

<b>Subject:</b> Terbutaline Continuous Subcutaneous Infusion for the Treatment of Preterm Labor		<b>Original Effective Date:</b> 12/12/2012
<b>Guidance Number:</b> MCG-126	<b>Revision Date(s):</b>	
<b>Medical Coverage Guidance Approval Date:</b> 12/12/2012	<b>Medical Affairs Committee Approval Date:</b>	

#### PREFACE

*This Medical Guidance is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusions or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the following website: <http://www.cms.hhs.gov/center/coverage.asp>.*

#### FDA INDICATIONS

The FDA <sup>6</sup> has approved Terbutaline sulphate injection to prevent and treat bronchospasm (narrowing of airways) associated with asthma, bronchitis, and emphysema. Subcutaneous infusion of terbutaline for the treatment of preterm labor is an off-label use of this drug. On February 17, 2011, the FDA notified healthcare professionals that terbutaline administered by injection or through an infusion pump should not be used in pregnant women for prevention or prolonged treatment (beyond 48 to 72 hours) of preterm labor in either the hospital or outpatient setting because of the potential for serious maternal heart problems. Death and serious adverse reactions, including increased heart rate, transient hyperglycemia, hypokalemia, cardiac arrhythmias, pulmonary edema, and myocardial ischemia have been reported after prolonged administration of oral or injectable terbutaline to pregnant women.

#### CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

*The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this Molina medical coverage guidance (MCG) document and provide the directive for all Medicare members. The directives from this MCG document may be followed if there are no available NCD or LCD documents available and outlined below.*

CMS does not have a NCD or LCD for continuous subcutaneous Terbutaline infusion for treatment of preterm labor.<sup>4</sup>

#### INITIAL COVERAGE CRITERIA

Continuous subcutaneous Terbutaline infusion for treatment of preterm labor is considered investigational based on the limited evidence from low-quality studies that do not substantiate that subcutaneous terbutaline may

prevent reinstatement of preterm labor, prolong gestation, and improve neonatal outcomes. The evidence also indicates serious safety concerns for the patient and lacks long-term safety data for the offspring.

#### CONTINUATION OF THERAPY

Continuous subcutaneous Terbutaline infusion for treatment of preterm labor is considered investigational as the technology is unproven.

#### COVERAGE EXCLUSIONS

Continuous subcutaneous Terbutaline infusion for treatment of preterm labor is considered investigational as the technology is unproven.

#### DESCRIPTION OF PROCEDURE/SERVICE/PHARMACEUTICAL

Terbutaline is a beta-adrenergic agonist and is FDA approved for the treatment of asthma. Terbutaline has been evaluated for off-label use as a long-term or maintenance tocolytic therapy due to its relaxing effects on the uterine muscles. Although the drug can be taken orally, subcutaneous administration has been proposed as a more effective route since this leads to fewer dose fluctuations and a lower daily dose, which may reduce complications, prevent desensitization of the uterus to terbutaline, and improve patient compliance. Women undergo subcutaneous terbutaline treatment after intensive tocolytic therapy has reduced preterm uterine contractions to fewer than 4 to 6 per hour. The recommended starting dosage of terbutaline is 0.25 mg subcutaneously every 20 minutes to 3 hours. Dosing should be held if the pulse exceeds 120 beats per minute. Depending on the treatment protocol, terbutaline is infused with a pump at 0.05 to 0.75 mg per hour with boluses of 0.25 mg at regular intervals or as needed for increases in uterine activity.<sup>1 2</sup>

#### Black Box Warning

Prolonged tocolysis: Terbutaline has not been approved and should not be used for prolonged tocolysis (beyond 48 to 72 hours). In particular, terbutaline should not be used for maintenance tocolysis in the outpatient or home setting. Serious adverse reactions, including death, have been reported after administration of terbutaline to pregnant women. In mothers, these adverse reactions include increased heart rate, transient hyperglycemia, hypokalemia, cardiac arrhythmias, pulmonary edema, and myocardial ischemia. Increased fetal heart rate and neonatal hypoglycemia may occur as a result of maternal administration.<sup>2 6 7</sup>

#### GENERAL INFORMATION

##### Summary of Medical Evidence

Gaudet and colleagues (2012) published a meta-analysis to systematically evaluate the effectiveness and safety of subcutaneous (SQ) terbutaline infusion by pump for maintenance tocolysis. Two randomized trials, one nonrandomized trial, and 11 observational studies met inclusion criteria. Non-comparative studies were considered only for pump-related harms. Case-reports were excluded but sought FDA summaries of post-

marketing surveillance data. Non-English records without an English abstract were excluded. Evidence of low strength from observational studies with risk of bias favored SQ terbutaline pump for the outcomes of delivery at <32 and <37 weeks, mean days of pregnancy prolongation, and neonatal death. Observational studies of medium to high risk of bias also demonstrated benefit for other surrogate outcomes, such as birthweight and neonatal intensive care unit (NICU) admission. Several cases of maternal deaths and maternal cardiovascular events have been reported in patients receiving terbutaline tocolysis. The authors concluded that although evidence suggests that pump therapy may be beneficial as maintenance tocolysis, our confidence in its validity and reproducibility is low, suggesting that its use should be limited to the research setting. Concerns regarding safety of therapy persist.<sup>16</sup>

Milwaldi and colleagues (2008) conducted a randomized controlled trial to compare the effectiveness, safety, and possible adverse effects of terbutaline and nifedipine in prolonging pregnancy beyond 48 h. 174 pregnant women admitted with preterm labor randomized into 2 groups, which were given terbutaline (95 patients) and nifedipine (79 patients), respectively. Bivariate and multivariate analyses, using logistic regression, were used to analyze the data. No statistically significant difference was found between the 2 groups in terms of prolongation of gestation to 48 h. The failure rate in terms of prolonging gestation for 24 h was found to be 12.6% for the terbutaline group and 10.1% for the nifedipine group, which was not found to be statistically significant ( $P$  value=0.61). Side effects were significantly more common in the terbutaline group, except for maternal hypotension. The authors concluded that terbutaline and nifedipine appear to be equally effective in their tocolytic action. However, nifedipine did have the advantage of ease of administration. It also had significantly less effect on the fetal heart rate.<sup>18</sup>

Fleming and associates (2004) published a study that was nearly identical to the study by Lam (2003) with the primary differences being that nifedipine was the only drug prescribed for oral tocolysis and 142 women were in each treatment group. This study displayed a statistically significant bias in assignment of patients to treatment groups since women in the Terbutaline Infusion Group were more likely to be married ( $P<0.02$ ). As expected based on the results of Lam et al., several statistically significant improvements in mean outcomes were seen for the Terbutaline Infusion Group compared with the Nifedipine Treatment Group including the following: delivery at  $36.6\pm 2.1$  versus  $35.7\pm 3.1$  weeks, birth weight of  $2900\pm 568$  versus  $2638\pm 74$  grams, 23% versus 44% admission to the NICU, and  $4.7\pm 8.3$  versus  $11.1\pm 17.0$  days of nursery care ( $P<0.005$  for each outcome).<sup>11</sup>

Lam and colleagues (2003) published the largest available study of subcutaneous terbutaline infusion for preterm labor in singleton pregnancies. This study was a retrospective, case-matched controlled trial in which records from a large, nationwide computer database were extracted and compared. The database search identified 279 women who underwent terbutaline infusion for preterm labor that occurred and reoccurred between 20 and 35 weeks of gestation. These women were matched on a 1:1 basis with women who underwent oral tocolytic treatment for the same indications with case-matching based on gestational age at recurrence of preterm labor. The oral medications prescribed were terbutaline for 95% of women and nifedipine, magnesium, indomethacin, or a combination of these drugs for the other 5%. A bias was observed in assignment of patients

to treatment groups since women assigned to subcutaneous terbutaline treatment were more likely to be married, less likely to smoke, and less likely to have prior preterm deliveries ( $P<0.05$  for each demographic factor). This study found that subcutaneous terbutaline infusion was associated with the following statistically significant improvements in mean outcomes compared with oral treatment: delivery at  $36.5\pm 2.1$  versus  $35.7\pm 2.8$  weeks, birth weight of  $2941\pm 556$  versus  $2676\pm 667$  grams, 19% versus 26% admission to the NICU, and  $4.9\pm 9.8$  versus  $8.7\pm 16.0$  days in nursery care ( $P<0.005$  for each outcome).<sup>10</sup>

Morrison and colleagues (2003) conducted a prospective, nonrandomized controlled study of continuous subcutaneous terbutaline infusion for preterm labor. For this study, only 15 women underwent terbutaline infusion and their outcomes were compared with outcomes of 45 women who had no long-term tocolytic therapy. All of these patients underwent successful tocolytic therapy for acute preterm labor before assignment to treatment groups. Patients assigned to terbutaline infusion had the following statistically significant improvements in mean outcomes compared with the Control Group: prolongation of pregnancy by  $50\pm 19$  versus  $25\pm 13$  days, delivery at  $37\pm 2$  versus  $33\pm 3$  weeks, NICU stay of  $2\pm 5$  versus  $20\pm 30$  days, maternal hospitalization for  $9.8\pm 2.1$  versus  $15.9\pm 7.9$  days, and birth weight of  $2700\pm 464$  versus  $1978\pm 670$  grams ( $P<0.005$  for each outcome).<sup>13</sup>

Lam and colleagues (2001) conducted another large retrospective study of subcutaneous terbutaline infusion versus oral tocolytics for preterm labor; however, in this study, the treatment was evaluated for twin pregnancies with 353 women in each treatment group. This study was a case-matched controlled trial that relied on records extracted from a large, nationwide database. The demographics reported by Lam et al. (2001) indicate that, like the retrospective studies described above, this study suffers from bias in assignment of patients to treatment groups. Specifically, women assigned to terbutaline infusion were older, more likely to be married, and had earlier gestational age at first preterm labor ( $P<0.02$  for each demographic factor). In addition, there was a strong trend toward a statistically significant difference between groups with the infusion group being less likely to have had prior preterm births ( $P=0.051$ ). The authors concluded that subcutaneous terbutaline infusion was associated with the following statistically significant improvements in mean outcomes compared with oral tocolysis: delivery at  $35.2\pm 2.0$  versus  $34.5\pm 2.3$  weeks, birth weight of  $2343\pm 493$  versus  $2207\pm 523$  grams, 39% versus 55% admission to the NICU, and  $9.0\pm 12.2$  versus  $12.9\pm 15.6$  days of nursery care ( $P<0.002$  for each outcome). This study also found that terbutaline infusion was associated with fewer perinatal losses (4 versus 15,  $P<0.02$ ).<sup>12</sup>

Guinn and colleagues (1998) published a randomized controlled trial to review continuous subcutaneous terbutaline infusion. 52 women were enrolled at 22 to 34 weeks gestation who were pregnant with a single fetus and who had cessation of preterm labor after treatment with magnesium sulfate with or without indomethacin. These women were then randomized to long-term subcutaneous infusion of terbutaline ( $n=24$ ) or saline ( $n=28$ ) in double-blinded fashion. Although infusion therapy was discontinued prematurely by 11 (46%) women in the Terbutaline Group and 9 (32%) women in the Control Group, this difference was not statistically significant. Terbutaline infusion was not found to cause any statistically significant improvement in any

pregnancy-related outcome measure including prolongation of pregnancy, neonatal intensive care unit (NICU) admission, or increase in birth weight. The authors concluded that this observation held true whether women who chose early discontinuation of treatment were included or excluded from the analysis.<sup>8</sup>

A smaller Randomized controlled trial was conducted by Wenstrom and associates (1997), who randomized 42 women with singleton (n=34) or twin (n=8) pregnancies to long-term maintenance with oral terbutaline (n=15) or continuous infusion of terbutaline (n=15) or saline (n=12). Although this study does not explicitly state that infusion was subcutaneous, this route seems to have been used since it was performed at the same institution as the study by Guinn et al. (1998) and it involved one of the same investigators. Randomization of women to terbutaline versus saline involved double blinding; however, problems with patient management required that blinding be violated before the end of the study for 9 (60%) women in the terbutaline infusion (TI) Group and for 8 (67%) women in the saline infusion (SI) Group. In addition, 1 (7%) woman in the TI Group crossed over to oral terbutaline and 3 (25%) women in the SI Group crossed over to terbutaline infusion. The authors concluded that there were no statistically significant differences between groups in any pregnancy-related outcome measure including pregnancy prolongation, birth weight, or hospital stay.<sup>9</sup>

Hayes, Cochrane, UpToDate, MD Consult etc.

Hayes:

There is Medical Technology Directory report called Continuous Subcutaneous Terbutaline Infusion for Treatment of Preterm Labor. This report summarizes that there is only a moderate amount of mostly poor-quality evidence regarding subcutaneous terbutaline administered by continuous infusion for the prevention of preterm birth in women in whom preterm labor has been arrested. Several large nonrandomized retrospective studies suggest that compared with no treatment or oral tocolytic treatment, subcutaneous terbutaline may prolong gestation and thereby increase birthweight. Two small randomized controlled trials did not find evidence for terbutaline effects on gestation length; however, these studies may have lacked adequate statistical power to detect such effects. There are serious safety concerns regarding prolonged use of terbutaline in pregnant women.<sup>1</sup>

Cochrane:

Nanda and colleagues (2002) conducted a review to determine the effectiveness and safety of terbutaline pump maintenance therapy after threatened preterm labor in preventing preterm birth and its complications. Randomized trials comparing terbutaline pump maintenance therapy with alternative therapy, placebo, or no therapy after threatened preterm labor were included. Two studies showed that terbutaline pump maintenance therapy did not appear to offer any advantages over the saline placebo pump or oral terbutaline maintenance therapy in preventing preterm births by prolonging pregnancy or its complications among women with arrested preterm labor. The weighted mean difference (WMD) for gestational age at birth was -0.1 weeks (95% confidence interval (CI) -1.7 to 1.4) for terbutaline pump therapy compared with saline placebo pump for both trials combined and 1.4 weeks (95% CI -1.1 to 3.9) for terbutaline pump versus oral terbutaline therapy for the first trial. The second trial reported a relative risk (RR) of 1.17 (95% CI 0.79 to 1.73) of preterm birth (less than

37 completed weeks) and a RR of 0.97 (95% CI 0.51 to 1.84) of very preterm birth (less than 34 completed weeks) for terbutaline pump compared with saline placebo pump. Terbutaline pump therapy also did not result in a higher rate of therapy continuation or a lower rate of infant complications. No data were reported on long-term infant outcomes, costs, or maternal assessment of therapy. The authors concluded that terbutaline pump maintenance therapy has not been shown to decrease the risk of preterm birth by prolonging pregnancy. Furthermore, the lack of information on the safety of the therapy, as well as its substantial expense, argues against its role in the management of arrested preterm labor. Future use should only be in the context of well-conducted, adequately powered randomized controlled trials.<sup>17</sup>

#### UpToDate:

The use of tocolytics for preterm labor is outlined in a report called Inhibition of Preterm Labor<sup>19</sup>. The beta-adrenergic receptor agonists ritodrine and terbutaline have been studied in several randomized, placebo-controlled trials but should be used with caution in women at risk for massive hemorrhage (such as women with placenta previa or abruption) since the resultant cardiovascular effects (tachycardia, hypotension) may interfere with the ability of the mother to respond to ongoing hemorrhage, and may confuse the clinical presentation. Additionally, the FDA has warned that injectable terbutaline should not be used in pregnant women for prevention or prolonged treatment (beyond 48 to 72 hours) of preterm labor in either the hospital or outpatient setting because of the potential for serious maternal heart problems and death. However, there are certain obstetrical conditions where the healthcare professional may decide that the benefit of terbutaline injection for an individual patient in a hospital setting clearly outweighs the risk. For example, a short course of injectable terbutaline is a reasonable option for acute tocolysis or for acute management of tetanic uterine contractions or tachysystole with abnormal fetal heart rate pattern in labor. The FDA also opined that oral terbutaline should not be used for prevention or any treatment of preterm labor because it has not been shown to be effective and has similar safety concerns.

#### Professional Organizations

##### American College of Obstetrics and Gynecology (ACOG)<sup>3</sup>:

An ACOG evidence-based Practice Bulletin states that tocolytic drugs do not seem to prolong pregnancy more than 2 to 7 days, and the only clear benefits of this treatment are to provide time for administration of steroids and transport to a facility with a neonatal intensive care unit. The ACOG Bulletin concluded that long-term or maintenance tocolytic therapy was not effective.

##### European Association of Perinatal Medicine<sup>15</sup>:

The European Association of Perinatal Medicine Study Group on Preterm Birth (2007) has stated that maintenance tocolysis is not recommended for routine practice due to insufficient evidence for any firm conclusions about whether maintenance tocolytic therapy following arrest of preterm labor is worthwhile.

Institute for Clinical Systems Improvement (ICSI) <sup>5</sup>:

ICSI published guidelines for the management of preterm labor in 2011, stating that Terbutaline is one of the commonly employed drugs from this class of medications for tocolysis. Available studies show a prolongation of pregnancy similar to the results of calcium channel blockers, but no significant reduction in perinatal morbidity or mortality. However, the U.S. Food and Drug Administration (FDA) recently notified health care professionals that oral and injectable terbutaline should not be used in pregnant women for prolonged treatment (beyond 48-72 hours) of preterm labor because of the potential for serious maternal heart problems and death.

Institute of Medicine of the National Board on Health Sciences Policy (IOM) <sup>14</sup>:

The IOM publication *Preterm Birth: Causes, Consequences, and Prevention* states that chronic tocolytic administration has not been useful for long-term maintenance of contraction inhibition, and in most studies has not improved perinatal outcomes, although its use does allow time for the administration of corticosteroids and maternal transfer to an appropriate hospital.

CODING INFORMATION	
<b>CPT</b>	<b>Description</b>
99601	Home infusion/specialty drug administration, per visit (up to 2 hours)
99602	each additional hour +(List separately in addition to code for primary procedure)
<b>HCPCS</b>	<b>Description</b>
E0779	Ambulatory infusion pump, mechanical, reusable, for infusion 8 hours or greater
E0780	Ambulatory infusion pump, mechanical, reusable, for infusion less than 8 hours
E0781	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
J3105	Injection, terbutaline sulfate, up to 1 mg
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	Description
644.00-644.03	Early or threatened labor

ICD-10	Description
O60-O60.03	Preterm labor

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