials evaluating calcium channel blockers for tocolysis, with a total of 1,029 women. (6) Compared to any other tocolytic agents, calcium channel blockers significantly reduced the incidence of birth within 7 days of treatment (RR: 0.76, 95% CI: 0.60-0.97) and before 34 weeks’ gestation (RR: 0.83, 95% CI: 0.69-0.99), and significantly reduced the likelihood that women would discontinue medication due to adverse effects (RR: 0.14, 95% CI: 0.05-0.36). The authors concluded that calcium channel blockers are preferred over other tocolytic agents.

The review did not include studies that compared calcium channel blockers to placebo for tocolysis. A 2005 Cochrane review by King and colleagues included 13 trials on cyclooxygenase (COX) inhibitors, with a total of 713 women; indomethacin was used in 10 of the trials. (7) Only one trial compared COX inhibitors to placebo. Pooled analysis of studies comparing COX inhibitors to other tocolytics found a significant reduction in the incidence of birth before 37 weeks’ gestation (RR: 0.53, 54 women). The authors noted that numbers were small, and thus estimates were imprecise and not definitive. Another Cochrane review, also published in 2005, identified 6 trials on oxytocin inhibitors, with a total of 1,695 women. (8) Pooled analyses did not demonstrate the superiority of oxytocin receptor antagonists over betamimetics or placebo in terms of reduction in preterm birth or neonatal outcomes. (Note: Oxytocin inhibitors are not approved by the FDA for use in the United States.)

Section summary: 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’ gestation. The optimal first-line medication is not certain. A 2012 network meta-analyses suggest that prostaglandin inhibitors and calcium channel blockers may have greater efficacy and fewer adverse effects than other classes of medication. However, there was considerable uncertainty in the estimates of which class of medication was the “best” for each of the outcomes.

Maintenance of tocolysis

Several meta-analyses of the published literature have been published. The 2011 Conde-Agudelo et al. meta-analysis, described above, (5) included 3 studies evaluating the calcium channel blocker nifedipine for maintenance tocolysis. A pooled analysis of these 3 trials (total n=215) did not find a significant difference in the rate of preterm birth before 37 weeks’ gestation with nifedipine compared to placebo or no treatment (RR: 0.87; 97% CI: 0.69 to
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. However, for the outcomes prevention of preterm birth before 34 weeks’ or 37 weeks’ gestation, there were only a sufficient number of trials to conduct pooled analyses for 2 comparisons. Neither of the analyses found a statistically significant benefit of tocolysis. In a pooled analysis of magnesium maintenance therapy to other tocolytic agents, the combined relative risk was 0.98 (95% CI: 0.56 to 1.72). In addition, a pooled analysis of 4 trials (total n=384) did not find a significant benefit of oral betamimetics compared to placebo or no treatment for preventing pre-term birth before 37 weeks’ gestation. The combined relative risk was 1.08 (95% CI: 0.88 to 1.22).

Several Cochrane reviews have addressed specific agents used for maintenance therapy. A 2010 review by Han and colleagues evaluated magnesium maintenance therapy and did not find a statistically significant effect of magnesium maintenance therapy on prevention of preterm birth before 37 weeks’ gestation. A meta-analysis of 2 studies (total n=99) that compared magnesium therapy to placebo or no treatment found a combined risk ratio of 0.98 (99% CI: 0.80 to 1.40). Two studies (total n=100) were also available for a meta-analysis of studies comparing magnesium therapy to an alternative treatment. In this analysis, the combined risk ratio was 0.99 (95% CI: 0.57 to 1.72). In 2012, Dodd and colleagues published a Cochrane review on oral betamimetics for maintenance tocolysis after threatened preterm labor. The authors identified 13 RCTs; some of these 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 for all outcomes due to a shortage of studies on a particular comparison. In a pooled analysis of 6 studies, there was not a statistically significant difference in the rate of preterm birth before 37 weeks’ in patients receiving a maintenance betamimetic versus 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 to placebo or no treatment, there were not statistically significant differences between groups in birthweight (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) and risk of respiratory distress syndrome in the infant (6 studies, RR: 1.10, 95% CI: 0.61 to 1.98).

As an example of a well-designed RCT on this topic, in 2013, Roos and colleagues published a multicenter double-blind RCT evaluating nifedipine for maintenance tocolysis. Women who experienced threatened preterm labor between 26 and 32 weeks’ gestation and had not delivered following 48 hours of acute tocolysis and corticosteroids were eligible to participate. The initial tocolytic agent varied according to local protocol, but was usually nifedipine or atosiban. A total of 406 women were randomly assigned to 12 days of maintenance tocolysis with nifedipine (n=201) or placebo (n=205). The primary outcome was a composite of adverse outcomes associated with premature birth and included perinatal mortality, neonatal sepsis, chronic lung disease, severe intraventricular hemorrhage (greater than grade 2), periventricular
leukomalacia (greater than grade 1) and necrotizing enterocolitis. In an intention-to-treat analysis, there was not a statistically significant difference between groups in the composite primary outcome. Adverse outcomes occurred in 24 of 201 patients (11.9%) in the nifedipine group and 28 of 205 patients (13.7%) in the placebo group; RR: 0.87, 95% CI: 0.53 to 1.45. Mean gestational age at delivery, a secondary outcome, was 34.1 weeks for the nifedipine group and 34.2 weeks for the placebo difference. The difference between groups was not significantly different (hazard ratio: 1.0, 95% CI: 0.83 to 1.2).

Section summary: There are fewer RCTs on maintenance tocolysis compared to acute tocolysis. RCTs and meta-analyses on maintenance tocolysis have not consistently found that tocolytic agents reduce rates of preterm birth.

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. (2) The FDA document stated 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, use of subcutaneous terbutaline was specified and in 5 cases, it was reported that oral terbutaline was used alone or in addition to subcutaneous terbutaline.

A 2011 commentary examined the human and animal evidence on risks of autism spectrum disorders associated with terbutaline. (13) The authors concluded that the literature does not support the hypothesis that beta-2-adrenergic agonists including terbutaline are associated with autism spectrum disorders in the offspring.

Clinical Input Received through Physician Medical Societies and Academic Medical Centers

In response to requests, input was received through 2 Physician Specialty Societies and 4 Academic Medical Centers while this policy was under review in 2012. 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. 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).

Summary

There is sufficient evidence that the commonly used tocolytic agents presented here are effective at inducing tocolysis in patients with preterm labor or threatened preterm labor.
Thus, these agents are considered medically necessary for the acute prevention of preterm delivery. There are data suggesting 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. A recent network meta-analysis suggests that prostaglandin inhibitors and calcium channel blockers have the best risk/benefit profile, but there was uncertainty in the estimates of which class of medication is “best” for each outcome.

There are fewer studies on medications to maintain tocolysis. The available evidence does not suggest that maintenance tocolysis improves health outcomes, and therefore maintenance tocolysis is considered investigational.

Practice Guidelines and Position Statements


The practice bulletin contains the following 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 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.
- Antibiotics should not be used to prolong gestation or improve neonatal outcomes in women with pre-term labor and intact membranes.”

Royal College of Obstetricians and Gynecologists, UK guideline (updated in February 2011) (14):

This evidence-based guideline on use of tocolysis for women in preterm labor included the following conclusions relevant to this policy:
• 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.

V. DEFINITIONS

PRETERM LABOR is labor that begins before completion of thirty-four (37) weeks from the last menstrual period.

SUBCUTANEOUS refers to beneath the skin.

SUBCUTANEOUS INFUSION is the injection of an isotonic or hypotonic solution into the subcutaneous tissue to supply a continuous and large amount of fluid, electrolytes and nutrients.

TOCOLYSIS- Refers to the inhibition of uterine contractions.

VI. BENEFIT VARIATIONS

The existence of this medical policy does not mean that this service is a covered benefit under the member's contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member’s individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member’s benefit information or contact Capital for benefit information.
VII. DISCLAIMER

Capital’s medical policies are developed to assist in administering a member’s benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member’s benefit information, the benefit information will govern. Capital considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when medically necessary:

<table>
<thead>
<tr>
<th>CPT Codes®</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HCPCS Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J3105</td>
<td>INJECTION, TERBUTALINE SULFATE, UP TO 1 MG</td>
</tr>
<tr>
<td>J3475</td>
<td>INJECTION, MAGNESIUM SULPHATE, PER 500 MG</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ICD-9-CM Diagnosis Code*</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>644.00 - 644.03</td>
<td>THREATENED PREMATURE LABOR</td>
</tr>
</tbody>
</table>

*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.
The following ICD-10 diagnosis codes will be effective October 1, 2015:

<table>
<thead>
<tr>
<th>ICD-10-CM Diagnosis Code*</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>O47.00-O47.9</td>
<td>False labor code range (includes threatened labor)</td>
</tr>
<tr>
<td>O60.00-O60.03</td>
<td>Preterm labor without delivery code range</td>
</tr>
</tbody>
</table>

*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.

IX. REFERENCES

2. FDA drug safety communication: New warnings against use of terbutaline to treat preterm labor; February 17, 2011.


Other Sources
Taber’s Cyclopedic Medical Dictionary, 19th edition.

X. POLICY HISTORY

<table>
<thead>
<tr>
<th>Policy Number</th>
<th>Date</th>
<th>Event Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>MP 7.022</td>
<td>CAC 4/29/03</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CAC 1/25/05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CAC 2/28/06</td>
<td>Consensus Review</td>
</tr>
<tr>
<td></td>
<td>CAC 7/25/06</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CAC 7/31/07</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CAC 7/29/08</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CAC 7/28/09</td>
<td>Consensus Review</td>
</tr>
<tr>
<td></td>
<td>CAC 3/30/10</td>
<td>Minor revision. Policy retitled Acute and Maintenance Tocolysis. Agents other than terbutaline are now addressed.</td>
</tr>
<tr>
<td></td>
<td>CAC 4/26/11</td>
<td>Policy statements revised to reflect boxed warnings regarding terbutaline issued 2/17/11.</td>
</tr>
<tr>
<td></td>
<td>CAC 4/24/12 and 6/26/12</td>
<td>Adopt BCBSA. The use of acute tocolytic agents was revised for induction of tocolysis in patients with preterm labor from &lt;34 weeks to &lt;37 weeks’ gestational age. Policy again discussed during June CAC. Decision stands regarding induction of tocolysis for preterm labor from &lt;34 weeks to &lt;37 weeks. Administrative code review complete.</td>
</tr>
<tr>
<td></td>
<td>CAC 7/22/14</td>
<td>Consensus No change to policy statements. Policy guidelines and rationale section added. Coding reviewed.</td>
</tr>
</tbody>
</table>

Top

Health care benefit programs issued or administered by Capital BlueCross and/or its subsidiaries, Capital Advantage Insurance Company®, Capital Advantage Assurance Company® and Keystone Health Plan® Central. Independent licensees of the BlueCross BlueShield Association. Communications issued by Capital BlueCross in its capacity as administrator of programs and provider relations for all companies.