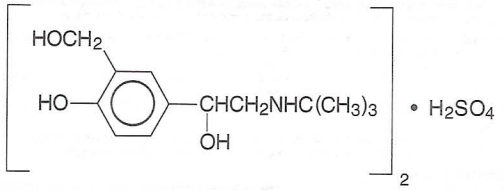
ALBUTEROL SULFATE INHALATION SOLUTION 0.083%*

℞ Only

(*Potency expressed as albuterol)

DESCRIPTION

Albuterol Sulfate Inhalation Solution contains albuterol sulfate, USP, the racemic form of albuterol, a relatively selective beta$_2$-adrenergic bronchodilator. Albuterol sulfate has the chemical name α^1-[(*tert*-Butylamino)methyl]-4-hydroxy-*m*-xylene-α,α'-diol sulfate (2:1) (salt), and the following chemical structure:



The molecular weight of albuterol sulfate is 576.7, and the molecular formula is $(C_{13}H_{21}NO_3)_2 \cdot H_2SO_4$. Albuterol sulfate is a white crystalline powder, soluble in water and slightly soluble in ethanol.

The World Health Organization recommended name for albuterol base is salbutamol.

Each mL of Albuterol Sulfate Inhalation Solution 0.083% contains 0.83 mg of albuterol (as 1.0 mg of albuterol sulfate, USP) in an isotonic, aqueous solution containing sodium chloride, USP; sulfuric acid is used to adjust the pH between 3 and 5. The 0.083% solution requires no dilution prior to administration by nebulization. Albuterol Sulfate Inhalation Solution 0.083% contains no sulfiting agents. It is supplied in 3 mL LDPE vials for unit-dose dispensing.

Albuterol Sulfate Inhalation Solution is a clear, colorless to light yellow solution.

CLINICAL PHARMACOLOGY

The primary action of beta-adrenergic drugs, including albuterol, is to stimulate adenyl cyclase, the enzyme which catalyzes the formation of cyclic-3',5'-adenosine monophosphate (cyclic AMP) from adenosine triphosphate (ATP) in beta-adrenergic cells. The cyclic AMP thus formed mediates the cellular responses. Increased cyclic AMP levels are associated with relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

In vitro studies and *in vivo* pharmacologic studies have demonstrated that albuterol has a preferential effect on beta$_2$-adrenergic receptors compared with isoproterenol. While it is recognized that beta$_2$-adrenergic receptors are the predominant receptors in bronchial smooth muscle, data indicate that there is a population of beta$_2$-receptors in the human heart existing in a concentration between 10% and 50%. The precise function of these receptors has not been established.

In controlled clinical trials, albuterol has been shown to have more effect on the respiratory tract, in the form of bronchial smooth muscle relaxation, than isoproterenol at comparable doses while producing fewer cardiovascular effects. Controlled clinical studies and other clinical experience have shown that inhaled albuterol, like other beta-adrenergic agonist drugs, can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms, and/or electrocardiogram (ECG) changes.

Albuterol is longer acting than isoproterenol in most patients by any route of administration because it is not a substrate for the cellular uptake processes for catecholamines nor for catechol-*O*-methyl transferase.

The effects of rising doses of albuterol and isoproterenol aerosols were studied in volunteers and asthmatic

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Mixing Compatability: The safety and effectiveness of Albuterol Sulfate Inhalation Solution have not been determined when one or more drugs are mixed with it in a nebulizer. Check with your doctor before mixing any medications in your nebulizer.

Microbial Contamination: To avoid microbial contamination, the entire contents of the unit-dose vial should be administered immediately after the vial has been opened.

Protect from light. Retain in foil pouch until time of use. Store between 2° and 25°C (36° and 77°F). Discard if solution becomes discolored. (Note: Albuterol Sulfate Inhalation Solution is a clear, colorless to light yellow solution.)

Manufactured by:

Catalent Pharma Solutions, LLC
2200 Lake Shore Drive
Woodstock,
IL 60098
USA

Manufactured for:

Cobalt Laboratories Inc.
Bonita Springs FL 34134

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ADVERSE REACTIONS

The results of clinical trials with Albuterol Sulfate Inhalation Solution in 135 patients showed the following side effects, which were considered probably or possibly drug related:

Percent Incidence of Adverse Reactions

Reaction		Percent Incidence
Central Nervous System		
	Tremors	20%
	Dizziness	7%
	Nervousness	4%
	Headache	3%
	Sleeplessness	1%
Gastrointestinal		
	Nausea	4%
	Dyspepsia	1%
Ear, nose, and throat		
	Nasal congestion	1%
	Pharyngitis	<1%
Cardiovascular		
	Tachycardia	1%
	Hypertension	1%
Respiratory		
	Bronchospasm	8%
	Cough	4%
	Bronchitis	4%
	Wheezing	1%

No clinically relevant laboratory abnormalities related to Albuterol Sulfate Inhalation Solution were determined in these studies.

Cases of urticaria, angioedema, rash, bronchospasm, hoarseness, oropharyngeal edema, and arrhythmias (including atrial fibrillation, supraventricular tachycardia, and extrasystoles) have also been reported after the use of inhaled albuterol.

OVERDOSAGE

The expected symptoms with over-dosage are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the symptoms listed under **ADVERSE REACTIONS**, e.g., angina, hypertension, tachycardia with rates up to 200 beats per minute, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, nausea, dizziness, malaise, and insomnia. In addition, seizures, hypotension, fatigue, and hypokalemia may also occur. As with all sympathomimetic aerosol medications, cardiac arrest and even death may be associated with abuse of Albuterol Sulfate Inhalation Solution. Treatment consists of discontinuation of Albuterol Sulfate Inhalation Solution 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 over-dosage of Albuterol Sulfate Inhalation Solution.

The oral median lethal dose of albuterol sulfate in mice is greater than 2000 mg/kg (approximately 810 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis). In mature rats, the subcutaneous (sc) median lethal dose of albuterol sulfate is approximately 450 mg/kg (approximately 360 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis). In small young rats, the sc median lethal dose is approximately 2000 mg/kg (approximately 1600 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis). The inhalational median lethal dose has not been determined in animals.

DOSAGE AND ADMINISTRATION

FOR ORAL INHALATION ONLY

The usual dosage for adults and pediatric patients 12 years of age and older is 2.5 mg of albuterol administered three to four times daily by nebulization. More frequent administration or higher doses are not recommended. To administer 2.5 mg of albuterol, administer the entire contents of one unit-dose vial (3 mL of 0.083% nebulizer solution) by nebulization. The flow rate is regulated to suit the particular nebulizer so that Albuterol Sulfate Inhalation Solution will be delivered over approximately 5 to 15 minutes.

Drug compatibility (physical and chemical), efficacy, and safety of Albuterol Sulfate Inhalation Solution when mixed with other drugs in a nebulizer have not been established.

The use of Albuterol Sulfate Inhalation Solution can be continued as medically indicated to control recurring bouts of bronchospasm. During treatment, most patients gain optimum benefit from regular use of the nebulizer solution.

If a previously effective dosage regimen fails to provide the usual relief, medical advice should be sought immediately, as this is often a sign of seriously worsening asthma, which would require reassessment of therapy.

Microbial Contamination: To avoid microbial contamination, the entire contents of the unit-dose vial should be administered immediately after the vial has been opened for the first time.

The nebulizer should be cleaned in accordance with the manufacturer's instructions. Failure to do so could lead to bacterial contamination of the nebulizer and possible infection.

HOW SUPPLIED

Albuterol Sulfate Inhalation Solution 0.083% is a clear, colorless to light yellow solution, and is supplied in unit-dose LDPE (low-density polyethylene) vials of 3 mL fill inside of an aluminum foil pouch.
Unit Dose Boxes of 25 each - NDC 16252-097-22
Unit Dose Boxes of 30 each - NDC 16252-097-33
Unit Dose Boxes of 60 each - NDC 16252-097-66
Unit Dose Boxes of 120 each - NDC 16252-097-11
Unit Dose Boxes of 360 each - NDC 16252-097-13

Protect from light. Retain in foil pouch until time of use. Store between 2° and 25°C (36° and 77°F).

Medical Affairs 800-206-8120

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Cobalt Laboratories, Inc.
Bonita Springs, FL 34134

Manufactured by:
Catalent Pharma Solutions, LLC
2200 Lake Shore Drive
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Albuterol Sulfate Inhalation Solution, 0.083%*
Brand of albuterol sulfate, USP

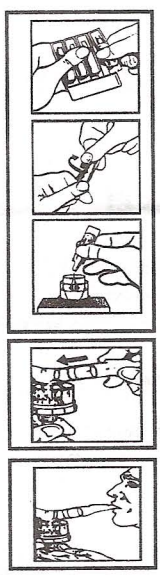
*Potency expressed as albuterol

FOR ORAL INHALATION ONLY

PATIENT'S INSTRUCTIONS FOR USE
Note: This is a unit-dose vial. No dilution is required.
Read complete instructions carefully before using.

1. Open the protective foil pouch and remove one unit dose vial from the strip (Figure 1).
2. Twist open the top of one vial by twisting off the tabbed top section (Figure 2).
3. Squeeze the entire contents into the nebulizer reservoir (Figure 3).
4. Connect the nebulizer reservoir to the mouthpiece or face mask (Figure 4).
5. Connect the nebulizer to the compressor.
6. Sit in a comfortable, upright position; place the mouthpiece in your mouth (Figure 5) (or put the face mask on); and turn the compressor on.
7. Breathe as calmly, deeply, and evenly as possible until no more mist is formed in the nebulizer chamber (about 5 to 15 minutes). At this point the treatment is finished.
8. Clean the nebulizer (see manufacturer's instructions). Failure to clean the nebulizer in accordance with the manufacturer's instructions could lead to bacterial contamination of the nebulizer and possible infection.

Note: Use only as directed by your doctor. More frequent administration or higher doses are not recommended.



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patients. Results in normal volunteers indicated that the propensity for increase in heart rate for albuterol is ½ to ¼ that of isoproterenol. In asthmatic patients, similar cardiovascular differentiation between the two drugs was also seen.

Preclinical: Intravenous studies in rats with albuterol sulfate have demonstrated that albuterol crosses the blood-brain barrier and reaches brain concentrations that are amounting to approximately 5.0% of the plasma concentrations. In structures outside the blood-brain barrier (pineal and pituitary glands), albuterol concentrations were found to be 100 times those in the whole brain.

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

Pharmacokinetics: After either IPPB (intermittent positive-pressure breathing) or nebulizer administration in asthmatic patients, less than 20% of a single albuterol dose was absorbed; the remaining amount was recovered from the nebulizer and apparatus and expired air. Most of the absorbed dose was recovered in the urine 24 hours after drug administration. Following a 3.0-mg dose of nebulized albuterol, the maximum albuterol plasma level at 0.5 hours were 2.1 ng/mL (range, 1.4 to 3.2 ng/mL). It has been demonstrated that following oral administration of 4 mg of albuterol, the elimination half-life was 5 to 6 hours.

Clinical Trials: In controlled clinical trials, most patients exhibited an onset of improvement in pulmonary function within 5 minutes as determined by FEV_1. FEV_1 measurements also showed that the maximum average improvement in pulmonary function usually occurred at approximately 1 hour following inhalation of 2.5 mg of albuterol by compressor-nebulizer, and remained close to peak for 2 hours. Clinically significant improvement in pulmonary function (defined as maintenance of a 15% or more increase in FEV_1 over baseline values) continued for 3 to 4 hours in most patients, and in some patients continued up to 6 hours.

INDICATIONS AND USAGE
Albuterol Sulfate Inhalation Solution is indicated for the relief of bronchospasm in patients 12 years of age and older with reversible obstructive airway disease and acute attacks of bronchospasm.

CONTRAINDICATIONS
Albuterol Sulfate Inhalation Solution is contraindicated in patients with a history of hypersensitivity to albuterol or any of its components.

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 Albuterol Sulfate Inhalation Solution than usual, this may be a marker of destabilization of asthma and requires reevaluation of the patient and the 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.

Paradoxical Bronchospasm: Albuterol Sulfate Inhalation Solution can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs, Albuterol Sulfate Inhalation Solution should be discontinued immediately and alternative therapy instituted. It should be recognized that paradoxical bronchospasm, when associated with inhaled formulations, frequently occurs with the first use of a new vial.

Cardiovascular Effects: Albuterol Sulfate Inhalation Solution, 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 Albuterol Sulfate Inhalation Solution 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, Albuterol Sulfate Inhalation Solution, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias and hypertension.

Immediate Hypersensitivity Reactions: Immediate hypersensitivity reactions may occur after administration of albuterol, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, anaphylaxis and oropharyngeal edema.

Microbial Contamination: To avoid microbial contamination, the entire contents of the unit-dose vial should be administered immediately after the vial has been opened for the first time.

PRECAUTIONS
General: Albuterol, as with all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias and hypertension; in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus; and in patients who are unusually responsive to sympathomimetic amines. Clinically 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.

Large doses of intravenous albuterol have been reported to aggravate pre-existing diabetes and ketoacidosis. As with other beta-agonist medications, albuterol 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 potassium supplementation.

Information For Patients: See illustrated **Patient's Instructions for Use.**

General: The action of Albuterol Sulfate Inhalation Solution may last up to 6 hours or longer. Albuterol Sulfate Inhalation Solution should not be used more frequently than recommended. Do not increase the dose or frequency of Albuterol Sulfate Inhalation Solution without consulting your physician. If you find that treatment with Albuterol Sulfate Inhalation Solution becomes less effective for symptomatic relief, your symptoms become worse, and/or you need to use the product more frequently than usual, you should seek medical attention immediately. While you are using Albuterol Sulfate Inhalation Solution, other inhaled drugs and asthma medications should be taken only as directed by your physician. Common adverse effects include palpitations, chest pain, rapid heart rate, tremor, or nervousness. If you are pregnant or nursing, contact your physician about use of Albuterol Sulfate Inhalation Solution. Effective use of Albuterol Sulfate Inhalation Solution includes an understanding of the way that it should be administered. See illustrated **Patient's Instructions for Use.**

Microbial Contamination: To avoid microbial contamination, the entire contents of the unit-dose vial should be administered immediately after the vial has been opened.

Mixing Different Inhalation Solutions: Drug compatibility (physical and chemical), efficacy, and safety of Albuterol Sulfate Inhalation Solution when mixed with other drugs in a nebulizer have not been established.

Drug Interactions: Other short-acting sympathomimetic aerosol bronchodilators or epinephrine should not be used concomitantly with albuterol.

Beta-Blockers: Beta-adrenergic receptor blocking agents not only block the pulmonary effect of beta-agonists, such as Albuterol Sulfate Inhalation Solution, 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.

Digoxin: Mean decreases of 16% to 22% in serum digoxin levels were demonstrated after single-dose intravenous and oral administration of albuterol, respectively, to normal volunteers who had received digoxin for 10 days. The clinical significance of this finding for patients with obstructive airway disease who are receiving albuterol and digoxin on a chronic basis is unclear. Nevertheless, it would be prudent to carefully evaluate the serum digoxin levels in patients who are currently receiving digoxin and albuterol.

Monoamine Oxidase Inhibitors or Tricyclic Antidepressants: Albuterol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of albuterol on the vascular system may be potentiated.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 2-year study in Sprague-Dawley rats, albuterol sulfate caused a significant dose-related increase in the incidence of benign leiomyomas of the mesovarium at and above dietary doses of 2 mg/kg (approximately two times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis). In another study, this effect was blocked by the coadministration of propranolol, a non-selective beta-adrenergic antagonist.

In an 18-month study in CD-1 mice, albuterol sulfate showed no evidence of tumorigenicity at dietary doses of up to 500 mg/kg (approximately 200 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis). In a 22-month study in the Golden Hamster, albuterol sulfate showed no evidence of tumorigenicity at dietary doses of up to 50 mg/kg (approximately 25 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis).

Albuterol sulfate was not mutagenic in the Ames test with or without metabolic activation using tester strains S. *typhimurium* TA1537, TA1538, and TA98 or E. *coli* WP2, WP2uvrA, and WP67. No forward mutation was seen in yeast strain S. *cerevisiae* S9 nor any mitotic gene conversion in yeast strain S. *cerevisiae* JD1 with or without metabolic activation. Fluctuation assays in S. *typhimurium* TA98 and E. *coli* WP2, both with metabolic activation, were negative. Albuterol sulfate was not clastogenic in a human peripheral lymphocyte assay or in an AH1 strain mouse micronucleus assay.

Reproduction studies in rats demonstrated no evidence of impaired fertility at oral doses of albuterol sulfate up to 50 mg/kg (approximately 40 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis).

Teratogenic Effects – Pregnancy Category C: Albuterol has been shown to be teratogenic in mice. A study in CD-1 mice at subcutaneous (sc) doses at and above 0.25 mg/kg (corresponding to less than the maximum recommended daily inhalation dose for adults on a mg/m^2 basis), induced cleft palate formation in 5 of 111 (4.5%) fetuses. At an sc dose of 2.5 mg/kg (approximately equal to the maximum recommended daily inhalation dose for adults on a mg/m^2 basis) albuterol sulfate induced cleft palate formation in 10 of 108 (9.3%) fetuses. The drug did not induce cleft palate formation when administered at an sc dose of 0.025 mg/kg (corresponding to less than the maximum recommended daily inhalation dose for adults on a mg/m^2 basis). Cleft palate also occurred in 22 of 72 (30.5%) fetuses from females treated with 2.5 mg/kg isoproterenol (positive control) administered subcutaneously.

A reproduction study in Stride Dutch rabbits revealed cranioschisis in 7 of 19 (37%) fetuses when albuterol was administered orally at a dose of 50 mg/kg (approximately 80 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis).

Studies in pregnant rats with tritiated albuterol demonstrated that approximately 10% of the circulating maternal drug is transferred to the fetus. Disposition in the fetal lungs is comparable to maternal lungs, but fetal liver disposition is 1% of the maternal liver levels.

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, albuterol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

During worldwide marketing experience, various congenital anomalies, including cleft palate and limb defects, have been reported in the offspring of patients being treated with albuterol. Some of the mothers were taking multiple medications during their pregnancies. Because no consistent pattern of defects can be discerned, a relationship between albuterol use and congenital anomalies has not been established.

Use in Labor and Delivery – Use in Labor: Because of the potential for beta-agonist interference with uterine contractility, use of Albuterol Sulfate Inhalation Solution for relief of bronchospasm during labor should be restricted to those patients in whom the benefits clearly outweigh the risk.

Tocolysis: Albuterol has not been approved for the management of preterm labor. The benefit:risk ratio when albuterol is administered for tocolysis has not been established. Serious adverse reactions, including maternal pulmonary edema, have been reported during or following treatment of premature labor with beta-agonists, including albuterol.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because of the potential for tumorigenicity shown for albuterol in some animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness of albuterol inhalation solution and solution for inhalation in children below the age of 12 years have not been established.