



# CIGNA HEALTHCARE COVERAGE POSITION

Subject **Terbutaline (Brethine®)**

Original Effective Date ..... 12/15/2005  
Coverage Position Number ..... 5032

## Table of Contents

Coverage Position.....	1
General Background .....	1
Coding/Billing Information .....	4
References .....	4

## Related Coverage Positions

### INSTRUCTIONS FOR USE

Coverage Positions are intended to supplement certain **standard** CIGNA HealthCare benefit plans. Please note, the terms of a participant'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 Positions are based. For example, a participant's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Position. In the event of a conflict, a participant's benefit plan document **always supercedes** the information in the Coverage Positions. 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 group benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Positions and; 4) the specific facts of the particular situation. Coverage Positions relate exclusively to the administration of health benefit plans. Coverage Positions are not recommendations for treatment and should never be used as treatment guidelines. ©2005 CIGNA Health Corporation

## Coverage Position

**CIGNA HealthCare covers terbutaline (Brethine®) as medically necessary when ANY of the following indications are met:**

- for the prevention and reversal of bronchospasm in patients with asthma and reversible bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema
- as initial tocolytic treatment given concomitantly with corticosteroids to suppress and delay premature labor for 24-48 hours when gestation is greater than 24 weeks and less than 34 weeks (subcutaneously [SC] ONLY)

**CIGNA HealthCare does not cover terbutaline (Brethine®) for the following indication because it is considered experimental, investigational or unproven (this list may not be all inclusive):**

- for the maintenance treatment of premature labor

## General Background

Terbutaline stimulates beta-adrenergic receptors found principally in bronchial, vascular, and uterine smooth muscles (beta2) and bronchial and vascular smooth muscle relaxation occurs with resultant reduced airway resistance. At usual doses it has little effect on cardiac (beta1) receptors and usually does not cause direct cardiostimulatory effects. Occasionally, a tachycardia develops which may be a result of either direct beta stimulation or a reflex response secondary to peripheral vasodilation. Terbutaline has virtually no alpha-adrenergic activity.

In humans, only about 33-50% of an oral dose is absorbed; peak bronchial effects occur within 2-3 hours and activity persists for up to eight hours. Terbutaline is well absorbed following subcutaneous (SC) administration with an onset of action occurring within 15 minutes, peak effects at 30-60 minutes, and a duration of activity for up to four hours. Terbutaline is distributed into milk, but at levels of approximately 1% of the oral dose given to the mother. Terbutaline is principally excreted unchanged in the urine (60%), but is also metabolized in the liver to an inactive sulfate conjugate.

### **Bronchospasm**

Controlled clinical studies have shown that terbutaline sulfate injection relieves bronchospasm in acute and chronic obstructive pulmonary disease (COPD) by significantly increasing pulmonary flow rates (e.g., an increase of 15% or more in forced expiratory volume in the first second [FEV1]). After subcutaneous administration of 0.25 mg of terbutaline sulfate injection, a measurable change in expiratory flow rate usually occurs within five minutes, and a clinically significant increase in FEV1 occurs within 15 minutes. The maximum effect usually occurs within 30-60 minutes, and clinically significant bronchodilator activity may continue for 1.5-4 hours. The duration of clinically significant improvement is comparable to that observed with equimilligram doses of epinephrine.

A limited number of studies are available that compare oral forms of beta-adrenergic, albuterol, metaproterenol, and terbutaline. The studies that have been performed are older, have involved small numbers of asthmatic patients, and do not have firm conclusions. In general, it is thought that all oral beta agonists work in the same manner and are effective in treating asthma symptoms. One small study showed that metaproterenol had a faster onset of action (i.e., it is quicker to provide relief of asthma symptoms), but that albuterol and terbutaline have a longer duration of activity (i.e., they control asthma symptoms for a longer period of time). What this means clinically is not clear. There doesn't appear to be any clear-cut advantage regarding effectiveness to choose one medication in this class over another.

### **Preterm Labor**

In 1998, the U.S. Food and Drug Administration issued an alert to physicians and other health professionals addressing concerns about subcutaneous administration of terbutaline sulfate via infusion pump for off-label use as treatment and prevention of preterm labor (i.e., tocolytic therapy). The approved labeling for terbutaline sulfate injection states that the drug should not be used for the management of preterm labor because studies have not been sponsored that specifically establish safety and efficacy for this use, and reports have been received of serious adverse effects. However, many clinicians, including the American College of Obstetricians and Gynecologists (ACOG), consider terbutaline the  $\beta$ -adrenergic tocolytic agents of choice when such therapy is indicated. While use of terbutaline sulfate may effectively delay delivery for at least 24-48 hours, the principal goal of prolongation of gestation is to potentially reduce the incidence of neonatal death, low-birthweight infants, respiratory distress syndrome, and long-term morbidity and mortality associated with prematurity; there currently is limited evidence substantiating the efficacy of  $\beta$ -adrenergic tocolytic agents in this regard. The main benefit currently derived from tocolytic therapy appears to be short-term to forestall labor prior to 34 weeks of gestation and prolong gestation (for 2-7 days), thus providing time for patients to receive other agents (e.g., corticosteroids) to increase fetal maturation and/or to be transferred to other (e.g., tertiary-care) facilities. Use of corticosteroids in women at risk for preterm delivery who have been successfully treated with tocolytic agents (e.g., as measured by control of labor for at least 24 hours) has reduced infant mortality, respiratory distress syndrome, and intraventricular hemorrhage.

A descriptive cohort study evaluated the effectiveness of continuous SC terbutaline in the home after recurrent preterm labor (RPTL). Women with RPTL at less than 32 weeks gestation were treated with continuous SC terbutaline administered in the home compared with matched control patients. Fifteen patients with SC terbutaline were compared with 45 women treated with no tocolytic therapy after hospitalization. Gestational age at delivery of the study group was more than 37 weeks which was 53% versus (vs.) 4% of the control group. Percentage of the study group delivered at less than 32 weeks was 0% vs. 47% for the controls. Overall pregnancy prolongation (49 days vs. 24 days) was significantly better in all patients in the study group ( $p < 0.001$ ). The total number of maternal hospital days (9 vs. 15,  $p < 0.0001$ ) and the duration of neonatal intensive care unit (NICU) stay (1.9 vs. 19.8,  $p < 0.001$ ) favored the study patients. The authors conclude that in this small study the use of SC terbutaline significantly

prolongs pregnancy, decreases serious neonatal complications, and reduces the duration of hospitalization for both mother and infant.

A Cochrane meta-analysis of trials conducted by Crowley (2002) confirmed that antenatal glucocorticoid therapy significantly decreased the incidence and severity of neonatal respiratory distress syndrome. Neonatal mortality was also significantly reduced as was the incidence of intraventricular hemorrhage and necrotizing enterocolitis. These benefits appeared to be maximal if delivery occurred more than 24 hours after the start of treatment but within seven days. The commonly utilized steroids for the enhancement of fetal maturity are betamethasone (12 mg intramuscularly every 24 hours, two doses) and dexamethasone. These two glucocorticoids have been identified as the most appropriate for antenatal use as they readily cross the placenta and have long half-lives and limited mineralocorticoid activity.

A meta-analysis of randomized controlled trials and other study designs was conducted by Berkman et al. (2003) to evaluate the evidence of the management of preterm labor. Treatment consisted of bed rest, hydration, pharmacologic interventions, and combinations of these. Berkman et al. systematically reviewed the effectiveness of tocolytics to stop uterine contractions (first-line therapy) or as maintenance therapy. The research objective was to evaluate the evidence of benefit/harm of five classes of tocolytic therapy for treating uterine contractions related to preterm labor, using beta-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-analyses. Studies of first-line tocolysis reveal a mixed outcome pattern with small improvement in pregnancy prolongation and birth at term relative to placebo. Data were insufficient to show directly 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 harm from beta-mimetics was rated high; all tocolytics were rated as low-risk for short-term neonatal harm. The authors concluded that management of uterine contractions with first-line tocolytic therapy can prolong gestation. Among the tocolytics, beta-mimetics appear to be no better than other drugs and pose significant potential harms for mothers; ethanol remains an inappropriate therapy. Continued maintenance tocolytic therapy has little or no value.

Terbutaline should be used with caution in patients with diabetes, hyperthyroidism, hypertension, seizure disorders, or cardiac disease (especially with concurrent arrhythmias). Use of terbutaline with other sympathomimetic amines may increase the risk of developing adverse cardiovascular effects. Beta-adrenergic blocking agents (e.g., propranolol) may antagonize the actions of terbutaline. Tricyclic antidepressants or monoamine oxidase inhibitors may potentiate the vascular effects of terbutaline. It should be used cautiously with inhalation anesthetics (e.g., halothane, isoflurane, methoxyflurane), as it may predispose the patient to ventricular arrhythmias, particularly in patients with preexisting cardiac disease. Use with digitalis glycosides may increase the risk of cardiac arrhythmias.

Most adverse effects are dose-related and are those that would be expected with sympathomimetic agents, including increased heart rate, tremors, nervousness, and dizziness. These effects are generally transient and mild and do not require discontinuation of therapy.

### **Dosage Recommendation**

**Bronchospasm** : Oral terbutaline sulfate therapy can be initiated at a dosage of 2.5 mg three or four times daily in adults; depending on the patient's clinical response, dosage may then be titrated upward if necessary. The usual adult oral maintenance dosage is 5 mg three times daily administered at approximately six-hour intervals while the patient is awake. Adults should not receive more than 15 mg of the drug daily. If disturbing adverse effects occur, dosage may be reduced to 2.5 mg three times daily. Children 12-15 years of age may receive 2.5 mg orally three times daily; dosage should not exceed 7.5 mg daily.

The usual subcutaneous dose of terbutaline sulfate injection is 0.25 mg injected into the lateral deltoid area. If significant clinical improvement does not occur within 15-30 minutes, a second dose of 0.25 mg may be administered. If the patient then fails to respond within another 15-30 minutes,

other therapeutic measures should be considered. The total dose within four hours should not exceed 0.5 mg.

**Preterm Labor:** The recommended dose of terbutalin given subcutaneously (SC) is 0.25 mg every one to six hours.

---

## Coding/Billing Information

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

### Covered when medically necessary:

CPT <sup>®</sup> * Codes	Description

HCPCS Codes	Description

ICD-9-CM Diagnosis Codes	Description

### Experimental/Investigational/Unproven/Not Covered:

CPT* Codes	Description

HCPCS Codes	Description

ICD-9-CM Diagnosis Codes	Description

\*Current Procedural Terminology (CPT<sup>®</sup>) ©2004 American Medical Association: Chicago, IL.

---

## References

1. ACOG News Release. Most Efforts to Prevent Preterm Labor Not Effective. Nov 2002. Accessed October 19, 2005. Available at URL address:  
[http://www.acog.com/from\\_home/publications/press\\_releases/nr11-01-02-2.cfm](http://www.acog.com/from_home/publications/press_releases/nr11-01-02-2.cfm)
2. Berkman N, Thorp J, Lohr K, Carey T, Hartmann K; Gavin N, Hasselblad V, Idicula A. Tocolytic treatment for the management of preterm labor: A review of the evidence. AJOG. 2003 June;188(6):648-1659

3. Crowley P. Prophylactic corticosteroids for preterm birth (Cochrane Review). In: The Cochrane Library, Issue 3, 2004. Oxford: Update Software.
4. Drug Facts & Comparisons. Facts and Comparisons. St. Louis, MO. 2005.
5. Drugdex Database. In: Gelman CJ, Rumack BH, editors. Denver: Micromedex Inc. 2000.
6. Grossman J, Morris RJ, White KD, et al. Improved stability in oral delivery of albuterol provides less variability in bronchodilation in adults with asthma. *Ann Allergy*. 1991;66:324-327.
7. Hussey EK, Donn KH, Powell JR. Albuterol extended-release products: a comparison of steady-state pharmacokinetics. *Pharmacotherapy*. 1991;11:131-135.
8. Legge JS, Gaddie J, Palmer KN. Comparison of two oral selective beta2-adrenergic stimulant drugs in bronchial asthma. *British Medical Journal*. 1971;1(750):637-639.
9. Milroy R, Carter R, Carlyle D, Boyd G. Clinical and pharmacologic study of a novel controlled release preparation. *Br J Clin Pharm*. 1990; 29(5):578-580.
10. Morrison J, Chatham S, Carroll C, Boil J, Megan E. Continuous subcutaneous terbutaline administration prolongs pregnancy after recurrent preterm labor. *AGOG* 2003;188(6):1460-1467
11. National Institutes of Health. National Heart, Lung, and Blood Institute. Global Initiative for Asthma. Global strategy for asthma management and prevention. Revised 2002. NIH Publication No. 02-3659. February 2002.
12. The United States Pharmacopeia Drug Information (USPDI) for the Health Care Professional. 25th ed. Greenwood Village, CO: Micromedex Thomson Healthcare; 2005.
13. Wolfe JD, Shapiro GG, Ratner PH. Comparison of albuterol and metaproterenol syrup in the treatment of childhood asthma. *Pediatrics*. 1991;88(2):312-319.
14. Wolfe JD, Yamate M, Biedermann AA, Chu TJ. Comparison of the acute cardiopulmonary effects of oral albuterol, metaproterenol, and terbutaline in asthmatics. *Journal of the American Medical Association*. 1985;253(14):2068-2072.