



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all health benefit plans administered by CIGNA Companies including plans formerly administered by Great-West Healthcare, which is now a part of CIGNA.

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Subject Parenteral Tocolytic Therapy

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Hyperlink to Related Coverage Policies

Home Uterine Activity Monitoring (HUAM)
Hydroxyprogesterone Caproate Injection
(Makena™)
Tests for the Evaluation of Preterm Labor

INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2011 CIGNA

Coverage Policy

CIGNA covers parenteral tocolytic therapy as medically necessary for up to 72 hours when provided in a hospital setting for the treatment of preterm labor when gestational age is less than 34 weeks.

CIGNA does not cover tocolytic therapy for any other indication, or for longer than 72 hours, because it is considered experimental, investigational or unproven.

General Background

Preterm labor is defined by the American Congress of Obstetricians and Gynecologists (ACOG) (2003) as regular contractions that occur before 37 weeks of gestation and are associated with changes in the cervix. Preterm birth is the leading cause of neonatal mortality in the United States, and preterm labor precedes 40–50% of preterm births. Preterm birth may also be preceded by rupture of membranes or other medical problems. Approximately 467,000 of U.S. births occur before term (11.5% of all live births) and are responsible for 75% of neonatal mortality and 50% of long-term neurologic impairments in children. Although numerous management methods have been proposed, the incidence of preterm birth has not significantly changed over the past 40 years. Approximately 50–75% of women presenting with symptoms of preterm labor, such as contractions and a small amount of cervical effacement or dilatation, will deliver at term without treatment. Ultrasonography and fetal fibronectin testing may be used to evaluate symptomatic women considered to be at high risk for preterm labor. The high negative predictive value of these tests may help avoid unnecessary intervention (ACOG, 2003, Reaffirmed, 2008; Goldenberg, 2002).

The use of pharmacologic agents to inhibit uterine contractions in preterm labor is referred to as tocolytic therapy. Numerous drugs have been explored as tocolytics, although most have not received FDA approval for this indication. Tocolytic agents include calcium channel blockers (e.g., nifedipine, nicardipine); oxytocin antagonists (e.g., atosiban); prostaglandin inhibitors (e.g., indomethacin, sulfide, nimesulide, keterolac, refecoxib, mefanamic acid); nitrates (e.g., nitroglycerin, glyceryl trinitrate); and beta-mimetics (β -mimetics) (e.g., ritodrine, hexoprenaline, ixosuprine, nydrilin, salbutamol, fenoterol, and terbutaline). β -mimetics are structurally related to epinephrine and norepinephrine, and act to relax smooth muscle. Ritodrine was approved by the FDA as a parenteral tocolytic in 1980, but it did not become widely used because of frequent maternal side effects. The most commonly used β -mimetic in the United States has been terbutaline (Gabbe: Obstetrics-Normal and Problem Pregnancies, 2007; Haas, 2009).

Although agents other than terbutaline may be considered for tocolytic therapy, this Coverage Policy focuses on the use of terbutaline administered subcutaneously, continuously and/or intermittently via an infusion pump.

Use of tocolytic therapy requires appropriate testing for the diagnosis of preterm labor, a diagnostic workup to rule out infection, abruption or other causes of labor that are contraindications to tocolysis, ultrasound to determine gestational age, size, presentation and the presence of absence of anomalies. Close monitoring in an inpatient setting is indicated for fetal and maternal safety. Complications may include sudden death, increased heart rate, transient hyperglycemia, hypokalemia, cardiac arrhythmias, pulmonary edema, and myocardial ischemia. Less serious, but more frequent effects of β -mimetics include palpitations, tremor, nausea, vomiting, headache, thirst, nervousness and restlessness. Tocolytic therapy may temporarily halt contractions and prolong pregnancy for at least 48 hours, to allow administration of antenatal corticosteroids and transfer to a tertiary care facility with a neonatal intensive care unit. Antenatal corticosteroids have been clearly shown to decrease neonatal morbidity and mortality. Tocolytics therefore are generally given concomitantly with corticosteroids. Because corticosteroids are not usually used at or after 34 weeks, and because the perinatal outcomes in later gestational age preterm infants are generally good, most authorities do not recommend use of tocolytics at or after 34 weeks gestational age. There is no consensus on a lower gestational age limit for the use of tocolytic agents. Individual determinations of the risks and benefits are therefore necessary (ACOG 2003; Creasy, Resnick and Iams, 2004; Danforth's Obstetrics & Gynecology, 2008, FDA, 2011).

Prolonged parenteral tocolytic therapy has not been shown to be effective in preventing preterm birth, reducing the risk of preterm labor, or improving fetal outcomes. According to ACOG guidelines, prolonged tocolytic treatment is not effective and may potentially increase the maternal-fetal risk without offering a clear benefit. A 2011 FDA Drug Safety Communication, detailed below, states that injectable terbutaline should not be used 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.

U.S. Food and Drug Administration (FDA)

Terbutaline was approved as a drug to prevent and treat bronchospasm, but has been used off-label to treat preterm labor and uterine hyperstimulation, despite labeling that stated that the drug should not be used for the management of preterm labor. An FDA MedWatch "Dear Colleague" letter issued in 1997 stated, "the demonstrated value of tocolytics in general is limited to an initial, brief period of treatment, probably no more than 48–72 hours. No benefit from prolonged treatment has been documented. In addition, the safety of long-term subcutaneous administration of terbutaline sulfate, especially on an outpatient basis, has not been adequately addressed." The letter further stated that "In the absence of data establishing the effectiveness and safety of the drug/device, FDA is alerting practitioners, home health care agencies, insurance carriers, and others that continuous subcutaneous administration of terbutaline sulfate has not been demonstrated to be effective and is potentially dangerous."

An FDA Drug Safety Communication issued on February 17, 2011 included new warnings against the use of terbutaline to treat preterm labor. The safety announcement states 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." The FDA is requiring the addition of a Boxed Warning and Contraindication to the terbutaline injection label warning against this use. The communication also states, "Although it may be clinically deemed appropriate based on the healthcare professional's judgment to administer terbutaline by injection in urgent and individual obstetrical

situations in a hospital setting, the prolonged use of this drug to prevent recurrent preterm labor can result in maternal heart problems and death. Terbutaline should not be used in the outpatient or home setting.”

Literature Review

Mawaldi et al. (2008) conducted a randomized controlled trial (n=174) to compare the effectiveness, safety, and possible adverse effects of terbutaline and nifedipine in prolonging pregnancy beyond 48 hours. Patients admitted in preterm labor were randomized to treatment with subcutaneous terbutaline (n=95) or oral nifedipine (n=79). Treatment failed to provide prolongation of labor for 24 hours in 12 patients in the terbutaline group and 8 patients in the nifedipine group. This difference was not statistically significant (p=0.61). Success in suppression of preterm labor for 48 hours was similar with either drug; 87.4% for terbutaline and 89.9% for nifedipine. Length of hospital stay and time to delivery were also similar in both groups. There was a statistically significant higher incidence in observed adverse effects, including maternal palpitations and vomiting, and fetal tachycardia, in the terbutaline group. Maternal hypotension was the only side effect seen more commonly in the nifedipine group (p=0.002).

A meta-analysis and decision analysis to determine the optimal first-line tocolytic agent for treatment of preterm labor included 58 randomized controlled trials of tocolysis (Haas et al., 2009). Tocolytic agents included beta-mimetics (β -mimetics) (e.g., terbutaline), calcium channel blockers, magnesium sulfate, oxytocin receptor antagonists, prostaglandin inhibitors, and nitrates. Outcomes included delay of delivery for 48 hours, 7 days, and until 37 weeks; adverse effects causing discontinuation of therapy; absence of respiratory distress syndrome; and neonatal survival. Meta-analysis showed that all tocolytic agents were superior to placebo or control groups at delaying delivery for at least 48 hours (53% for placebo compared to 75–93% for tocolytics) and for 7 days (39% for placebo compared to 61–78% for tocolytics). There were no statistically different differences in other outcomes. Individual treatment options were compared for each outcome to determine which agent might be considered the optimal first-line treatment. Prostaglandin inhibitors provided superior results for all outcomes except delaying delivery until 37 weeks, an outcome for which calcium channel blockers were found superior. The authors concluded that, based on the decision model, prostaglandin inhibitors were superior to the other agents and may be considered the optimal first-line agent before 32 weeks gestation to delay delivery.

A Cochrane systematic review conducted by Anatayanonth et al. (2004, assessed as up-to-date in 2006) evaluated 17 randomized trials to determine the effect of β -mimetics, including terbutaline and ritodrine, in inhibiting preterm labor. β -mimetics decreased the number of women in preterm labor giving birth within 48 hours, but there was no decrease in the number of births within seven days, after carrying out a sensitivity analysis of studies with adequate allocation of concealment. There was no demonstrated benefit for β -mimetics in terms of perinatal death or neonatal death, and no significant effect for respiratory distress syndrome. The authors concluded that β -mimetics are effective in delaying birth for 48 hours, sufficient time to allow the transfer of a woman to a higher level of care and to allow completion of a course of antenatal corticosteroids to facilitate fetal lung maturation. This benefit, however, is balanced by more frequent unpleasant and sometimes potentially life-threatening adverse effects which significantly increase discontinuation of the β -mimetics.

Sanchez-Ramos et al. (2003) conducted a systematic review of the therapeutic value of maintenance tocolytics. Eighteen randomized controlled trials were reviewed with a total of 1981 patients enrolled. Fourteen of these trials compared the effectiveness of a maintenance tocolytic to placebo or no treatment. The additional four trials included study groups comparing two active drugs for maintenance tocolytic therapy. The authors reported that maintenance tocolytic therapy was not associated with a significant reduction in the rates of recurrent preterm labor or preterm delivery or with a significant improvement in the gestational age at delivery. When compared with patients receiving placebo or no treatment, maintenance tocolysis was not associated with a significant reduction in perinatal morbidity and mortality. Similar results were seen when subgroups of patients receiving specific tocolytics were evaluated separately.

Berkman et al. (2003) conducted a systematic review of the effectiveness of tocolytics to stop uterine contractions (first-line therapy) or maintain quiescence (maintenance therapy). The objective was to evaluate the evidence on the benefits and harms of five classes of tocolytic therapy for preterm labor: beta-mimetics (β -mimetics), calcium channel blockers, magnesium, nonsteroidal anti-inflammatory agents, and ethanol. Studies on women with preterm labor between 1966 and 1999 and who met the inclusion criteria were included. Of the 256 articles evaluated, 16 first-line and eight maintenance studies met requirements for meta-analysis. Studies of first-line tocolysis revealed a mixed outcome pattern, with small improvements in pregnancy prolongation and

birth at term compared to placebo. Data were insufficient to directly show a beneficial effect on neonatal morbidity or mortality. Ethanol was less beneficial than, and beta-mimetics were not superior to, other tocolytic options. Maintenance tocolytics showed no improvements in birth or infant outcomes relative to placebo. In contrast to other tocolytic treatments, maternal harms from beta-mimetics were rated high. All tocolytics were rated as low-risk for short-term neonatal harm.

Nanda et al. (2002) conducted a Cochrane systematic review to determine the effectiveness and safety of terbutaline pump maintenance therapy after threatened preterm labor. The review evaluated the randomized controlled trial conducted by Guinn, described below, and a randomized controlled trial by Wenstrom, et al. (1997). Terbutaline pump therapy was not found in either trial to be effective in increasing gestational age at birth or in reducing preterm birth and its complications. The authors also stated that the safety of terbutaline pump maintenance therapy was not adequately assessed in either trial. Neither trial was designed to have adequate statistical power to evaluate significant adverse events that occur infrequently.

Guinn et al. (1998) conducted a randomized double-blind trial to evaluate the efficacy of subcutaneous terbutaline therapy administered by pump compared to placebo for prolonging gestation in women with preterm labor who had labor successfully arrested with intravenous magnesium sulfate. The women were randomly assigned to receive either terbutaline or normal saline solution placebo by subcutaneous infusion pump. Terbutaline therapy was discontinued and parenteral magnesium was resumed if recurrent preterm labor developed while women were on the therapeutic regimen at < 34 weeks gestation and no contraindication for tocolysis existed. If recurrent labor was arrested, pump therapy was restarted according to the original treatment. A sample size of 48 women was required to detect a two-week intergroup difference in mean time to delivery. Analyses were based on intent to treat. Fifty-two women received terbutaline (n=24) or placebo (n=28). Overall there was a one day difference in mean time to delivery between the groups (terbutaline 29 days and placebo 28 days, p=0.78). There were no differences in the rates of preterm delivery at < 34 and < 37 weeks' gestation, and neonatal outcomes were similar.

A review article on prevention of preterm labor (Simhan and Caritis, 2007) states that because uterine contractions are the most frequently recognized antecedent of preterm birth, stopping contractions has been the focus of therapeutic approaches. This approach is based on the assumption that clinically apparent contractions represent the start of childbirth, and that inhibiting contractions will prevent delivery. In the three decades since they were introduced, no tocolytic agent has lived up to the expectation that prematurity rates would decrease. The authors state that tocolysis has probably had limited success because the available tocolytic drugs do not alter the fundamental process leading to myometrial activation. More than 80% of women who are treated with tocolytics, however, do have their pregnancies maintained for 24 to 48 hours, long enough to allow the administration of corticosteroids. The initial benefit of corticosteroid therapy occurs approximately 18 hours after the first dose is administered, with maximal benefit occurring approximately 48 hours after the first dose. Acute treatment with tocolysis may therefore allow time for the administration and therapeutic effect of corticosteroids, and may also permit transport of the mother, if indicated, to a regional facility specializing in premature neonate care.

Authoritative textbooks describe short-term tocolysis as a method that may delay delivery for several days, allowing time for maternal transfer, corticosteroid treatment and group B streptococcus prophylaxis. However, continued suppression of contractions after acute tocolysis (i.e., maintenance tocolysis) is not supported, because of the potential for adverse effects on the mother and neonate, and the lack of evidence that maintenance tocolysis reduces the rate of preterm birth or improves neonatal outcomes (Danforth, 2008; Gabbe, 2007).

Professional Societies/Organizations

American Congress of Obstetricians and Gynecologists (ACOG): ACOG practice bulletin number 43, a clinical management guideline for obstetrician-gynecologists on the management of preterm labor, states that the most beneficial intervention for patients in true preterm labor is the administration of corticosteroids. Antenatal betamethasone has been shown to decrease neonatal mortality. Antenatal corticosteroids have also been shown to significantly reduce the incidence and severity of neonatal respiratory distress syndrome and reduce the incidence of intraventricular hemorrhage and necrotizing enterocolitis. The guideline states that all women between 24 and 34 weeks gestation are potential candidates for corticosteroid therapy (ACOG, 2003, reaffirmed, 2008).

The guideline states that tocolytic drugs may prolong gestation for two to seven days, which can provide time for administration of steroids to improve fetal lung maturity and the consideration of maternal transport to a facility with a neonatal intensive care unit. The benefits of prolonging pregnancy for two to seven days are otherwise unclear. Neither maintenance treatment with tocolytic drugs, nor repeated acute tocolysis, improves perinatal outcomes. The guideline states that prolonged oral, subcutaneous, or intravenous tocolytic treatment is not effective, and cautions that prolonged use of any tocolytic may potentially increase the maternal-fetal risk without offering a clear benefit.

ACOG Practice bulletin 31: Assessment of Risk Factors for Preterm Birth, states that the ability to predict whether a woman is at risk of preterm delivery has value only if an intervention is available that is likely to improve the outcome. Maternal tocolytic therapy may prolong pregnancy for up to 48 hours in some women, during which time corticosteroids can be administered. Because tocolytic and steroid therapy may result in untoward maternal and fetal consequences, use of these therapies should be limited to women with true preterm labor at high-risk for spontaneous preterm birth. In women being managed at hospitals without appropriate neonatal resources, identifying women at risk allows for appropriate maternal transport to a tertiary care center (ACOG, 2001, reaffirmed 2010).

Summary

Short-term parenteral tocolytic therapy (i.e., terbutaline) may be indicated to temporarily halt contractions in carefully selected women in preterm labor, allowing the administration of antenatal corticosteroids and the consideration of transfer to a facility with a neonatal intensive care unit. Antenatal corticosteroids have been clearly shown to decrease neonatal morbidity and mortality. -Because corticosteroids are not usually used at or after 34 weeks, and because the perinatal outcomes in later gestational age preterm infants are generally good, most authorities do not recommend use of tocolytics at or after 34 weeks gestational age. There is no consensus on a lower gestational age limit for the use of tocolytic agents. Individual determinations of the risks and benefits are therefore necessary.

A 2011 U.S. Food and Drug Administration (FDA) Drug Safety Communication states that injectable terbutaline should not be used 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. The communication also states that although it may be clinically deemed appropriate to administer terbutaline by injection in urgent and individual obstetrical situations in a hospital setting, the prolonged use of this drug to prevent recurrent preterm labor can result in maternal heart problems and death. Terbutaline should not be used in the outpatient or home setting. Prolonged tocolysis (i.e., longer than 72 hours) has not been shown to be effective in preventing preterm birth, reducing the risk of preterm labor, or improving fetal outcomes. According to the American Congress of Obstetricians and Gynecologists (2003), prolonged tocolytic treatment is not effective and may potentially increase the maternal-fetal risk without offering a clear benefit.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Short-term tocolytic therapy (i.e., up to 72 hours)

Covered when medically necessary:

HCPSC Codes	Description
J3105	Injection, terbutaline sulfate, up to 1 mg

ICD-9-CM Diagnosis Codes	Description
644.00	Threatened premature labor; unspecified as to episode of care or not applicable
644.03	Threatened premature labor; antepartum condition or complication

Maintenance tocolytic therapy (i.e., beyond 72 hours)

Experimental/Investigational/Unproven/Not Covered:

HCPCS Codes	Description
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

ICD-9-CM Diagnosis Codes	Description
	All codes

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Policy History

<u>Pre-Merger Organizations</u>	<u>Last Review Date</u>	<u>Policy Number</u>	<u>Title</u>
CIGNA HealthCare	9/15/2008	0379	Parenteral Tocolytic Therapy

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