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## Albuterol Sulfate Inhalation Solution, 0.042%\*

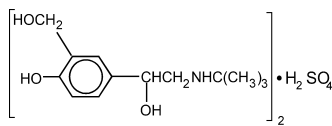
1.25 mg / 3 mL\*

\*Potency expressed as albuterol, equivalent to 1.5 mg albuterol sulfate.

### PRESCRIBING INFORMATION

#### DESCRIPTION

Albuterol Sulfate Inhalation Solution, 0.042% is a sterile, clear, colorless solution of the sulfate salt of racemic albuterol, albuterol sulfate. Albuterol sulfate is a relatively selective beta<sub>2</sub>-adrenergic bronchodilator (see CLINICAL PHARMACOLOGY). The chemical name for albuterol sulfate is  $\alpha$ ,  $\alpha'$ -[(*tert*-butylamino)methyl]-4-hydroxy-*m*-xylylene- $\alpha$ ,  $\alpha'$ -diol sulfate (2:1) (salt), and its established chemical structure is as follows:



The molecular weight of albuterol sulfate is 576.7 and the empirical formula is  $(C_{23}H_{37}NO_7)_2 \cdot H_2SO_4$ . Albuterol sulfate is a white crystalline powder, soluble in water and slightly soluble in ethanol. The World Health Organization recommended name for albuterol is salbutamol.

Albuterol Sulfate Inhalation Solution, 0.042% is supplied in one strength in unit dose vials. Each unit dose vial contains 1.50 mg of albuterol sulfate (equivalent to 1.25 mg of albuterol) with sodium chloride and sulfuric acid in a 3-mL isotonic, sterile, aqueous solution. Sodium chloride is added to adjust isotonicity of the solution and sulfuric acid is added to adjust pH of the solution to between 3 and 5 (see HOW SUPPLIED).

Albuterol Sulfate Inhalation Solution, 0.042% does not require dilution prior to administration by nebulization. For Albuterol Sulfate Inhalation Solution, 0.042%, like all other nebulized treatments, the amount delivered to the lungs will depend on patient factors, the jet nebulizer utilized, and compressor performance. Using the Pari LC Plus™ nebulizer (with face mask or mouthpiece) connected to a Pari PRONEB™ compressor, under in vitro conditions, the mean delivered dose from the mouthpiece (% normal dose) was approximately 43% of albuterol (1.25 mg strength) at a mean flow rate of 3.6 L/min. The mean nebulization time was 15 minutes or less. Albuterol Sulfate Inhalation Solution, 0.042% should be administered from a jet nebulizer at an adequate flow rate, via a mouthpiece or face mask (see DOSAGE AND ADMINISTRATION).

#### CLINICAL PHARMACOLOGY

The prime action of beta-adrenergic drugs is to stimulate adenylyl cyclase, the enzyme which catalyzes the formation of cyclic-3'-5'-adenosine monophosphate (cyclic AMP) from adenosine triphosphate (ATP). The cyclic AMP thus formed mediates the cellular responses. In vitro studies and in vivo pharmacologic studies have demonstrated that albuterol has a preferential effect on beta<sub>2</sub>-adrenergic receptors compared with isoproterenol. While it is recognized that beta<sub>2</sub>-adrenergic receptors are the predominant receptors in bronchial smooth muscle, recent data indicate that 10% to 50% of the beta-receptors in the human heart may be beta<sub>2</sub>-receptors. The precise function of these receptors, however, is not yet established. Controlled clinical studies and other clinical experience have shown that inhaled albuterol, like other beta<sub>2</sub>-adrenergic agonist drugs, can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms, and/or electrocardiographic 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.

**Pharmacokinetics:** Studies in asthmatic patients have shown that less than 20% of a single albuterol dose was absorbed following either intermittent positive-pressure breathing (IPPB) or nebulizer administration; the remaining amount was recovered from the nebulizer and apparatus, and expired air. Most of the absorbed dose was recovered in urine collected during the 24 hours after drug administration. Following oral administration of 4 mg albuterol, the elimination half-life was five to six hours. Following a 3 mg dose of nebulized albuterol in adults, the mean maximum albuterol plasma level at 0.5 hours was 2.1 ng/mL (range, 1.4 to 3.2 ng/mL). The pharmacokinetics of albuterol following administration of 1.25 mg albuterol sulfate inhalation solution by nebulization have not been determined in children 2 to 12 years old.

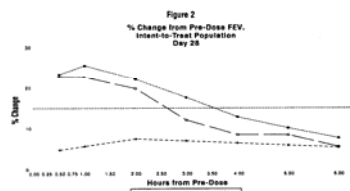
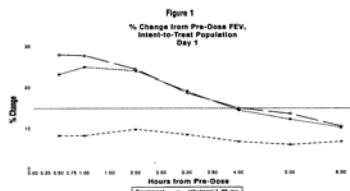
**Animal Pharmacology/Toxicology:** Intravenous studies in rats with albuterol sulfate have demonstrated that albuterol crosses the blood-brain barrier and reaches brain concentrations amounting to approximately 5% of plasma concentrations. In structures outside the blood-brain barrier (pineal and pituitary glands), albuterol concentrations were found to be 100 times those found in 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-agonist and methylxanthines are administered concurrently. The clinical significance of these findings is unknown.

**Clinical Trials:** The safety and efficacy of Albuterol Sulfate Inhalation Solution, 0.042% was evaluated in a 4-week, multi-center, randomized, double-blind, placebo-controlled, parallel group in 349 children 6 to 12 years of age with mild-to-moderate asthma (mean baseline FEV<sub>1</sub>: 60% to 70% of predicted). Approximately half of the patients were also receiving inhaled corticosteroids. Patients were randomized to receive AccuNeb 0.63 mg, Albuterol Sulfate Inhalation Solution, 0.042% or placebo three times a day administered via a Pari LC Plus™ nebulizer and a Pari PRONEB™ compressor. Racemic albuterol, delivered by chlorofluorocarbon (CFC) metered dose inhaler (MDI) or nebulized, was used on an as-needed basis as the rescue medication.

Efficacy, as measured by the mean percent change from baseline in the area under the 6-hour curve for FEV<sub>1</sub>, was demonstrated for both the active treatment regimens (n=112 [1.25 mg group] and n=110 [0.63 mg group]) compared with placebo (n=110) on day 1 and day 28. Figures 1 and 2 illustrate the mean

percentage change from pre-dose FEV<sub>1</sub> on day 1 and day 28, respectively. The mean baseline FEV<sub>1</sub> for all patients was 1.49 L.



onset of a 15% increase in FEV<sub>1</sub> over baseline for doses of Albuterol Sulfate Inhalation Solution, 0.042% and AccuNeb 0.63 mg was seen at 30 minutes (the first post-dose assessment). The mean time to peak effect was approximately 30 to 60 minutes for both doses on day 1 and after 4 weeks of treatment. The mean duration of effect, as measured by a >15% increase from baseline in FEV<sub>1</sub>, was approximately 2.5 hours for both doses on day 1 and approximately 2 hours for both doses after 4 weeks of treatment. In some patients, the duration of effect was as long as 6 hours.

#### INDICATIONS AND USAGE

Albuterol Sulfate Inhalation Solution, 0.042% is indicated for the relief of bronchospasm in patients 2 to 12 years of age with asthma (reversible obstructive airway disease).

#### CONTRAINDICATIONS

Albuterol Sulfate Inhalation Solution, 0.042% is contraindicated in patients with a history of hypersensitivity to any of its components.

#### WARNINGS

**Paradoxical Bronchospasm:** As with all other inhaled beta-adrenergic agonists, Albuterol Sulfate Inhalation Solution, 0.042% can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs, Albuterol Sulfate Inhalation Solution, 0.042% should be discontinued immediately and alternative therapy instituted. It should be noted that paradoxical bronchospasm, when associated with inhaled formulations, frequently occurs with the first used of a new canister or vial.

**Use of Anti-Inflammatory Agents:** The use of beta-adrenergic 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).

**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, 0.042% than usual, this may be a marker of destabilization of asthma and requires reevaluation of the patient and the treatment regimen, giving special consideration of the possible need for anti-inflammatory treatment (e.g., corticosteroids).

Fatality has been reported in association with excessive use of inhaled sympathomimetic drugs and with the home use of nebulizers. It is, therefore, essential that the physician instruct the patient in the need for further evaluation, if his/her asthma becomes worse.

**Cardiovascular effects:** Albuterol Sulfate Inhalation Solution, 0.042%, like 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 for Albuterol Sulfate Inhalation Solution, 0.042% at the recommended dose, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce 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, 0.042%, like all other 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, and oropharyngeal edema.

#### PRECAUTIONS

**General:** Large doses of intravenous albuterol have been reported to aggravate pre-existing diabetes mellitus and ketoacidosis. As with other beta-agonists, inhaled and intravenous albuterol may produce a 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:** The action of Albuterol Sulfate Inhalation Solution, 0.042% may last up to six hours, and therefore it should not be used more frequently than recommended. Do not increase the dose or frequency of medication without consulting your physician. If you find that treatment with Albuterol Sulfate Inhalation Solution, 0.042% 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. All asthma medication should only be used under the supervision and direction of a physician. Common effects with medications such as Albuterol Sulfate Inhalation Solution, 0.042% include palpitations, chest pain, rapid heart rate, tremor, or nervousness.

If you are pregnant or nursing, consult your physician about the use of Albuterol Sulfate Inhalation Solution, 0.042%. Effective and safe use of Albuterol Sulfate Inhalation Solution, 0.042% includes an understanding of the way it should be administered.

If the solution in the vial changes color or becomes cloudy, you should not use it.

The drug compatibility (physical and chemical), clinical efficacy, and safety of Albuterol Sulfate Inhalation Solution, 0.042%, when mixed with other drugs in a nebulizer, has not been established.

See illustrated Patient's Instructions for Use.

**Drug Interactions:** Other short-acting sympathomimetic aerosol bronchodilators or epinephrine should not be used concomitantly with Albuterol Sulfate Inhalation Solution, 0.042%.

Albuterol Sulfate Inhalation Solution, 0.042% 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, since the action of albuterol on the vascular system may be potentiated.

Beta-receptor blocking agents not only block the pulmonary effect of beta-agonists, such as Albuterol Sulfate Inhalation Solution, 0.042%, 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. 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 should be considered, although they should be administered with caution.

## Patient's Instructions for Use Albuterol Sulfate Inhalation Solution, 0.042%\*

\*Potency expressed as albuterol, equivalent to 1.5 mg albuterol sulfate.

Read this patient information completely every time your prescription is filled as information may have changed. Keep these instructions with your medication, as you may want to read them again.

Albuterol Sulfate Inhalation Solution, 0.042% should only be used under the direction of a physician. Your physician and pharmacist have more information about Albuterol Sulfate Inhalation Solution, 0.042% and the condition for which it has been prescribed. Contact them if you have additional questions.

### Storing your medicine

Store Albuterol Sulfate Inhalation Solution, 0.042% between 2°C and 25°C (36°F and 77°F). Vials should be protected from light before use, therefore, keep unused vial in the foil pouch. Do not use after the expiration (EXP) date printed on the vial.

### Dose

Albuterol Sulfate Inhalation Solution, 0.042% is supplied as a single-dose, ready-to-use vial containing 3 mL of solution. No mixing or dilution is needed. Use one new vial with each nebulizer treatment.

### Instructions for Use

1. Remove the vial from the foil pouch.
2. Twist the cap completely off the vial and squeeze the contents into the nebulizer reservoir (Figure 1).

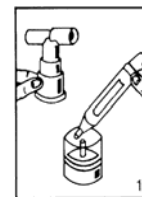


Figure 1

3. Connect the nebulizer to the mouthpiece or face mask (Figure 2).

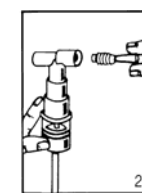


Figure 2

4. Connect the nebulizer to the compressor.
5. Sit in a comfortable, upright position; place the mouthpiece in your mouth (Figure 3) or put on the face mask (Figure 4); and turn on the compressor.



Figure 3

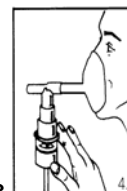


Figure 4

6. Breathe as calmly, deeply and evenly as possible through your mouth until no more mist is formed in the nebulizer chamber (about 5-15 minutes). At this point, the treatment is finished.

7. Clean the nebulizer (see manufacturer's instructions).

(Continued on other side)

