

AccuNeb® (albuterol sulfate) Inhalation Solution

1.25 mg*3 mL and 0.63 mg*3 mL

(*Potency expressed as albuterol, equivalent to 1.5 mg and 0.75 mg albuterol sulfate)

PATIENT'S INSTRUCTIONS FOR USE

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.

AccuNeb should only be used under the direction of a physician. Your physician and pharmacist have more information about AccuNeb and the condition for which it has been prescribed. Contact them if you have additional questions.

Storing your Medicine

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

Dose
AccuNeb 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 one vial from the foil pouch. Place remaining vials back into foil pouch for storage.
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).

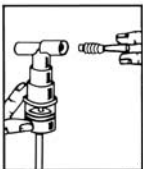


Figure 2

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).



DEY®, Napa, CA 94558

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DOSEAGE AND ADMINISTRATION

The usual starting dosage for patients 2 to 12 years of age is 1.25 mg or 0.63 mg of AccuNeb administered 3 or 4 times daily, as needed, by nebulization. More frequent administration is not recommended.

To administer 1.25 mg or 0.63 mg of albuterol, use the entire contents of one unit-dose vial (3 mL of 1.25 mg or 0.63 mg inhalation solution) by nebulization. Adjust nebulizer flow rate to deliver AccuNeb over 5 to 15 minutes.

The use of AccuNeb can be continued as medically indicated to control recurring bouts of bronchospasm. During this time most patients gain optimum benefit from regular use of the inhalation solution.
Patients 6 to 12 years of age with more severe asthma (baseline FEV₁ less than 60% predicted), weight >40 kg, or patients 11 to 12 years of age may achieve a better initial response with the 1.25 mg dose.

AccuNeb has not been studied in the setting of acute attacks of bronchospasm. A 2.5 mg dose of albuterol provided by a higher concentration product (2.5 mg albuterol per 3 mL) may be more appropriate for treating acute exacerbations, particularly in children 6 years old and above.

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.

The drug compatibility (physical and chemical), clinical efficacy and safety of AccuNeb solution, when mixed with other drugs in a nebulizer have not been established.

The safety and efficacy of AccuNeb have been established in clinical trials when administered using the Pari LC Plus™ nebulizer and Pari PRONEB™ compressor. The safety and efficacy of AccuNeb when administered with other nebulizer systems have not been established.

AccuNeb should be administered via jet nebulizer connected to an air compressor with adequate air flow, equipped with a mouthpiece or suitable face mask.

HOW SUPPLIED

AccuNeb (albuterol sulfate) Inhalation Solution is supplied as a 3 mL, clear, colorless, sterile, preservative-free, aqueous solution in two different strengths: 0.63 mg and 1.25 mg, of albuterol (equivalent to 0.75 mg and 1.5 mg of albuterol sulfate per 3 mL) in unit-dose low-density polyethylene (LDPE) vials. Each unit-dose LDPE vial is protected in a foil pouch, and each foil pouch contains 5 unit-dose LDPE vials. Each strength of AccuNeb (albuterol sulfate) Inhalation Solution is available in a shelf cart containing multiple foil pouches.

AccuNeb® (albuterol sulfate) Inhalation Solution, 0.63 mg (potency expressed as albuterol) contains 0.75 mg albuterol sulfate per 3 mL in unit-dose vials and is available in the following packaging configuration.

NDC 49502-692-03 5 foil pouches, each containing 5 vials, total 25 vials per carton

AccuNeb® (albuterol sulfate) Inhalation Solution, 1.25 mg (potency expressed as albuterol) contains 1.50 mg albuterol sulfate per 3 mL in unit-dose vials and is available in the following packaging configuration.

NDC 49502-693-03 5 foil pouches, each containing 5 vials, total 25 vials per carton

Rx Only.

STORAGE

Store between 2°C and 25°C (36°F - 77°F). Protect from light and excessive heat.

Store unit-dose vials in protective foil pouch at all times. Once removed from the foil pouch, use vial(s) within one week. Discard the vial if the solution is not colorless.

Keep out of the reach of children.

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AccuNeb® (albuterol sulfate) Inhalation Solution

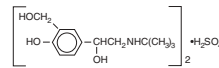
1.25 mg*3 mL and 0.63 mg*3 mL

(*Potency expressed as albuterol, equivalent to 1.5 mg and 0.75 mg albuterol sulfate)

PRESCRIBING INFORMATION

DESCRIPTION

AccuNeb® (albuterol sulfate) inhalation solution is a sterile, clear, colorless solution of the sulfate salt of racemic albuterol, albuterol sulfate. Albuterol sulfate is a relatively selective beta₂-adrenergic bronchodilator (see CLINICAL PHARMACOLOGY). The chemical name for albuterol is: (1R,2S)-2-(tert-butylamino) methyl-3-(isopropylamino)-xyloxy-α,β-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 (C₂₃H₃₇NO₇)₂·H₂SO₄. 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.

AccuNeb (albuterol sulfate) Inhalation Solution is supplied in two strengths in unit dose vials. Each unit dose vial contains either 0.75 mg of albuterol sulfate (equivalent to 0.63 mg of albuterol) or 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 3.5 (see HOW SUPPLIED).

AccuNeb (albuterol sulfate) Inhalation Solution does not require dilution prior to administration by nebulization. For AccuNeb, 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 mouth piece (nominal dose) was approximately 43% of albuterol (1.25 mg strength) and 39% of albuterol (0.63 mg strength) at a mean flow rate of 3.6 L/min. The mean nebulization time was 15 minutes or less. AccuNeb should be administered from a jet nebulizer at an adequate flow rate, via a mouthpiece or face mask (see DOSEAGE 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 beta₂-adrenergic receptors compared with isoproterenol. While it is recognized that beta₂-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 beta₂-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-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 0.63 mg or 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-agonists and methylxanthines are administered concurrently. The clinical significance of these findings is unknown.

Clinical Trials: The safety and efficacy of AccuNeb was evaluated in a 4-week, multi-center, randomized, double-blind, placebo-controlled, parallel group study in 349 children 6 to 12 years of age with mild-to-moderate asthma (mean baseline FEV₁ 60% to 70% of predicted). Approximately half of the patients were also receiving inhaled corticosteroids. Patients were randomized to receive AccuNeb 0.63 mg, AccuNeb 1.25 mg, or placebo three times a day administered via a Pari LC Plus™ nebulizer and a Pari PRONEB™ compressor. Racemic albuterol, delivered by a chlorofluorocarbon (CFC) metered dose inhaler (MDI) or nebulized, was used as 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 FEV₁, was demonstrated for both 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 FEV₁ on day 1 and day 28, respectively. The mean baseline FEV₁ for all patients was 1.49 L.

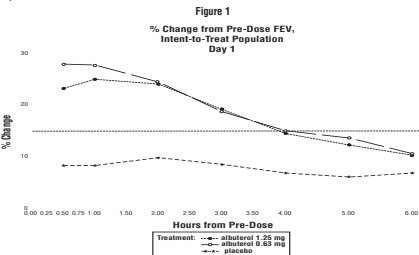


Figure 1

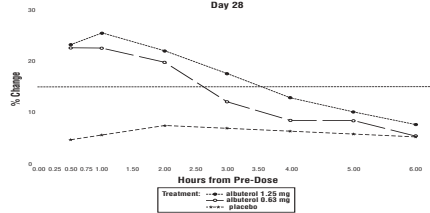


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Figure 2
% Change from Pre-Dose FEV₁
Intent-to-Treat Population
Day 28



The onset of a 15% increase in FEV₁ over baseline for both doses of AccuNeb 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 FEV₁, 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

AccuNeb is indicated for the relief of bronchospasm in patients 2 to 12 years of age with asthma (reversible obstructive airway disease).

CONTRAINDICATIONS

AccuNeb is contraindicated in patients with a history of hypersensitivity to any of its components.

WARNINGS

Paradoxical Bronchospasm: As with other inhaled beta-adrenergic agonists, AccuNeb can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs, AccuNeb 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 use 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 AccuNeb than usual, this may be a marker of destabilization of asthma and requires re-evaluation of the patient and the treatment regimen, giving special consideration of the possible need for anti-inflammatory treatment (e.g., corticosteroids).

Fatalities have 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: AccuNeb, 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 AccuNeb at recommended doses, 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, AccuNeb 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 AccuNeb 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 AccuNeb 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 AccuNeb include palpitations, chest pain, rapid heart rate, tremor, or nervousness.

If you are pregnant or nursing, contact your physician about the use of AccuNeb. Effective and safe use of AccuNeb 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 AccuNeb solution, 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 AccuNeb.

AccuNeb 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 AccuNeb, 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.

The ECG changes and/or hypokalemia that may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the dose of the beta-agonist is exceeded. Although the clinical significance of these effects is unknown, caution is advised in the co-administration of beta-agonists with non-potassium sparing diuretics.

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 these findings 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.

Carcinogenesis, Mutagenesis, and 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 and above dietary doses of 2 mg/kg (approx-

imately equivalent to the maximum recommended daily inhalation dose for AccuNeb on a mg/m³ basis). In another study, this effect was blocked by the co-administration 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 up to 500 mg/kg (approximately 140 times the maximum recommended daily inhalation dose of AccuNeb on a mg/m³ basis). In a 22-month study in Golden hamsters, albuterol sulfate showed no evidence of tumorigenicity at dietary doses up to 50 mg/kg (approximately 20 times the maximum recommended daily inhalation dose of AccuNeb on a mg/m³ basis).

Albuterol sulfate was not mutagenic in the Ames test or a mutation test in yeast. 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 30 times the maximum recommended daily inhalation dose of AccuNeb on a mg/m³ basis).

Pregnancy: Teratogenic Effects: Pregnancy Category C: Albuterol has been shown to be teratogenic in mice. A study in CD-1 mice given albuterol subcutaneously showed cleft palate formation in 5 of 111 (4.5%) fetuses at 0.25 mg/kg (less than the maximum recommended daily inhalation dose of AccuNeb on a mg/m³ basis) and cleft palate formation in 10 of 108 (9.3%) fetuses at 2.5 mg/kg (approximately equal to the maximum recommended daily inhalation dose of AccuNeb on a mg/m³ basis). The drug did not induce cleft palate formation when administered subcutaneously at a dose of 0.025 mg/kg (less than the maximum recommended daily inhalation dose of AccuNeb on a mg/m³ basis). Cleft palate formation also occurred in 23 of 72 (30.5%) fetuses from females treated subcutaneously with 2.5 mg/kg isoproterenol (positive control). A reproduction study in Sprague-Dawley rats revealed cranioschisis in 7 of 19 (37%) fetuses when albuterol sulfate was administered orally at 50 mg/kg (approximately 50 times the maximum recommended daily inhalation dose of AccuNeb on a mg/m³ basis).

A study in which pregnant rats were dosed with radiolabelled albuterol sulfate demonstrated that drug-related material was transferred from the maternal circulation to the fetus.

There are no adequate and well-controlled studies of the use of albuterol sulfate in pregnant women. 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.

Labor and Delivery: Oral albuterol has been shown to delay pre-term labor in some reports. There are presently no well-controlled studies that demonstrate that it will stop pre-term labor or prevent labor at term. Because of the potential for beta agonist interference with uterine contractility, use of AccuNeb for relief of bronchospasm during labor should be restricted to those patients in whom the benefits clearly outweigh the risk.

Albuterol has not been approved for the management of pre-term labor. The benefit-risk ratio when albuterol is administered for tocolysis has not been established. Serious adverse reactions, including pulmonary edema, have been reported following administration of albuterol to women in labor.

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 AccuNeb 1.25 mg and 0.63 mg have been established in pediatric patients between the ages of 2 and 12 years. The use of AccuNeb in these age groups is supported by evidence from adequate and well-controlled studies of AccuNeb in children age 6 to 12 years and published reports of albuterol sulfate trials in pediatric patients 3 years of age and older. The safety and effectiveness of AccuNeb in children below 2 years of age have not been established.

ADVERSE REACTIONS

Adverse events reported in >1% of patients receiving AccuNeb and more frequently than in patients receiving placebo in a four-week double-blind study are listed in the following table.

Table 1: Adverse Events with an Incidence of >1% of Patients Receiving AccuNeb and Greater than Placebo (expressed as % of treatment group)			
	1.25 mg AccuNeb (N=115)	0.63 mg AccuNeb (N=117)	Placebo (N=117)
Asthma Exacerbation	13	11.1	8.5
Otitis Media	4.3	0.9	0
Allergic Reaction	0.9	3.4	1.7
Gastroenteritis	0.9	3.4	0.9
Cold Symptoms	0	3.4	1.7
Flu Syndrome	2.6	2.6	1.7
Lymphadenopathy	2.6	0.9	1.7
Skin/Appendage Infection	1.7	0	0
Urticaria	1.7	0.9	0
Migraine	0.9	1.7	0
Chest Pain	0.9	1.7	0
Bronchitis	0.9	1.7	0.9
Nausea	1.7	0.9	0.9

There was one case of ST segment depression in the 1.25 mg AccuNeb treatment group.

No clinically relevant laboratory abnormalities related to AccuNeb administration were seen in this study.

OVERDOSAGE

The expected symptoms with overdosage are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of symptoms such as seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats per minute, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, insomnia, and exaggeration of the pharmacological effects listed in ADVERSE REACTIONS. Hypokalemia may also occur. As with all sympathomimetic aerosol medications, cardiac arrest and even death may be associated with abuse of AccuNeb. Treatment consists of discontinuation of AccuNeb together with appropriate symptomatic therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of AccuNeb.

The oral median lethal dose of albuterol sulfate in mice is greater than 2000 mg/kg (approximately 580 times the maximum recommended daily inhalation dose of AccuNeb on a mg/m³ basis). The subcutaneous median lethal dose of albuterol sulfate in mature rats and small young rats is approximately 450 mg/kg and 2000 mg/kg, respectively (approximately 260 and 2000 times the maximum recommended daily inhalation dose of AccuNeb on a mg/m³ basis). The inhalation median lethal dose has not been determined in animals.