

PRODUCT MONOGRAPH

PrBRICANYL[®] TURBUHALER[®]

(terbutaline sulfate)

0.5 mg/Metered Dose

Bronchodilator

AstraZeneca Canada Inc.
1004 Middlegate Road
Mississauga, Ontario
L4Y 1M4

Date of Preparation:
April 18, 2000

Date of Revision:
December 20, 2005

Previously Control No. 070963

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PRODUCT MONOGRAPH

NAME OF DRUG

PrBRICANYL[®] TURBUHALER[®]

(terbutaline sulfate)

0.5 mg/Metered Dose

THERAPEUTIC CLASSIFICATION

Bronchodilator

ACTIONS AND CLINICAL PHARMACOLOGY

BRICANYL TURBUHALER (terbutaline sulfate) produces bronchodilation by stimulation of the β_2 -adrenergic receptors in bronchial smooth muscle, thereby causing relaxation of muscle fibers. This action is manifested by an increase in pulmonary function as demonstrated by FEV₁ measurements. BRICANYL TURBUHALER also produces a decrease in airway and pulmonary resistance.

Following inhalation of BRICANYL TURBUHALER, a significant improvement in pulmonary function measurements is well established after 5 minutes. 20 - 30% of the metered dose is deposited in the lungs with an inspiration flow rate of about 60 L/min.

The maximal response is usually attained between 15 and 60 minutes following administration. Significant bronchodilator activity has been observed to persist for 4 to 7 hours.

INDICATIONS AND CLINICAL USE

BRICANYL TURBUHALER (terbutaline sulfate) is indicated as a bronchodilator for the symptomatic relief of bronchial asthma and for relief of reversible bronchospasm which may occur in association with bronchitis and emphysema.

CONTRAINDICATIONS

BRICANYL TURBUHALER (terbutaline sulfate) is contraindicated when there is known hypersensitivity to sympathomimetic amines and, like other sympathomimetic amines, should not be used in patients with tachyarrhythmias.

WARNINGS

Like other β_2 -agonist inhalers, BRICANYL TURBUHALER (terbutaline sulfate) should not be used on a regular daily basis without appropriate concomitant anti-inflammatory therapy (see DOSAGE AND ADMINISTRATION).

BRICANYL TURBUHALER should be used with caution in patients with diabetes, hypertension, hyperthyroidism, and a history of seizures. As with other sympathomimetic bronchodilator agents, BRICANYL TURBUHALER should be administered cautiously to cardiac patients, especially those with associated arrhythmias, and coronary insufficiency, to elderly or to patients who are unusually responsive to sympathomimetic amines. Due to the hyperglycemic effects of β_2 -agonists, additional blood glucose controls are recommended initially in diabetic patients.

Occasionally, patients have been reported to have developed severe paradoxical bronchospasm with repeated use of sympathomimetic inhalant preparations. In such instances, the preparation should be discontinued immediately and alternate therapy instituted. Fatalities, the exact cause of which are unknown, have been reported following excessive use of inhaled preparations containing sympathomimetic amines. Cardiac arrest was noted in several instances.

Beta-receptor blocking agents (including eye-drops), especially those which are non-cardioselective, may partially or totally inhibit the effect of beta-receptor stimulants. Severe resistant bronchospasm may be produced with the use of beta-blockers in asthmatic patients.

Potentially serious hypokalemia may result from β_2 -agonist therapy, mainly from parenteral or nebulized administration. Particular caution is advised in acute severe asthma as this may be potentiated by hypoxia and concomitant treatment with xanthine derivatives, steroids and diuretics; it is recommended that serum potassium levels be monitored in such situations.

Use in Pregnancy

The safe use of BRICANYL TURBUHALER has not been established in human pregnancy. The use of this drug in pregnancy, lactation, or women of child-bearing potential requires that the expected therapeutic benefit of the drug be weighed against its possible hazards to the mother or child. Animal reproductive studies have shown no adverse effects on fetal development.

Transient hypoglycemia has been reported in newborn pre-term infants after maternal β_2 -agonist treatment.

Systemic β_2 -agonists should be used with caution before childbirth in view of their inhibiting effect on uterine contractions.

Nursing Mothers

Terbutaline is excreted in breast milk. Caution should be exercised when BRICANYL TURBUHALER is administered to nursing women.

Use in Pediatrics

BRICANYL TURBUHALER is not presently recommended for children below 6 years of age due to limited clinical data in this pediatric group.

PRECAUTIONS

If therapy does not produce a significant improvement or if the patient's condition gets worse, medical advice must be sought in order to determine a new plan of treatment.

In the case of acute or rapidly worsening dyspnea, a doctor should be consulted immediately.

Increasing use of β_2 -agonists to control symptoms of bronchial obstruction, especially administration on a regular basis or in high amounts, indicates deterioration of asthma control. Under these conditions, the patient's therapy plan has to be revised. It is inadequate simply to increase the use of bronchodilators under these circumstances, in particular over extended periods of time (see DOSAGE AND ADMINISTRATION). The revised treatment regimen should include concomitant use of other anti-asthma drugs, such as anti-inflammatory agents.

To ensure optimal delivery of BRICANYL (terbutaline sulfate) to the bronchial tree, the patient should be properly instructed in the use of TURBUHALER.

In patients in whom the administration of BRICANYL TURBUHALER induces cardiac irregularities, the administration of the drug should be stopped. If a reduced response to BRICANYL TURBUHALER becomes apparent, the patient should seek medical advice.

In patients requiring concomitant treatment with BRICANYL TURBUHALER and a beta-blocker, it is recommended that a beta-blocker (e.g., metoprolol) with less predominant β_2 -blocking effects be considered. If concomitant treatment is necessary, patients should be monitored carefully for possible deterioration in pulmonary function and the need to adjust the dosage of either drug (see Drug Interactions).

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

Drug Interactions

Sympathomimetic Bronchodilators and Epinephrine

The concomitant use of BRICANYL TURBUHALER with other sympathomimetic bronchodilators or epinephrine is not generally recommended since their combined effect on the cardiovascular system may be deleterious to the patient. If additional adrenergic drugs are to be administered by any route to the patient using BRICANYL TURBUHALER, the adrenergic drugs must be used with caution. Such concomitant use, however, should be individualized and not given on a routine basis. If regular co-administration is required, alternative therapy should be considered.

MAO Inhibitors and Tricyclic Antidepressants

BRICANYL TURBUHALER should be administered with caution in patients being treated with monoamine oxidase (MAO) inhibitors or tricyclic antidepressants, since the action of BRICANYL on the vascular system may be potentiated.

Beta-Adrenergic Receptor Blockers

Beta-adrenergic receptor blocking agents not only block the pulmonary effect of terbutaline but may produce severe asthmatic attacks in asthmatic patients. Therefore, patients requiring treatment for both bronchospastic disease and hypertension should be treated with medication other than beta-adrenergic blocking agents for their hypertension.

BRICANYL TURBUHALER contains terbutaline sulfate which is sensitive to moisture. Patients should be instructed to avoid exhaling into the device and to replace the cover after using TURBUHALER.

ADVERSE REACTIONS

When treatment with BRICANYL TURBUHALER (terbutaline sulfate) is started, the following adverse reactions can be classified as frequent (i.e., > 1/100): tremor, palpitations, restlessness, headache, muscle cramps, nervousness. Other reported reactions include increased heart rate, tachycardia, ectopic beats, drowsiness, nausea, vomiting, sweating and dizziness. As for all β_2 -agonists, cardiac arrhythmias, e.g., atrial fibrillation, supraventricular tachycardia and extrasystoles have been rarely reported.

These adverse reactions are all characteristic of sympathomimetic amines and initial dose titrations will often reduce these reactions. With the possible exception of muscle cramps, all have been spontaneously reversible within the first two weeks of treatment. Urticaria and exanthema may also occur.

Sleep disturbances and behavioural disturbances, such as agitation, hyperactivity and restlessness, have been observed. As with other inhalation therapy, the potential for paradoxical bronchospasm should be kept in mind with BRICANYL TURBUHALER. If it occurs, the preparation should be discontinued immediately and alternative therapy instituted. Potentially serious hypokalemia may result from β_2 -agonist therapy.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

The symptoms of overdose are similar to those described above under ADVERSE REACTIONS, and are attributable to excessive β -adrenergic stimulation. To antagonize the effect of excessive stimulation, the judicious use of a β -adrenergic blocking agent such as propranolol may be considered, bearing in mind the danger of inducing an asthmatic attack.

DOSAGE AND ADMINISTRATION

Dosage should be individualized, and patient response should be monitored by the prescribing physician on an ongoing basis.

BRICANYL TURBUHALER

Adults and Children \geq 6 Years

The generally recommended dose of BRICANYL TURBUHALER (terbutaline sulfate) is one inhalation (0.5 mg) taken as required. This will usually be adequate to relieve bronchospasm in the majority of patients, however, if required, a second dose may be taken, preferably after waiting five minutes for the effect of the first dose to be obtained. If a more severe attack has not been relieved by the second administration, higher doses may be required. In these cases, patients should immediately consult their doctor or the nearest hospital.

More than six doses (six inhalations of BRICANYL TURBUHALER) should not be necessary in any 24 hour period.

If a previously effective dosage regimen fails to provide the usual relief, or the effects of a dose last for less than three hours, medical advice should be sought immediately; this is a sign of seriously worsening asthma that requires reassessment of therapy.

Treatment with β_2 -agonists in bronchial asthma should be on demand, e.g., symptoms oriented. **Patients must not use them on a daily basis for control of bronchospasm without using other concomitant anti-asthma medication(s) according to the present practice for asthma treatment to control airway inflammation.**

The daily dose of BRICANYL TURBUHALER should not be increased without adequate reassessment of the therapy plan.

As with other β_2 -agonists, increasing demand for BRICANYL TURBUHALER (terbutaline sulfate) in bronchial asthma is a sign of poor asthma control and indicates that the treatment plan should be revised.

When prescribing BRICANYL TURBUHALER to children, it is necessary to ascertain that they can follow the instructions for use. BRICANYL TURBUHALER is not recommended for use in children below the age of 6 years.

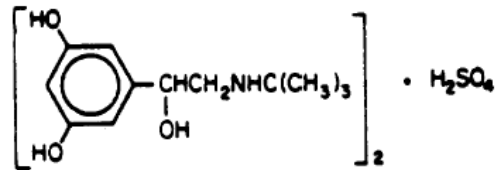
NOTE: The medication from BRICANYL TURBUHALER is delivered to the lungs as the patient inhales and, therefore, it is important to instruct the patient to breathe in forcefully and deeply through the mouthpiece. The patient may not taste or feel any medication when using BRICANYL TURBUHALER due to the small amount of drug dispensed.

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: terbutaline sulfate

Chemical Structure:



Molecular Formula: (C₁₂H₁₉NO₃)₂·H₂SO₄

Molecular Weight: 548.6

Chemical Name: 1-(3,5-dihydroxyphenyl)2-t-butylamino ethanol sulfate

Description: Terbutaline sulfate is a water soluble, white to off-white crystalline powder.

Dosage Form

Composition:

BRICANYL TURBUHALER

Ingredient *mg/inhalation*

terbutaline sulfate 0.5

Stability and Storage Recommendations

BRICANYL TURBUHALER should be stored with the cover tightened, at room temperature (15 - 30°C), in a dry place, away from moisture.

AVAILABILITY OF DOSAGE FORMS

TURBUHALER

BRICANYL TURBUHALER (terbutaline sulfate) is supplied in 50 doses and 200 doses of micronized terbutaline sulfate. Each inhalation from the multiple dose powder inhaler contains 0.5 mg of terbutaline sulfate; no additives or carrier substances are included in the inhalation. BRICANYL TURBUHALER cannot be re-filled and should be discarded when empty.

INFORMATION FOR THE CONSUMER

IMPORTANT INFORMATION YOU SHOULD KNOW ABOUT

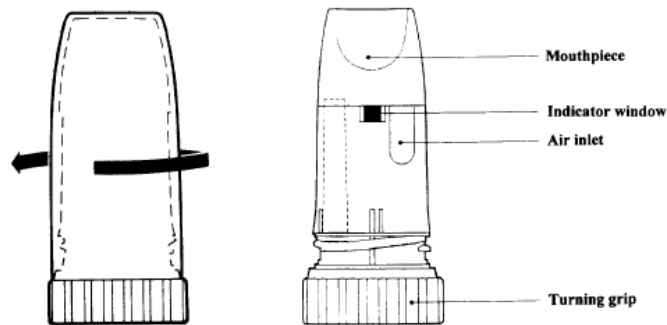
 **BRICANYL® TURBUHALER®**

terbutaline sulfate

Before using BRICANYL TURBUHALER, read this leaflet carefully. It contains general points about BRICANYL TURBUHALER and should add to more specific advice from your doctor or pharmacist.

Please keep this leaflet to refer to until you have used up all medication in BRICANYL TURBUHALER.

WHAT IS BRICANYL TURBUHALER USED FOR AND HOW DOES IT WORK?



BRICANYL is a brand name for a drug called terbutaline. It is used to treat asthma, chronic bronchitis or other disorders which lead to breathing difficulties. Terbutaline belongs to the class of drugs referred to as bronchodilators.

TURBUHALER is the brand name for a multiple dose, dry-powder inhaler. When you breathe in through the inhaler, your indrawn breath provides the necessary force to deliver the drug to your lungs.

BRICANYL TURBUHALER is used to improve your breathing during times such as an asthma attack. It opens up airways in people with asthma or other breathing problems. It relieves symptoms such as wheezing, cough and shortness of breath.

WHAT IS IN BRICANYL TURBUHALER?

BRICANYL TURBUHALER contains terbutaline sulfate as the active ingredient and comes in a concentration of 0.5 mg per inhalation. If you happen to shake the inhaler, the sound you hear is the drying agent built into the blue turning grip. This is not the medication and cannot be inhaled. BRICANYL TURBUHALER contains no other ingredients.

WHAT SHOULD I TELL MY DOCTOR BEFORE TAKING BRICANYL TURBUHALER?

Tell your doctor:

- about **all** health problems you have now or have had in the past, especially heart problems such as irregular heart beat and high blood pressure;
- about other medicines you take, including ones you can buy without a prescription;
- if you have ever had a bad, unusual or allergic reaction to terbutaline;
- if you are pregnant, plan to become pregnant or are breastfeeding.

HOW DO I TAKE BRICANYL TURBUHALER PROPERLY?

Use BRICANYL TURBUHALER for relief of an asthma attack or when you feel a tightening of the airways. You usually get an effect within a few minutes. The effect lasts up to 7 hours. Treatment with BRICANYL TURBUHALER is effective even if you have an acute asthmatic attack.

TURBUHALER is a multi-dose inhaler from which very small amounts of powder are administered. When you breathe in through TURBUHALER the powder is delivered to the lungs. It is therefore important that you **inhale forcefully and deeply** through the mouthpiece.

BRICANYL TURBUHALER is **very** easy to use.

Note: You may not taste or feel any medication when inhaling from BRICANYL TURBUHALER. This is common.

If you follow the instructions below, you will receive the medication.

Using the inhaler

To administer a dose, simply follow the instructions below.

Fig. 1

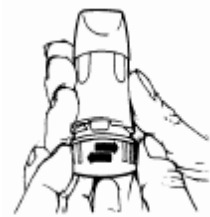


Fig. 2



Unscrew and lift off the cover.

TURN

Hold the inhaler upright with the grip downwards (Fig. 1). To load the inhaler with a dose **turn the blue grip as far as it will go in one direction and then back to the original position.**

CLICK

The “click” you heard means the inhaler is ready to use. **Breathe out.** Do **not** breathe out through the mouthpiece.

INHALE

Place the mouthpiece gently between your teeth, close your lips and breathe in **forcefully and deeply** through your mouth (Fig. 2). Do not chew or bite on the mouthpiece.

Note: Do not use TURBUHALER if it has been damaged or if the mouthpiece has become detached.

Remove the inhaler from your mouth, before breathing out.

If more than one dose has been prescribed, repeat the above steps. Replace the cover.

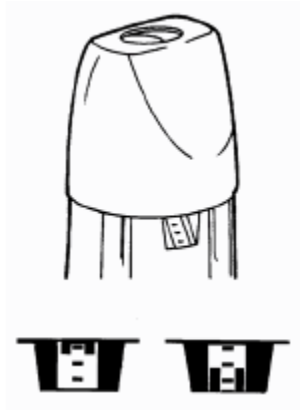
If you accidentally drop, shake or breathe out into BRICANYL TURBUHALER after it is loaded, you will lose your dose. If this happens, you should load a new dose and inhale it.

Note: Never breathe out through the mouthpiece. Always replace the cover properly after use.

As the amount of powder dispensed is very small, you may not be able to taste it after inhalation. However, you can still be confident that the dose has been inhaled if you have followed the instructions.

Cleaning: Clean the outside of the mouthpiece once a week with a **dry** tissue. **Never** use water or any other fluid. If fluid enters the inhaler it may not work properly.

HOW DO I KNOW WHEN BRICANYL TURBUHALER IS EMPTY?



Approx. 20 doses left **EMPTY**

BRICANYL TURBUHALER has a dose indicator. When a red mark first appears in the little window underneath the mouthpiece, there are approximately 20 doses left. Now is the time to obtain your next inhaler.

When the red mark reaches the bottom of the window, BRICANYL TURBUHALER is EMPTY. If you shake the inhaler when it is empty, you will still be able to hear the sound of the drying agent. BRICANYL TURBUHALER cannot be re-filled with drug and should be discarded.

HOW MUCH BRICANYL TURBUHALER SHOULD I TAKE?

The dosage of BRICANYL TURBUHALER is individual.

Follow your doctor's directions carefully. They may differ from the information in this leaflet.

The usual dose for adults and children 6 years of age and older is one inhalation as required. If symptoms persist, further inhalations may be required and you should immediately consult your doctor or the nearest hospital. More than six inhalations (3.0 mg) should not be required in a 24 hour period.

You should see a doctor if:

- your usual dose does not provide relief;
- the effects of one dose last less than three hours;
- you are using BRICANYL TURBUHALER every day to relieve symptoms.

These may be signs that your asthma is getting worse. Your doctor may prescribe this medication in association with other anti-asthma medication that controls airway inflammation.

Do NOT exceed the dose prescribed by your doctor.

WHAT SHOULD I DO IN CASE OF OVERDOSE?

Telephone your doctor or go to your nearest hospital right away if you think that you or anyone else may have taken too much BRICANYL TURBUHALER.

ARE THERE ANY SIDE EFFECTS?

Like any medication, BRICANYL TURBUHALER may cause side effects in some people. The most common side effects are nervousness and shakiness. These side effects disappear in most cases over the first few days of treatment. Headache, increased heart rate, flushing, occasional muscle cramps, sleeplessness, stomach upset, weakness, dizziness, nausea and sweating have also been reported. Irregular heart beats have been rarely reported.

Medicines affect different people in different ways. Just because side effects have occurred in some patients, does not mean that you will get them. If any side effects bother you, please contact your doctor.

DRIVING AND USING MACHINES

Use of BRICANYL TURBUHALER will not affect your ability to drive or to operate any tools or machines.

WHERE SHOULD I KEEP BRICANYL TURBUHALER?

Remember to **keep BRICANYL TURBUHALER out of the reach of children** when you are not using it.

Always replace the cover after using BRICANYL TURBUHALER. Store the inhaler at room temperature in a dry place, away from moisture.

Do not keep or use BRICANYL TURBUHALER after the expiry date indicated on the label.

Important Note:

This leaflet alerts you to some of the times you should contact your doctor. Other situations which cannot be predicted may arise. Nothing about this leaflet should stop you from calling your doctor or pharmacist with any questions or concerns you have about using BRICANYL TURBUHALER.

NOTE: This INFORMATION FOR THE CONSUMER leaflet provides you with the most current information at the time of printing. Please refer to the Consumer Information Leaflet located at: www.astrazeneca.ca, under the heading "Patients with Prescriptions", to see if more up-to-date information has been posted.

Customer Inquiries: 1 800 668-6000

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Last revised: December 20, 2005

PHARMACOLOGY

Animal

Terbutaline sulfate has been shown by pharmacological studies in animals to exert a preferential effect on β_2 -adrenergic receptors, such as those located in bronchial smooth muscle.

Bronchodilator Effect

In Vitro Studies

The bronchospasmolytic effect of terbutaline sulfate, L-epinephrine, orciprenaline and isoproterenol has been studied on spirally cut trachea from guinea pig and rabbit, and on cat bronchi. All four compounds relaxed pilocarpine induced contraction. The order of potency (by weight) was as follows: isoproterenol, L-epinephrine, terbutaline sulfate (dl form), orciprenaline.

Terbutaline sulfate was added to organ baths containing spirally cut guinea pig trachea and right auricle. Epinephrine was studied as a reference drug. At low concentration rates, terbutaline sulfate produced a relaxation of the trachea without increasing the force of auricular contraction while epinephrine produced a similar degree of tracheal relaxation but also increased auricular contraction force. At higher concentrations, terbutaline sulfate also stimulated auricular contraction force.

In Vivo Studies

The bronchospasmolytic effect of terbutaline sulfate, orciprenaline and isoproterenol was studied in anesthetized guinea pigs, cats and dogs. It was found that the bronchospasm induced by histamine or acetylcholine could be prevented by appropriate intravenous doses of these agents. The order of potency was as in the *in vitro* studies described above.

Terbutaline sulfate, orciprenaline and isoproterenol administered orally or intraperitoneally to unanesthetized guinea pigs protected the animals against histamine induced bronchoconstriction. As determined graphically, the intraperitoneal doses protecting 50% of the animals were in the following order of potency: Isoproterenol (0.065 mg/kg), terbutaline sulfate (0.15 mg/kg), orciprenaline (0.60 mg/kg). The ED₅₀ following oral administration of each drug showed the following order of potency: terbutaline sulfate (0.4 mg/kg), orciprenaline (1.2 mg/kg), isoproterenol (1.4 mg/kg).

Circulatory Effect

In Vitro Studies

Isolated heart muscle from guinea pigs and rabbits was used to compare the direct effect of terbutaline sulfate, isoproterenol, epinephrine and orciprenaline. The four substances produced increases in both contractile force and heart rate. Relative to the effect of

epinephrine, the potencies of the different compounds with respect to the production of 20% inotropic and chronotropic increases were as follows: isoproterenol (15.3 - 42.0), epinephrine (1.0), orciprenaline (0.05 - 0.33), terbutaline sulfate (0.005 - 0.05).

Similar results were obtained using left auricle and papillary muscle preparations from the cat.

In Vivo Studies

In the anesthetized cat, terbutaline sulfate decreased mean arterial pressure, increased pulse pressure and increased heart rate. Decreases in mean arterial pressure were noted at intravenous doses greater than 0.07 µg/kg. Following intravenous isoproterenol administration, increased heart rate and decreased arterial blood pressure were seen at 0.008 µg/kg, which was the lowest dose studied.

In the anesthetized dog, increased heart rate and decreased mean arterial blood pressure were seen at doses of 0.005 µg/kg of isoproterenol, 0.5 µg/kg of orciprenaline and 1.0 µg/kg of terbutaline sulfate.

Other Pharmacological Activities

Terbutaline sulfate was shown to have an inhibiting effect on spontaneous contractions of the rabbit duodenum. In cats, terbutaline sulfate has been shown *in vitro* and *in vivo* to have a relaxing effect on the sphincter of Oddi. Terbutaline sulfate has demonstrated a relaxing effect on rabbit urinary bladder and rat uterine muscle.

Human

Absorption, Distribution, Metabolism and Excretion

Following oral administration of tritiated drug to man, plasma radioactivity peaked at 60 - 90 minutes, and declined with a half-life of 4 - 6 hours. Approximately 24% of the dose was absorbed, as indicated by recovery of radioactivity in urine; 5 - 6% of the dose was excreted in urine as unchanged drug and the remainder was identified as a sulfate conjugate.

Fecal radioactivity accounted for 35 - 56% of the original dose and was identified as unchanged drug.

The disposition of tritiated terbutaline sulfate following inhalation has been studied in man. Serum concentrations of total radioactivity were low. Peak concentrations were seen 3 - 6 hours following administration. Between 2 - 37% of the delivered drug was recovered in feces and 3 - 35% in urine. As with other routes of administration, inhaled drug was shown to be biotransformed by conjugation.

Following intravenous administration to man, 78 - 85% of the administered radioactivity was excreted in urine; 52 - 60% of the dose was excreted as unchanged drug, and 4 - 19% as sulfate conjugate. Less than 3% of the administered dose appeared in feces. Biliary excretion

following intravenous dosing has been studied in two subjects with biliary drainage; less than 1% of the administered dose was excreted by this route.

Following subcutaneous administration to man, plasma levels plateaued from 10 - 40 minutes after dosing. Ultimately, 92 - 95% of the administered dose was recovered in the urine; approximately 60% of the administered radioactivity was excreted as unchanged drug. Less than 3% of the dose was excreted in feces.

In vitro experiments indicated that terbutaline sulfate is not metabolized by rat and human liver O-methyltransferases and monoamine oxidases, nor did it inhibit these enzymes significantly.

Plasma-binding of terbutaline sulfate has been studied *in vitro* using plasma prepared from human citrated blood. In the concentration range of 0.7 - 64.5 ng/mL, 25% of the drug was bound to plasma protein.

TOXICOLOGY

Acute Toxicity Studies with orally and parenterally administered terbutaline sulfate are summarized below.

Table 1

Species	Route	LD ₅₀ mg/kg
Mouse	i.v.	≈56
	i.p.	263
	s.c.	295
	oral	3,000
Rat	i.v.	≈74
	i.p.	316
	s.c.	800
	oral	≈1,800
Rabbit	i.v.	≈65
	s.c.	≈ 1,600
	oral	≈9,000
Dog	i.v.	> 125
	s.c.	≈300
	oral	≈ 1,000 - 2,000

Similar studies were performed on monkeys exposed in head chambers to an estimated dose of 80.5 mg/kg over 2 hours. Exudate around the mouth, and circumorbital erythema, were seen. Slight bradycardia was observed. Animals recovered and behaved normally during the

post-exposure period. At autopsy, marked pulmonary congestion and edema were seen in half of the animals.

In animals, theophylline, chlorpromazine, meprobamate, chlorodiazepoxide, imipramine and phenylbutazone, in doses corresponding to twice the maximal clinical dose, did not influence the toxicity of terbutaline sulfate. Nialamide, however, caused a slight increase in the toxicity. Pre-treatment of animals with a dose corresponding to one third of the LD₅₀ of the above drugs increased the toxicity of terbutaline sulfate. This increase was slight with all drugs except for nialamide, which at this high dose level strongly increased the toxicity.

Subacute and Chronic Toxicity Studies

The effect of repeated daily administration of terbutaline sulfate, subcutaneously and orally, has been studied in rats and dogs. Other sympathomimetic amines were included as reference compounds in most studies.

Clinical manifestations of toxicity included hyperemia of mucous membrane and skin, vomiting after initial dosing, and abnormal quietness or irritability. Dose-related increased heart rate was seen in both species. Decreased blood glucose concentrations were observed in an 18 month rat study.

Myocardial changes, such as focal necrosis or fibrosis or chronic focal myocarditis, were the most significant pathological findings related to treatment and were also seen with each of four other sympathomimetic amines studied as reference compounds. These findings, in relation to terbutaline sulfate, are summarized in Table 2 which shows the dose levels studied for each species and route of administration. Those levels at which myocardial lesions were seen are underlined.

Table 2

Species	Route	Duration	Dose Levels (mg/kg/day)
Dog	subcutaneous	2 weeks	0.0, 0.025, <u>0.5</u> , <u>5.0</u>
		4 weeks	0.0, 0.005, 0.01, 0.025, <u>0.1</u>
	oral	1 month	0.025, 0.25, <u>4.0</u> , <u>20.0</u>
		3 months	0.0, 0.2, 1.0, <u>10.0</u>
		6 months	0.0, 0.3, <u>2.0</u> , <u>10.0-20.0</u>
12 months	0.0, 0.3, 2.0, 10.0-20.0		
Rat	subcutaneous	3 days	0.0, <u>0.025</u> , 0.1, <u>0.5</u> , 1.0, <u>10.0</u> , <u>50.0</u>
		1 month	0.0, 0.1, <u>1.0</u> , <u>5.0</u> , <u>25.0-50.0</u>
	oral	1 month	<u>0.0</u> , <u>10.0</u> , <u>100.0</u> , <u>500.0</u>
		3 months	<u>0.0</u> , <u>0.2</u> , <u>2.0</u> , <u>50.0</u>
		18 months	<u>0.0</u> , <u>2.0</u> , <u>20.0</u> , <u>200.0</u>

In the dog, myocardial lesions were observed after the intratracheal administration of 0.7 mg/kg/day for two days. Morphologically similar toxicity was seen with reference bronchodilating compounds. In a 4 week rat study, myocardial lesions were seen in 4 of 10 animals exposed for 90 min/day to an aerosol cloud containing 4 - 6 mg/L. These lesions were considered similar to the findings in rats and dogs treated with orally or subcutaneously administered drug.

Three-month studies, in which rats and monkeys were exposed to terbutaline sulfate under circumstances calculated to provide inhaled doses of up to 25 and 27.3 mg/kg/day, respectively, failed to reveal drug-related pathology of the myocardium or other tissues.

Reproduction and Teratology Studies

Reproduction and Teratology studies have been performed in mice, rats and rabbits. None of these studies revealed any adverse effects on the reproductive performance, or development of fetus, attributable to terbutaline sulfate.

Carcinogenicity Studies

Carcinogenicity studies were conducted in mice and rats. Terbutaline sulfate was given orally at dose levels from 2 - 200 mg/kg/day for 18 months. Results obtained did not suggest carcinogenicity since the number of tumors in control and treated animals were statistically comparable.

Mutagenicity Studies

Studies of terbutaline sulfate have not been conducted to determine mutagenic potential.

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