PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

BRICANYL® TURBUHALER®

terbutaline sulfate

Dry powder, 0.5 mg/dose, Oral Inhalation

Bronchodilator

AstraZeneca Canada Inc.
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RECENT MAJOR LABEL CHANGES

1 INDICATIONS, 1.1 Pediatrics	06/2021
1 INDICATIONS, 1.2 Geriatrics	06/2021
2 CONTRAINDICATIONS	06/2021
7 WARNINGS AND PRECAUTIONS, General	12/2022
7 WARNINGS AND PRECAUTIONS, Sensitivity/Resistance	06/2021

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

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.

1.1 Pediatrics

Pediatrics (≥6 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of BRICANYL TURBUHALER in pediatric patients has been established. Therefore, Health Canada has authorized an indication for pediatric use. BRICANYL TURBUHALER is not recommended for children under the age of 6.

1.2 Geriatrics

BRICANYL TURBUHALER should be administered with caution to elderly patients (see Cardiovascular).

2 CONTRAINDICATIONS

BRICANYL TURBUHALER (terbutaline sulfate) is contraindicated:

- in patients who are hypersensitive to terbutaline, or lactose (which may contain milk protein residue), or sympathomimetic amines;
- like other sympathomimetic amines, in patients who are known to have tachyarrhythmias;
- as a tocolytic in patients at risk of premature labour or threatened abortion.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

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

4.2 Recommended Dose and Dosage Adjustment

Adults and Children ≥ 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 healthcare professional 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 worsening of the underlying condition and warrants a 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-inflammatory 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 use of BRICANYL TURBUHALER in bronchial asthma is a sign of poor asthma control and indicates that the treatment plan should be revised.

4.4 Administration

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.

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.

5 OVERDOSAGE

The symptoms of overdosage are similar to those described under 8 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.

There is a potential for progressive accumulation of dry powder in the mouthpiece of BRICANYL TURBUHALER (terbutaline sulfate) that could be released if dropped (e.g., from a table) towards the end of inhaler life. To minimize unnecessary systemic exposure to terbutaline, the patients should be advised to, when possible, rinse their mouth after each use (see General).

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths and Composition

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral Inhalation	Dry powder 0.5 mg terbutaline sulfate per dose	Lactose monohydrate

BRICANYL TURBUHALER (terbutaline sulfate) is a multidose, inspiratory flow driven metered

dose dry powder inhaler which is supplied in one strength: 0.5 mg/dose. This corresponds to a delivered dose (the dose leaving the mouthpiece) of 0.4 mg terbutaline sulfate. Each inhaler contains 120 doses. The inhaler is made of plastic parts.

BRICANYL TURBUHALER also contains lactose monohydrate (which may contain milk protein residue). Each delivered dose contains approximately 0.4 mg of lactose monohydrate. This amount does not normally cause problems in lactose-intolerant people.

7 WARNINGS AND PRECAUTIONS

General

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 4 DOSAGE AND ADMINISTRATION).

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

With each inhalation a fraction of the delivered dose will be deposited in the oral cavity. To minimize unnecessary systemic exposure to terbutaline, the patients should be advised to, when possible, rinse their mouth after each use (see 5 OVERDOSAGE).

Excessive Use

Irrespective of asthma severity, having uncontrolled asthma is an important risk factor for exacerbations. Prescription of three or more short acting beta-agonist (SABA) inhalers in a year is associated with an increased risk of severe exacerbations and mortality. The risk increases with the number of inhalers prescribed.

In mild asthma patients, there is an increased risk of severe exacerbations associated with over-reliance on SABA monotherapy.

Patients who are prescribed maintenance anti-inflammatory therapy should be advised to continue taking their anti-inflammatory medication even when symptoms decrease and they do not require BRICANYL TURBUHALER.

Cardiovascular

BRICANYL TURBUHALER should be used with caution in patients with hypertension. 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.

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 (see Monitoring and Laboratory Tests).

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.

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.

Endocrine and Metabolism
BRICANYL TURBUHALER should be used with caution in patients with diabetes and hyperthyroidism. Due to the hyperglycemic effects of β_2-agonists, additional blood glucose controls are recommended initially in diabetic 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.

Monitoring and Laboratory Tests
If concomitant treatment with a beta-blocker is necessary, patients should be monitored carefully for possible deterioration in pulmonary function and the need to adjust the dosage of either drug (see 9.4 Drug-Drug Interactions).

Monitoring Control of Asthma
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 healthcare professional 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 4 DOSAGE AND ADMINISTRATION). The revised treatment regimen should include concomitant use of anti-inflammatory drugs.

Neurologic
BRICANYL TURBUHALER should be used with caution in patients with a history of seizures.

Respiratory
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 causes of which are unknown, have been reported following excessive use of inhaled preparations containing sympathomimetic amines. Cardiac arrest was noted in several instances.

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

BRICANYL TURBUHALER inhalation powder contains lactose. The excipient lactose may contain small amounts of milk protein residues. In patients with hypersensitivity to milk protein, these small amounts may cause allergic reactions. The amount of lactose in BRICANYL

TURBUHALER does not normally cause problems in lactose intolerant people (see 2 CONTRAINDICATIONS).

7.1 Special Populations

7.1.1 Pregnant Women

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.

7.1.2 Breast-feeding

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

7.1.3 Pediatrics

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

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

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, myocardial ischemia, 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.

9 DRUG INTERACTIONS

9.4 Drug-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 TURBUHALER 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.

Halogenated anesthetics
Halothane anesthesia should be avoided during β_2-agonists treatment, since it increases the risk of cardiac arrhythmias. Other halogenated anesthetics should be used cautiously together with β_2-agonists.

Potassium depleting agents and hypokalemia
Owing to the hypokalemic effect of beta-agonists, concurrent administration with BRICANYL TURBUHALER of serum potassium depleting agents known to exacerbate the risk of hypokalemia, such as diuretics, methyl xanthines and corticosteroids, should be administered cautiously after careful evaluation of the benefits and risks with special regard to the increased risk of cardiac arrhythmias arising as a result of hypokalemia. Hypokalemia also predisposes to digoxin toxicity.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

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 Forced Expiratory Volume in 1 second (FEV_1) measurements. BRICANYL TURBUHALER also produces a decrease in airway and pulmonary resistance.

10.2 Pharmacodynamics

Following inhalation of BRICANYL TURBUHALER, a significant improvement in pulmonary function measurements is well established after 5 minutes.

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.

Animal Pharmacodynamics
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 ED_{50} 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.

10.3 Pharmacokinetics

Table 2 - Summary of BRICANYL TURBUHALER Pharmacokinetic Parameters in Healthy Volunteers

	C_{max}	T_{max}	$t_{½}$	AUC
Single 1.5 mg dose[1]	12 nmol/L	1.3 hours	12 hours	89 nmol*h/L

[1] 3 inhalations of 0.5 mg

Absorption, Distribution, Metabolism and Elimination
The absolute pulmonary bioavailability is about 16% of the delivered dose at a normal inhalation flow rate.

Terbutaline is mainly metabolised by conjugation with sulphuric acid and excreted as the sulphate conjugate. No active metabolites are formed.

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.

11 STORAGE, STABILITY AND DISPOSAL

BRICANYL TURBUHALER should be stored with the cover tightened, at room temperature (15 - 30°C). BRICANYL TURBUHALER is sensitive to moisture.

BRICANYL TURBUHALER cannot be re-filled and should be discarded when empty.

12 SPECIAL HANDLING INSTRUCTIONS

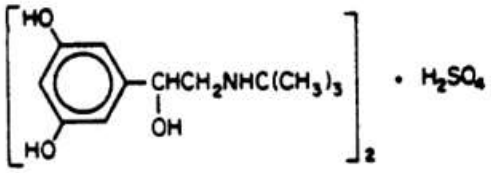
No special instructions for handling are required.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance
Proper name: terbutaline sulfate
Chemical name: 1-(3,5-Dihydroxyphenyl)-2-t-butylaminoethanol sulfate
Molecular formula and molecular mass: $(C_{12}H_{19}NO_3)_2.H_2SO_4$; 548.6

Structural formula:



Physicochemical properties: terbutaline sulfate is water soluble
Product Characteristics: white to off-white crystalline powder

14 CLINICAL TRIALS

14.1 Clinical Trial by Indication

The clinical trial data on which the indication(s) was originally authorized is not available.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

Acute Toxicity: Acute toxicity studies with orally and parenterally administered terbutaline sulfate are summarized below.

Table 3

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 Toxicology: 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 4 which shows the dose levels studied for each species and route of administration. Those levels at which myocardial lesions were seen are underlined.

Table 4

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

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.

Carcinogenicity
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.

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

Reproductive and Developmental Toxicology
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.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

BRICANYL® TURBUHALER®
Terbutaline sulfate dry powder for oral inhalation

Read this carefully before you/your child start(s) taking **BRICANYL TURBUHALER** and each time you/your child get(s) a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your/your child's healthcare professional about your/your child's medical condition and treatment and ask if there is any new information about **BRICANYL TURBUHALER**.

What is BRICANYL TURBUHALER used for?
BRICANYL TURBUHALER is used to treat asthma, bronchitis and emphysema in adults and children 6 years of age and older.

How does BRICANYL TURBUHALER work?
BRICANYL TURBUHALER belongs to a class of drugs called bronchodilators. Bronchodilators relax the muscles in your airways. This helps to open your airways, making it easier for you/your child to breathe. BRICANYL TURBUHALER relieves sudden symptoms such as wheezing, cough and shortness of breath.

The effect of BRICANYL TURBUHALER starts within 5 minutes after you/your child have inhaled it and lasts for up to 7 hours.

What are the ingredients in BRICANYL TURBUHALER?
Medicinal ingredient: terbutaline sulfate
Non-medicinal ingredients: lactose monohydrate (may contain small amounts of milk protein residue)

BRICANYL TURBUHALER comes in the following dosage forms:
Dry powder for oral inhalation: 0.5 mg per dose

Do not use BRICANYL TURBUHALER if:
- you/your child are allergic to terbutaline sulfate;
- you/your child are allergic to lactose;
- you/your child have a heart problem called tachyarrhythmia (fast and/or irregular heartbeat);
- you/your child are allergic to sympathomimetic amines such as ephedrine or pseudoephedrine.

BRICANYL TURBUHALER should not be used to treat or prevent premature labour or miscarriage.

To help avoid side effects and ensure proper use, talk to your/your child's healthcare professional before you/your child take(s) BRICANYL TURBUHALER. Talk about any health conditions or problems you/your child may have, including if you/your child:
- have heart problems such as irregular heartbeat, chest pain;
- have uncontrolled asthma;
- have high blood pressure;

- have diabetes;
- have thyroid problems;
- have a history of seizures;
- have low levels of potassium in the blood;
- have ever had an allergic reaction to terbutaline or lactose, or to any other similar medicines;
- are over 65 years old;
- are pregnant, plan to become pregnant or are breastfeeding.

Other warnings you should know about:

Use During Pregnancy: Premature babies born to mothers who use BRICANYL TURBUHALER at the end of pregnancy may experience low blood sugar levels. Symptoms may include jitteriness, poor body tone and/or poor feeding, but the symptoms may also resemble other conditions. Talk to your baby's healthcare professional if you are concerned.

Excessive Use: Excessive regular use of BRICANYL TURBUHALER should be avoided as it may increase the risk of asthma attacks that may be life threatening or even fatal. You/your child may then need additional medication to control your/your child's asthma. You must contact your/your child's healthcare professional as soon as possible if you/your child need(s) higher doses of BRICANYL TURBUHALER than usual to relieve your/your child's breathing problems.

Tell your/your child's healthcare professional about all the medicines you/your child take(s), including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with BRICANYL TURBUHALER:
- Other medicines like BRICANYL TURBUHALER (bronchodilators);
- Beta-blockers (some medicines for high blood pressure, heart conditions and some eye-drops);
- Epinephrine (also known as adrenaline or adrenalin) for life threatening allergic reactions;
- Monoamine Oxidase Inhibitors for depression;
- Tricyclic Antidepressants for depression;
- Steroid medicines (such as prednisolone);
- Medicines called 'xanthines' (such as theophylline);
- Water pills (diuretics);
- Halothane or halogenated anesthesia. If you/your child are having surgery, tell the healthcare professional that you/your child are taking BRICANYL TURBUHALER.

How to take BRICANYL TURBUHALER:

- The dosage of BRICANYL TURBUHALER is individual. Follow your/your child's healthcare professional's directions carefully. They may differ from the information in this leaflet. Check with your/your child's healthcare professional if you are not sure.
- Before using, read the Instructions for Use at the end of this Patient Medication Information and follow the instructions carefully. **Make sure you/your child understand and can follow these instructions.**
- Never give your/your child's medicine to anyone else, BRICANYL TURBUHALER has been prescribed specifically for you/your child.
- Use as needed, rather than regularly.

Taking BRICANYL TURBUHALER alone for asthma without additional medication (such as an inhaled corticosteroid) may increase your/your child's risk of severe asthma attack.

If you/your child are also prescribed regular anti-inflammatory medication for asthma (such as an inhaled corticosteroid or leukotriene antagonist), continue using it even if you/your child do not need to use your/your child's BRICANYL TURBUHALER.

See a healthcare professional right away if:
- your/your child's usual dose does not provide relief;
- your/your child's breathing condition gets worse (breathlessness, wheezing or tight chest);
- you/your child are too breathless to speak, eat or sleep;
- the effects of one dose last less than three hours;
- you/your child are using BRICANYL TURBUHALER every day to relieve symptoms.

These may be signs that your/your child's asthma is getting worse.

Usual dose:

Adults and children 6 years of age and older:
- One inhalation as needed.
- If needed, you/your child may take a second dose. Wait five minutes for the first dose to take effect before taking the second dose.
- If your/your child's symptoms persist after the second dose, consult your/your child's healthcare professional or the nearest hospital right away.
- You/your child should not take more than six inhalations (3.0 mg) in a 24 hour period.

Overdose:

If you think you, or a person you are caring for, have taken too much BRICANYL TURBUHALER, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
BRICANYL TURBUHALER should be used as needed rather than regularly. However, if you/your child have been prescribed regular treatment and you/your child forget to take a dose, take one as soon as you/your child remember(s). If it is very close to the next dosing time, wait until then.

What are possible side effects from using BRICANYL TURBUHALER?
These are not all the possible side effects you/your child may have when taking BRICANYL TURBUHALER. If you/your child experience(s) any side effects not listed here, tell your/your child's healthcare professional.

The most common side effects are nervousness and shakiness. In most cases these side effects disappear over the first few days of treatment.

Side effects may include:
- headache;
- flushing, sweating, hives and rash;
- occasional muscle cramps;

- sleeplessness, drowsiness;
- nervousness, restlessness, agitation, hyperactivity;
- shakiness;
- stomach upset, nausea, vomiting;
- weakness, dizziness;
- nausea and sweating.

BRICANYL TURBUHALER may affect blood sugar levels. If you/your child are diabetic you/your child may need to check your/your child's blood glucose more frequently. Your/your child's healthcare professional will advise you about this.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
RARE			
Low potassium levels in the blood: irregular heartbeats, muscle weakness and spasms		✓	
UNKNOWN FREQUENCY			
Allergic Reaction: swelling of the face, lips, tongue or throat, difficulty swallowing or breathing (or rash and hives in combination with the above)			✓
Fast or irregular heartbeats for an extended period of time		✓	
Myocardial Ischemia: chest pain related to heart problems and shortness of breath		✓	
Paradoxical Bronchospasm: shortness of breath, chest tightness which causes wheezing immediately after inhaling your dose			✓

If you/your child have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your/your child's daily activities, tell your/your child's healthcare professional.

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Always replace and tighten the cover after using BRICANYL TURBUHALER. Store the inhaler at room temperature (15-30°C).

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

Keep out of reach and sight of children.

If you want more information about BRICANYL TURBUHALER:

- Talk to your/your child's healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website: www.astrazeneca.ca, or by calling 1-800-668-6000.
- This Patient Medication Information is current at the time of printing. The most up-to-date version can be found at www.astrazeneca.ca.

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AstraZeneca

INSTRUCTIONS FOR USE

BRICANYL® TURBUHALER®
Terbutaline sulfate dry powder for oral inhalation

Before you/your child start(s) using BRICANYL TURBUHALER for the first time it is important that you read the instructions below and follow them carefully.

TURBUHALER is a multidose inhaler from which very small amounts of powder are administered. When you/your child breathe(s) in through BRICANYL TURBUHALER the powder is delivered to the lungs. It is therefore important that you/your child **inhale as deeply and strongly** as you/your child can through the mouthpiece.

Cover
Mouthpiece
Dose indicator
Grip

Before you use a **NEW** inhaler for the first time you must prepare the inhaler for use. Follow the steps under "**A. How to prepare a NEW inhaler for use:**".

For usual use of your inhaler follow the steps under "**B. How to take a dose:**".

A. How to prepare a NEW inhaler for use:
You only need to prepare your **NEW** inhaler for use **once**. You do not need to repeat these steps even if your inhaler is not used frequently.

STEP ① Unscrew and lift off the cover (Figure 1). You will hear a rattling sound when you unscrew the cover. This is normal.

Figure 1

STEP ② Hold the inhaler upright. Do not hold the inhaler by the mouthpiece.

- Turn the **blue grip** as far as it will go in one direction (clockwise or counter-clockwise, it does not matter which way you turn it first).
- Then turn the blue grip as far as it will go in the opposite direction (Figure 2).
- At some point when you are turning the grip you will hear a "**click**". This is part of the preparation process.

Figure 2

STEP ③ **Repeat STEP ②** one more time. Then follow the steps under "**B. How to take a dose:", starting at STEP ②**.

B. How to take a dose:

To properly take a dose, follow these 4 steps:

STEP ① Unscrew and lift off the cover (Figure 1). You will hear a rattling sound when you unscrew the cover. This is normal.

Figure 1

STEP ② Hold the inhaler upright. Do not hold the inhaler by the mouthpiece.

- Turn the **blue grip** as far as it will go in one direction (clockwise or counter-clockwise, it does not matter which way you turn it first).
- Then turn the blue grip as far as it will go in the opposite direction (Figure 2).

Figure 2

A dose has now been loaded.

- At some point when you are turning the blue grip, you will hear a "**click**". This is part of the loading process.

NOTE: If you accidentally **drop, shake** or **breathe out** into BRICANYL TURBUHALER after the dose has been loaded, you will lose your dose. If this happens, repeat STEP ② to load a new dose.

STEP ③ **Breathe out**, with your mouth away from the mouthpiece (Figure 3). Then, place the mouthpiece gently between your teeth.

Figure 3

STEP ④ Now close your lips over the mouthpiece. Do not bite or chew the mouthpiece.

Figure 4

- **Inhale as deeply and strongly** as you can (Figure 4).
- You may not feel or taste the medication when inhaling. This is common.
- Before you exhale, remember to remove the inhaler from your mouth.

Repeat STEPS ②-④ if more than one dose has been prescribed. When you have taken the prescribed amount of doses, **replace the cover of the inhaler by screwing it back on**. With each inhalation some medication may stick to the inside of your mouth and throat. To reduce the risk of side effects rinse your mouth with water, and do not swallow.

Note: Do not try to remove the mouthpiece or to twist it unnecessarily. It is fixed to the inhaler and must not be taken off. Do not use BRICANYL TURBUHALER if it has been damaged or if the mouthpiece has come apart from your TURBUHALER.

I cannot remember how many times I turned the blue grip. What should I do?

The TURBUHALER is designed to load only one dose at a time. If you can't remember how many times you have turned the blue grip, you can start the process again. Follow the steps below. You will not end up loading two doses.

If you are using a **NEW** inhaler for the first time, start at the beginning of STEP ② under the section "**A. How to prepare a NEW inhaler for use:**".

For usual use of your inhaler, start at the beginning of STEP ② under the section "**B. How to take a dose:**".

How do I know my dose has been loaded?

By turning the blue grip all the way in BOTH directions, you will properly load a dose of your medication. At some point when you are turning the grip you will hear a "click". This is part of the loading process. If you are not sure you heard the "click", repeat from the beginning of STEP ② under the section "**B. How to take a dose:**". This will not result in two doses being loaded. The TURBUHALER is designed to load only one dose at a time. If you do not hear the "click" sound when the turning grip is rotated, you will not receive any medication. If this problem persists, you need to replace the BRICANYL TURBUHALER.

How do I clean my inhaler?

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 to start a new inhaler?

BRICANYL TURBUHALER has a dose indicator. The dose indicator tells you around how many doses are left in the inhaler, starting with 120 when full. The dose indicator moves slowly each time you load a dose. Every 20th dose is marked with a number and every 10th dose is marked with a dash (Figure 5). For the last 10 doses, the background of the indicator is red. When the "0" on the red background has reached the middle of the window, you should throw out your inhaler and start a new inhaler. Even when the dose indicator registers zero, it is still possible to turn the grip. However, the indicator stops moving and the zero remains in the window. The sound you hear if you shake the inhaler is produced by a drying agent, not the medication. BRICANYL TURBUHALER cannot be refilled with drug and should be thrown away.

Figure 5

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