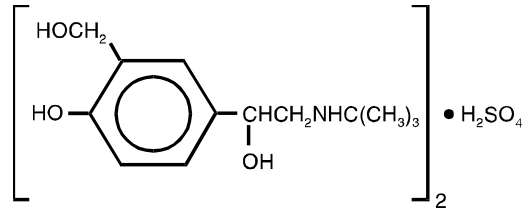


VENTOLIN®
(albuterol sulfate, USP)
Tablets

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DESCRIPTION: VENTOLIN Tablets contain albuterol sulfate, USP, the racemic form of albuterol and a relatively selective beta₂-adrenergic bronchodilator. Albuterol sulfate has the chemical name (±) α¹-[(*tert*-butylamino)methyl]-4-hydroxy-*m*-xylene-α,α'-diol sulfate (2:1)(salt) and the following chemical structure:



Albuterol sulfate has a molecular weight of 576.7, and the empirical formula is (C₁₃H₂₁NO₃)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 base is salbutamol.

Each VENTOLIN Tablet contains 2 or 4 mg of albuterol as 2.4 or 4.8 mg, respectively, of albuterol sulfate for oral administration. Each tablet also contains the inactive ingredients corn starch, lactose, and magnesium stearate.

CLINICAL PHARMACOLOGY: 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, data indicate that there is a population of beta₂-receptors in the human heart existing in a concentration between 10% and 50%. The precise function of these receptors has not been established (see WARNINGS).

The pharmacologic effects of beta-adrenergic agonist drugs, including albuterol, are at least in part attributable to stimulation through beta-adrenergic receptors of intracellular adenylyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic AMP). 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.

Albuterol has been shown in most controlled clinical trials 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.

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.

Preclinical: Intravenous studies in rats with albuterol sulfate have demonstrated that albuterol crosses the blood-brain barrier and reaches brain concentrations amounting to approximately 5.0% of the plasma concentrations. In structures outside the 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.

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Pharmacokinetics: Albuterol is rapidly absorbed after oral administration of 4-mg VENTOLIN Tablets in normal volunteers. Maximum plasma concentrations of about 18 ng/mL of albuterol are achieved within 2 hours, and the drug is eliminated with a half-life of about 5 hours.

In other studies, the analysis of urine samples of patients given 8 mg of tritiated albuterol orally showed that 76% of the dose was excreted over 3 days, with the majority of the dose being excreted within the first 24 hours. Sixty percent of this radioactivity was shown to be the metabolite. Feces collected over this period contained 4% of the administered dose.

Clinical Trials: In controlled clinical trials in patients with asthma, the onset of improvement in pulmonary function, as measured by maximum midexpiratory flow rate (MMEF), was within 30 minutes after a dose of VENTOLIN Tablets, with peak improvement occurring between 2 and 3 hours. In controlled clinical trials in which measurements were conducted for 6 hours, clinically significant improvement (defined as maintaining a 15% or more increase in forced expiratory volume in 1 second [FEV₁] and a 20% or more increase in MMEF over baseline values) was observed in 60% of patients at 4 hours and in 40% at 6 hours. In other single-dose, controlled clinical trials, clinically significant improvement was observed in at least 40% of the patients at 8 hours. No decrease in the effectiveness of VENTOLIN Tablets was reported in patients who received long-term treatment with the drug in uncontrolled studies for periods up to 6 months.

INDICATIONS AND USAGE: VENTOLIN Tablets are indicated for the relief of bronchospasm in adults and children 6 years of age and older with reversible obstructive airway disease.

CONTRAINDICATIONS: VENTOLIN Tablets are contraindicated in patients with a history of hypersensitivity to albuterol or any of its components.

WARNINGS:

Paradoxical Bronchospasm: VENTOLIN Tablets can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs, VENTOLIN Tablets should be discontinued immediately and alternative therapy instituted.

Cardiovascular Effects: VENTOLIN Tablets, 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 VENTOLIN Tablets 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 QT_c interval, and ST segment depression. The clinical significance of these findings is unknown. Therefore, VENTOLIN Tablets, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

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 VENTOLIN Tablets than usual, this may be a marker of destabilization of asthma and requires reevaluation of the patient and 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.

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. Albuterol, like other beta-adrenergic agonists, can produce a significant cardiovascular

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effect in some patients, as measured by pulse rate, blood pressure, symptoms, and/or electrocardiographic changes.

Rarely, erythema multiforme and Stevens-Johnson syndrome have been associated with the administration of oral albuterol sulfate in children.

PRECAUTIONS:

General: Albuterol, as with all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, hypertension, and cardiac arrhythmia; 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 in individual patients 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 preexisting diabetes mellitus and ketoacidosis. As with other beta-agonists, 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 supplementation.

Information for Patients: The action of VENTOLIN Tablets may last up to 8 hours or longer. VENTOLIN Tablets should not be taken more frequently than recommended. Do not increase the dose or frequency of VENTOLIN Tablets without consulting your physician. If you find that treatment with VENTOLIN Tablets becomes less effective for symptomatic relief, your symptoms get worse, and/or you need to take the product more frequently than usual, you should seek medical attention immediately. While you are taking VENTOLIN Tablets, other asthma medications and inhaled drugs should be taken only as directed by your physician. Common adverse effects include palpitations, chest pain, rapid heart rate, and tremor or nervousness. If you are pregnant or nursing, contact your physician about use of VENTOLIN Tablets. Effective and safe use of VENTOLIN Tablets includes an understanding of the way that it should be administered.

Drug Interactions: The concomitant use of VENTOLIN Tablets and other oral sympathomimetic agents is not recommended since such combined use may lead to deleterious cardiovascular effects. This recommendation does not preclude the judicious use of an aerosol bronchodilator of the adrenergic stimulant type in patients receiving VENTOLIN Tablets. Such concomitant use, however, should be individualized and not given on a routine basis. If regular coadministration is required, then alternative therapy should be considered.

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.

Beta-Blockers: Beta-adrenergic receptor blocking agents not only block the pulmonary effect of beta-agonists, such as VENTOLIN Tablets, 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.

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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 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, 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 dietary doses of 2.0, 10, and 50 mg/kg (approximately 1/2, 3, and 15 times, respectively, the maximum recommended daily oral dose for adults on a mg/m² basis or 2/5, 2, and 10 times, respectively, the maximum recommended daily oral dose for children on a mg/m² 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 65 times the maximum recommended daily oral dose for adults on a mg/m² basis or approximately 50 times the maximum recommended daily oral dose for children on a mg/m² 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 8 times the maximum recommended daily oral dose for adults on a mg/m² basis or approximately 7 times the maximum recommended daily oral dose for children on a mg/m² 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 at intraperitoneal doses of up to 200 mg/kg.

Reproduction studies in rats demonstrated no evidence of impaired fertility at oral doses up to 50 mg/kg (approximately 15 times the maximum recommended daily oral dose for adults on a mg/m² basis).

Pregnancy: Teratogenic Effects: Pregnancy Category C. Albuterol has been shown to be teratogenic in mice. A study in CD-1 mice at subcutaneous (sc) doses of 0.025, 0.25, and 2.5 mg/kg (approximately 3/1000, 3/100, and 3/10 times, respectively, the maximum recommended daily oral dose for adults on a mg/m² basis) showed cleft palate formation in 5 of 111 (4.5%) fetuses at 0.25 mg/kg and in 10 of 108 (9.3%) fetuses at 2.5 mg/kg. The drug did not induce cleft palate formation at the lowest dose, 0.025 mg/kg. Cleft palate also occurred in 22 of 72 (30.5%) fetuses from females treated with 2.5 mg/kg of isoproterenol (positive control) subcutaneously (approximately 3/10 times the maximum recommended daily oral dose for adults on a mg/m² basis).

A reproduction study in Stride Dutch rabbits revealed cranioschisis in 7 of 19 (37%) fetuses when albuterol was administered orally at a 50-mg/kg dose (approximately 25 times the maximum recommended daily oral dose for adults on a mg/m² basis).

There are no adequate and well-controlled studies 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 rarely reported in the offspring of patients being treated with albuterol. Some of the mothers were taking multiple medications during their pregnancies. No consistent pattern of defects can be discerned, and a relationship between albuterol use and congenital anomalies has not been established.

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Use in Labor and Delivery: Because of the potential for beta-agonist interference with uterine contractility, use of VENTOLIN Tablets 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 beta₂-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 in children below 6 years of age have not been established.

ADVERSE REACTIONS: In clinical trials, the most frequent adverse reactions to VENTOLIN Tablets were:

| Percent Incidence of Adverse Reactions | |
|--|-------------------|
| Reaction | Percent Incidence |
| Central nervous system | |
| Nervousness | 20% |
| Tremor | 20% |
| Headache | 7% |
| Sleeplessness | 2% |
| Weakness | 2% |
| Dizziness | 2% |
| Drowsiness | <1% |
| Restlessness | <1% |
| Irritability | <1% |
| Cardiovascular | |
| Tachycardia | 5% |
| Palpitations | 5% |
| Chest discomfort | <1% |
| Flushing | <1% |
| Musculoskeletal | |
| Muscle cramps | 3% |
| Gastrointestinal | |
| Nausea | 2% |
| Genitourinary | |
| Difficulty in micturition | <1% |

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

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In addition, albuterol, like other sympathomimetic agents, can cause adverse reactions such as hypertension, angina, vomiting, vertigo, central nervous system stimulation, unusual taste, and drying or irritation of the oropharynx.

The reactions are generally transient in nature, and it is usually not necessary to discontinue treatment with VENTOLIN Tablets. In selected cases, however, dosage may be reduced temporarily; after the reaction has subsided, dosage should be increased in small increments to the optimal dosage.

OVERDOSAGE: The expected symptoms with overdosage are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the symptoms listed under ADVERSE REACTIONS, e.g., seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and sleeplessness. Hypokalemia may also occur. As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of VENTOLIN Tablets. Treatment consists of discontinuation of VENTOLIN Tablets 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 VENTOLIN Tablets.

The oral median lethal dose of albuterol sulfate in mice is greater than 2000 mg/kg (approximately 250 times the maximum recommended daily oral dose for adults on a mg/m² basis or approximately 200 times the maximum recommended daily oral dose for children on a mg/m² basis). In mature rats, the subcutaneous median lethal dose of albuterol sulfate is approximately 450 mg/kg (approximately 110 times the maximum recommended daily oral dose for adults on a mg/m² basis or approximately 90 times the maximum recommended daily oral dose for children on a mg/m² basis). In small young rats, the subcutaneous median lethal dose is approximately 2000 mg/kg (approximately 500 times the maximum recommended daily oral dose for adults on a mg/m² basis or approximately 400 times the maximum recommended daily oral dose for children on a mg/m² basis).

DOSAGE AND ADMINISTRATION: The following dosages of VENTOLIN Tablets are expressed in terms of albuterol base.

Usual Dosage: Adults and Children Over 12 Years of Age: The usual starting dosage for adults and children 12 years and older is 2 or 4 mg three or four times a day.

Children 6 to 12 Years of Age: The usual starting dosage for children 6 to 12 years of age is 2 mg three or four times a day.

Dosage Adjustment: Adults and Children Over 12 Years of Age: For adults and children 12 years and older, a dosage above 4 mg four times a day should be used *only* when the patient fails to respond. If a favorable response does not occur with the 4-mg initial dosage, it should be cautiously increased stepwise up to a maximum of 8 mg four times a day as tolerated.

Children 6 to 12 Years of Age Who Fail to Respond to the Initial Starting Dosage of 2 mg Four Times a Day: For children from 6 to 12 years of age who fail to respond to the initial starting dosage of 2 mg four times a day, the dosage may be cautiously increased stepwise, but not to exceed 24 mg/day (given in divided doses).

Elderly Patients and Those Sensitive to Beta-adrenergic Stimulators: An initial dosage of 2 mg three or four times a day is recommended for elderly patients and for those with a history of unusual sensitivity to beta-adrenergic stimulators. If adequate bronchodilatation is not obtained, dosage may be increased gradually to as much as 8 mg three or four times a day.

The total daily dose should not exceed 32 mg in adults and children 12 years and older.

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HOW SUPPLIED: VENTOLIN Tablets, 2 mg of albuterol as the sulfate, are white, round, compressed tablets impressed with the product name (VENTOLIN) and the number 2 on one side and scored on the other with "GLAXO" impressed on each side of the score in white plastic HDPE bottles of 100 (NDC 0173-0341-43) and 500 (NDC 0173-0341-44).

VENTOLIN Tablets, 4 mg of albuterol as the sulfate, are white, round, compressed tablets impressed with the product name (VENTOLIN) and the number 4 on one side and scored on the other with "GLAXO" impressed on each side of the score in white plastic HDPE bottles of 100 (NDC 0173-0342-43) and 500 (NDC 0173-0342-44).

Store between 2° and 25°C (36° and 77°F). Replace cap securely after each opening.

Rx only

GlaxoWellcome

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