

TERBUTALINE SULFATE- terbutaline sulfate injection

Akorn

TERBUTALINE SULFATE INJECTION, USP

Ampules

A sterile aqueous solution for subcutaneous injection

R_x only

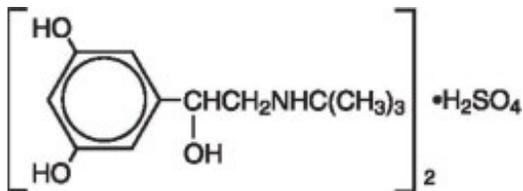
WARNING: PROLONGED TOCOLYSIS

Terbutaline sulfate has not been approved and should not be used for prolonged tocolysis (beyond 48 - 72 hours). In particular, terbutaline sulfate 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 sulfate to pregnant women. In the mother, 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. [See *Contraindications, Prolonged Tocolysis.*]

DESCRIPTION

Terbutaline sulfate USP, the active ingredient, is a beta-adrenergic agonist bronchodilator available as a sterile, nonpyrogenic, aqueous solution in ampules, for subcutaneous administration. Each milliliter of solution contains 1 mg of terbutaline sulfate USP (0.82 mg of the free base); sodium chloride USP, for isotonicity; hydrochloric acid NF, for adjustment to a target pH of 4; and water for injection.

Terbutaline sulfate is (±)-α-[(*tert*-butylamino) methyl]-3,5-dihydroxybenzyl alcohol sulfate (2:1) (salt). The empirical formula is (C₁₂H₁₉NO₃)₂ • H₂SO₄ and the structural formula is:



Terbutaline sulfate USP is a white to gray-white crystalline powder. It is odorless or has a faint odor of acetic acid. It is soluble in water and in 0.1 N hydrochloric acid, slightly soluble in methanol, and insoluble in chloroform. Its molecular weight is 548.65.

CLINICAL PHARMACOLOGY

Terbutaline Sulfate Injection, USP is a beta-adrenergic receptor agonist. *In vitro* and *in vivo* pharmacologic studies have demonstrated that terbutaline exerts a preferential effect on beta₂-adrenergic receptors. While it is recognized that beta₂-adrenergic receptors are the predominant receptors in bronchial smooth muscle, data indicate that there is a population of beta₂-receptors in the human heart, existing in a concentration between 10%-50%. The precise function of these receptors has not been established (see WARNINGS). Controlled clinical studies in patients given terbutaline subcutaneously have not revealed a preferential beta₂-adrenergic effect.

The pharmacologic effects of beta-adrenergic agonists, including terbutaline, are at least in part

attributable to stimulation through beta-adrenergic receptors of intracellular adenylyl cyclase, the enzyme which catalyzes the conversion of adenosine triphosphate (ATP) to cyclic 3', 5'-adenosine monophosphate (cAMP). Increased cAMP levels are associated with relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

Controlled clinical studies have shown that Terbutaline Sulfate Injection, USP relieves bronchospasm in acute and chronic obstructive pulmonary disease by significantly increasing pulmonary flow rates (e.g., an increase of 15% or more in FEV₁). After subcutaneous administration of 0.25 mg of Terbutaline Sulfate Injection, USP, a measurable change in expiratory flow rate usually occurs within 5 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 to 4 hours. The duration of clinically significant improvement is comparable to that observed with equimilligram doses of epinephrine.

Preclinical

Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histological evidence of myocardial necrosis) when beta-agonists and methylxanthines are administered concurrently. The clinical significance of these findings is unknown.

Pharmacokinetics

Subcutaneous administration of 0.5 mg of terbutaline sulfate to 17 healthy, adult, male subjects resulted in mean (SD) peak plasma terbutaline concentrations of 9.6 (3.6) ng/mL, which was observed at a median (range) time of 0.5 (0.08-1.0) hours after dosing. The mean (SD) AUC (0-48) and total body clearance values were 29.4 (14.2) hr•ng/mL, and 311 (112) mL/min respectively. The terminal half-life was determined in 9 of the 17 subjects and had a mean (SD) of 5.7 (2.0) hours.

After subcutaneous administration of 0.25 mg of terbutaline sulfate to two male subjects, peak terbutaline serum concentrations of 5.2 and 5.3 ng/mL were observed at about 20 minutes after dosing.

Elimination half-life of the drug in 10 of 14 patients was approximately 2.9 hours after subcutaneous administration, but longer elimination half-lives (between 6-14 hours) were found in the other 4 patients. About 90% of the drug was excreted in the urine at 96 hours after subcutaneous administration, with about 60% of this being unchanged drug. It appears that the sulfate conjugate is a major metabolite of terbutaline and urinary excretion is the primary route of elimination.

INDICATIONS AND USAGE

Terbutaline Sulfate Injection, USP is indicated for the prevention and reversal of bronchospasm in patients 12 years of age and older with asthma and reversible bronchospasm associated with bronchitis and emphysema.

CONTRAINDICATIONS

1. Prolonged Tocolysis

Terbutaline sulfate has not been approved and should not be used for prolonged tocolysis (beyond 48 - 72 hours). In particular, terbutaline sulfate should not be used for maintenance tocolysis in the outpatient or home setting. [See *Boxed Warning, Prolonged Tocolysis*.]

2. Hypersensitivity

Terbutaline sulfate injection is contraindicated in patients known to be hypersensitive to sympathomimetic amines or any component of this drug product.

WARNINGS

Deterioration of Asthma

Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient needs more doses of terbutaline sulfate than usual, this may be a marker of destabilization of asthma and requires re-evaluation of the patient and treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, e.g., corticosteroids.

Use of Anti-Inflammatory Agents

The use of beta-adrenergic agonist bronchodilators alone may not be adequate to control asthma in many patients. Early consideration should be given to adding anti-inflammatory agents, e.g., corticosteroids.

Cardiovascular Effects

Terbutaline sulfate like all other beta-adrenergic agonists, can produce a clinically significant cardiovascular effect in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of terbutaline sulfate at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiogram (ECG) changes, such as flattening of the T wave, prolongation of the QTc interval and ST segment depression. The clinical significance of these findings is unknown. Therefore, terbutaline sulfate, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Seizures

There have been rare reports of seizures in patients receiving terbutaline; seizures did not recur in these patients after the drug was discontinued.

PRECAUTIONS

General

Terbutaline, as with all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, including ischemic heart disease, hypertension, and cardiac arrhythmias; in patients with hyperthyroidism or diabetes mellitus; and in patients who are unusually responsive to sympathomimetic amines or who have convulsive disorders. Significant changes in systolic and diastolic blood pressure have been seen and could be expected to occur in some patients after use of any beta-adrenergic bronchodilator.

Immediate hypersensitivity reactions and exacerbations of bronchospasm have been reported after terbutaline administration.

Beta-adrenergic agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation.

Large doses of intravenous terbutaline have been reported to aggravate pre-existing diabetes mellitus and ketoacidosis.

Drug Interaction

The concomitant use of Terbutaline Sulfate Injection, USP with other sympathomimetic agents is not recommended, since the combined effect on the cardiovascular system may be deleterious to the patient.

Monoamine Oxidase Inhibitors or Tricyclic Antidepressants:

Terbutaline should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within two weeks of discontinuation of such agents, since the action of terbutaline on the vascular system may be potentiated.

Beta-Blockers:

Beta-adrenergic receptor blocking agents not only block the pulmonary effect of beta-agonists, such as Terbutaline Sulfate Injection, USP, but may produce severe bronchospasm in asthmatic patients. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with asthma. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

Diuretics:

The ECG changes and/or hypokalemia that may result from the administration of nonpotassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta-agonists with nonpotassium-sparing diuretics.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year study in Sprague-Dawley rats, terbutaline sulfate caused a significant and dose-related increase in the incidence of benign leiomyomas of the mesovarium at dietary doses of 50 mg/kg and above (approximately 810 times the maximum recommended daily subcutaneous (sc) dose for adults on a mg/m² basis). In a 21 month study in CD-1 mice, terbutaline sulfate showed no evidence of tumorigenicity at dietary doses of up to 200 mg/kg (approximately 1,600 times the maximum recommended daily sc dose for adults on a mg/m² basis). The mutagenicity potential of terbutaline sulfate has not been determined.

Reproductive studies in rats using terbutaline sulfate demonstrated no impairment of fertility at oral doses up to 50 mg/kg (approximately 810 times the maximum recommended daily sc dose for adults on a mg/m² basis.)

Pregnancy - Teratogenic Effects

Pregnancy Category C

There are no adequate and well-controlled studies of terbutaline sulfate in pregnant women. Published animal studies show that rat offspring exhibit alterations in behavior and brain development, including decreased cellular proliferation and differentiation when dams were treated subcutaneously with terbutaline during the late stage of pregnancy and lactation period. Terbutaline exposures in rat dams were approximately 24 to 48 times the common human dose in adults of 2-4 mg/day, on a mg/m² basis.

Terbutaline sulfate has not been approved and should not be used for prolonged tocolysis (beyond 48-72 hours). In particular, terbutaline sulfate 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 sulfate to pregnant women. In the mother, 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. [See *Boxed Warning, Prolonged Tocolysis and Contraindications, Prolonged Tocolysis.*]

In animal embryofetal developmental studies, no teratogenic effects were observed in offspring when pregnant rats and rabbits received terbutaline sulfate at oral doses up to 50 mg/kg/day, approximately 810 and 1600 times, respectively, the maximum recommended daily subcutaneous dose for adults, on a mg/m² basis.

Terbutaline sulfate should be used during pregnancy only if the potential benefits justify the potential

risk to the fetus.

Use in Labor and Delivery

Because of the potential for beta-agonist interference with uterine contractility, use of Terbutaline Sulfate Injection, USP for relief of bronchospasm during labor should be restricted to those patients in whom the benefits clearly outweigh the risk. Terbutaline crosses the placenta. After single dose IV administration of terbutaline to 22 women in late pregnancy who were delivered by elective Cesarean section due to clinical reasons, umbilical blood levels of terbutaline were found to range from 11% to 48% of the maternal blood levels.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Therefore, Terbutaline Sulfate Injection, USP should be used during nursing only if the potential benefit justifies the possible risk to the newborn.

Pediatric Use

Terbutaline Sulfate Injection, USP is not recommended for patients under the age of 12 years because of insufficient clinical data to establish safety and effectiveness.

Geriatric Use

Clinical Studies of terbutaline sulfate injection did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Adverse reactions observed with Terbutaline Sulfate Injection, USP are similar to those commonly seen with other sympathomimetic agents. All these reactions are transient in nature and usually do not require treatment.

The following table compares adverse reactions seen in patients treated with terbutaline sulfate Injection (0.25 mg and 0.5 mg), with those seen in patients treated with epinephrine injection (0.25 mg and 0.5 mg), during eight double-blind crossover studies involving a total of 214 patients.

	Incidence (%) of Adverse Reactions			
	Terbutaline (%)		Epinephrine (%)	
	0.25 mg N = 77	0.5 mg N = 205	0.25 mg N = 153	0.5 mg N = 61

Reaction

Central Nervous System

Tremor	7.8	38.0	16.3	18.0
Nervousness	16.9	30.7	8.5	31.1
Dizziness	1.3	10.2	7.8	3.3
Headache	7.8	8.8	3.3	9.8
Drowsiness	11.7	9.8	14.4	8.2

Cardiovascular

Palpitations	7.8	22.9	7.8	29.5
Tachycardia	1.3	1.5	2.6	0.0

Respiratory

Dyspnea	0.0	2.0	2.0	0.0
Chest Discomfort	1.3	1.5	2.6	0.0

Gastrointestinal

Nausea/Vomiting	1.3	3.9	1.3	11.5
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Systemic

Weakness	1.3	0.5	2.6	1.6
Flushed feeling	0.0	2.4	1.3	0.0
Sweating	0.0	2.4	0.0	0.0
Pain at Injection Site	2.6	0.5	2.6	1.6

Note: Some patients received more than one dosage strength of terbutaline sulfate and epinephrine. In addition, there were reports of anxiety, muscle cramps, and dry mouth (<0.5%). There have been rare reports of elevations in liver enzymes and hypersensitivity vasculitis with terbutaline administration.

OVERDOSAGE

The median sc lethal dose of terbutaline sulfate in mature rats was approximately 165 mg/kg (approximately 2,700 times the maximum recommended daily sc dose for adults on mg/m² basis). The median sc lethal dose of terbutaline sulfate injection in young rats was approximately 2,000 mg/kg (approximately 32,000 times the maximum recommended daily sc dose for adults on a mg/m² basis).

The expected symptoms with overdosage are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the symptoms listed under ADVERSE REACTIONS, e.g., seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats per minute, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and insomnia. Hypokalemia may also occur. There is no specific antidote. Treatment consists of discontinuation of Terbutaline Sulfate injection, USP together with appropriate symptomatic therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of terbutaline sulfate.

DOSAGE AND ADMINISTRATION

Ampules should be used only for subcutaneous administration and not intravenous infusion. Sterility and accurate dosing cannot be assured if the ampules are not used in accordance with **DOSAGE AND ADMINISTRATION**.

The usual subcutaneous dose of Terbutaline Sulfate Injection, USP 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 4 hours should not exceed 0.5 mg.

Note: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

Ampules 1 mg/mL – The drug is supplied at a volume of 1 mL contained in a 2 mL clear glass ampule. Each ampule contains 1 mg of terbutaline sulfate per 1 mL of solution; 0.25 mL of solution will provide the clinical dose of 0.25 mg.

Ampules are expiration-dated
Discard unused portion after single patient use.

Terbutaline Sulfate Injection, USP, 1 mg/mL is available as a 1 mL ampule in packs of 10.
NDC 17478-933-01

STORAGE: Store at 20° to 25° C (68° to 77°F). [See USP Controlled Room Temperature].

Protect from light by storing ampules in original carton until dispensed.

Do not use if solution is discolored.

Akorn

Manufactured by: **Akorn, Inc.**

Lake Forest, IL 60045

TB00N Rev. 03/11

Principal Display Panel

Ampule Label -

NDC 17478-933-01 Akorn

Terbutaline Sulfate

Injection, USP

1 mg/mL

For Subcutaneous Injection Only

Protect from light

1 mL Ampule

Rx only TBAAL Rev 06/08



Carton Label -

NDC 17478-933-01
Terbutaline Sulfate
Injection, USP
1 mg/mL

A sterile, nonpyrogenic, aqueous solution for
subcutaneous injection.

Rx only Akorn 10 ampules (1mL each)

Do not use if solution is discolored Singles-dose Ampules



TERBUTALINE SULFATE			
terbutaline sulfate injection			
Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:17478-933
Route of Administration	SUBCUTANEOUS		
Active Ingredient/Active Moiety			

Ingredient Name		Basis of Strength	Strength	
terbutaline sulfate (UNII: 576PU70Y8E) (terbutaline - UNII:N8ONU3L3PG)		terbutaline sulfate	1 mg in 1 mL	
Inactive Ingredients				
Ingredient Name		Strength		
sodium chloride (UNII: 451W47IQ8X)				
hydrochloric acid (UNII: QTT17582CB)				
water (UNII: 059QF0KO0R)				
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:17478-933-01	10 in 1 CARTON	02/01/2010	
1		1 mL in 1 AMPULE; Type 0: Not a Combination Product		
Marketing Information				
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date	
ANDA	ANDA078151	02/01/2010		

Labeler - Akorn (117696770)

Registrant - Akorn Operating Company LLC (117693100)

Establishment

Name	Address	ID/FEI	Business Operations
Akorn, Inc		117696832	MANUFACTURE(17478-933) , STERILIZE(17478-933) , ANALYSIS(17478-933)

Establishment

Name	Address	ID/FEI	Business Operations
Akorn, Inc		117696790	PACK(17478-933) , LABEL(17478-933)

Revised: 10/2020

Akorn