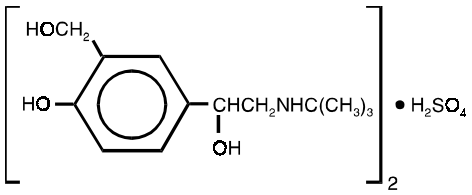
PRODUCT INFORMATION

VENTOLIN® HFA

(albuterol sulfate HFA inhalation aerosol)

Bronchodilator Aerosol
For Oral Inhalation Only

DESCRIPTION: The active component of VENTOLIN HFA (albuterol sulfate HFA inhalation aerosol) is albuterol sulfate, USP, the racemic form of albuterol and 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:



Albuterol sulfate has a molecular weight of 576.7, and the empirical formula is $(C_{13}H_{21}NO_3)_2 \bullet H_2SO_4$. 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.

VENTOLIN HFA is a pressurized metered-dose aerosol unit for oral inhalation. It contains a microcrystalline suspension of albuterol sulfate in propellant HFA-134a (1,1,1,2-tetrafluoroethane). It contains no other excipients.

It is recommended to prime the inhaler before using for the first time and in cases where the inhaler has not been used for more than 2 weeks by releasing 4 test sprays into the air, away from the face. After priming with 4 actuations, each actuation delivers 120 mcg of albuterol sulfate, USP in 75 mg of suspension from the valve and 108 mcg of albuterol sulfate, USP from the mouthpiece (equivalent to 90 mcg of albuterol base from the mouthpiece). Each 18-g canister provides 200 inhalations.

This product does not contain chlorofluorocarbons (CFCs) as the propellant.

CLINICAL PHARMACOLOGY:

Mechanism of Action: 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% of cardiac beta-adrenergic receptors. The precise function of these receptors has not been established (see WARNINGS: Cardiovascular Effects).

Activation of beta$_2$-adrenergic receptors on airway smooth muscle leads to the activation of adenylcyclase and to an increase in the intracellular concentration of cyclic-3′,5′-adenosine

monophosphate (cyclic AMP). This increase of cyclic AMP leads to the activation of protein kinase A, which inhibits the phosphorylation of myosin and lowers intracellular ionic calcium concentrations, resulting in relaxation. Albuterol relaxes the smooth muscles of all airways, from the trachea to the terminal bronchioles. Albuterol acts as a functional antagonist to relax the airway irrespective of the spasmogen involved, thus protecting against all bronchoconstrictor challenges. Increased cyclic AMP concentrations are also associated with the inhibition of release of mediators from mast cells in the airway.

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. 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.

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 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.

Propellant HFA-134a is devoid of pharmacological activity except at very high doses in animals (380 to 1300 times the maximum human exposure based on comparisons of AUC values), primarily producing ataxia, tremors, dyspnea, or salivation. These are similar to effects produced by the structurally related chlorofluorocarbons (CFCs), which have been used extensively in metered-dose inhalers.

In animals and humans, propellant HFA-134a was found to be rapidly absorbed and rapidly eliminated, with an elimination half-life of 3 to 27 minutes in animals and 5 to 7 minutes in humans. Time to maximum plasma concentration (t_{max}) and mean residence time are both extremely short, leading to a transient appearance of HFA-134a in the blood with no evidence of accumulation.

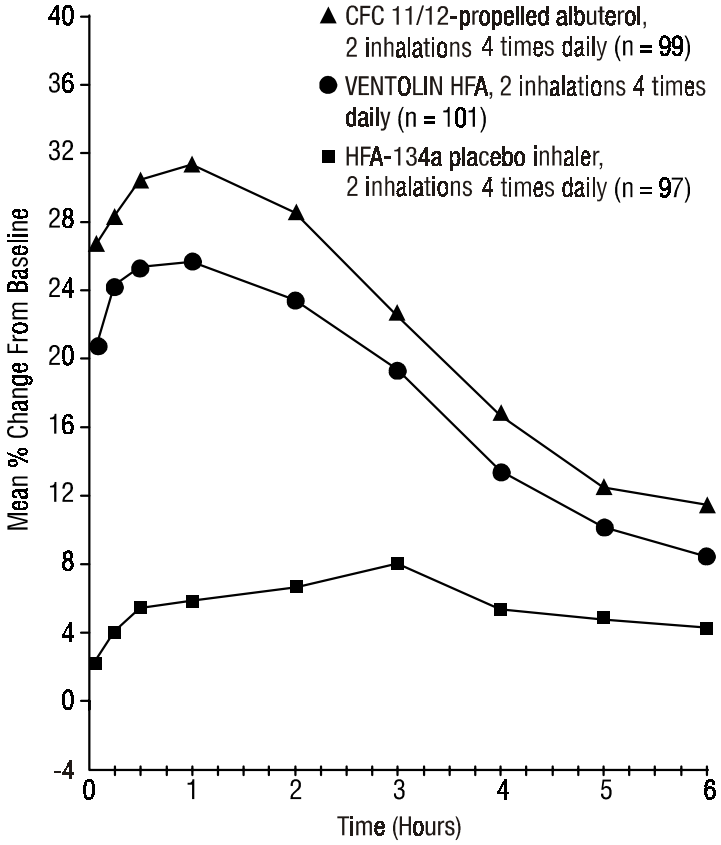
Pharmacokinetics: The systemic levels of albuterol are low after inhalation of recommended doses. A study conducted in 12 healthy male and female subjects using a higher dose (1080 mcg of albuterol base) showed that mean peak plasma concentrations of approximately 3 ng/mL occurred after dosing when albuterol was delivered using propellant HFA-134a. The mean time to peak concentrations (t_{max}) was delayed after administration of VENTOLIN HFA (t_{max} = 0.42 hours) as compared to CFC-propelled albuterol inhaler (t_{max} = 0.17 hours). Apparent terminal plasma half-life of albuterol is approximately 4.6 hours. No further pharmacokinetic studies for VENTOLIN HFA were conducted in neonates, children, or elderly subjects.

Clinical Trials: In a 12-week, randomized, double-blind study, VENTOLIN HFA (101 patients) was compared to CFC 11/12-propelled albuterol (99 patients) and an HFA-134a placebo inhaler (97

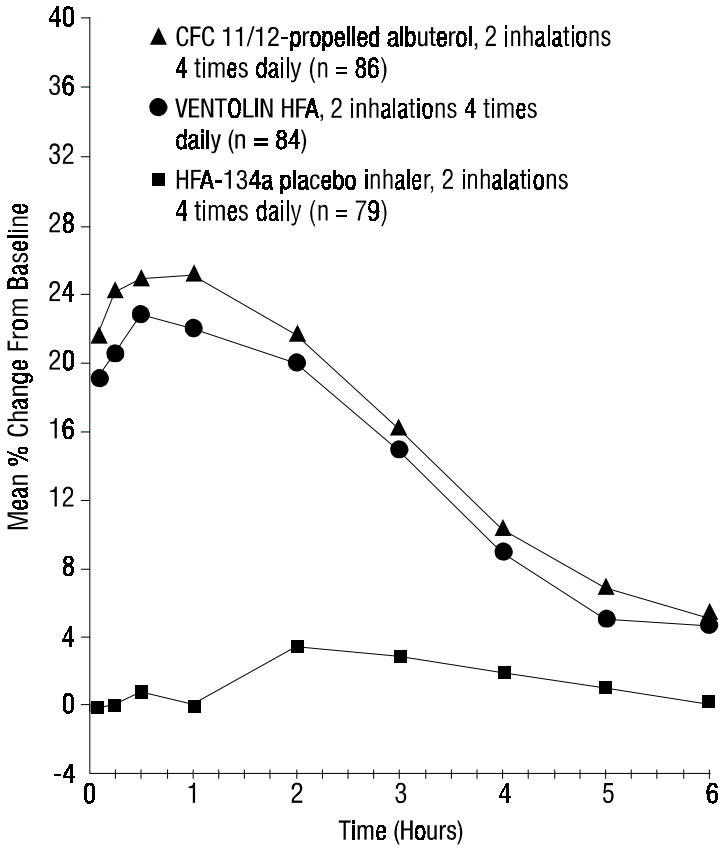
patients) in adolescent and adult patients 12 to 76 years of age with mild to moderate asthma. Serial forced expiratory volume in 1 second (FEV_1) measurements [shown below as percent change from test-day baseline at Day 1 (n = 297) and at Week 12 (n = 249)] demonstrated that 2 inhalations of VENTOLIN HFA produced significantly greater improvement in FEV_1 over the pretreatment value than placebo. Patients taking the HFA-134a placebo inhaler also took VENTOLIN HFA for asthma symptom relief on an as-needed basis.

FEV_1 as Percent Change From Predose in a Large, 12-Week Clinical Trial

Day 1



Week 12



In the responder population (≥15% increase in FEV_1 within 30 minutes postdose) treated with VENTOLIN HFA, the mean time to onset of a 15% increase in FEV_1 over the pretreatment value was 5.4 minutes, and the mean time to peak effect was 56 minutes. The mean duration of effect as measured by a 15% increase in FEV_1 over the pretreatment value was approximately 4 hours. In some patients, duration of effect was as long as 6 hours.

A second 12-week randomized, double-blind study was conducted to evaluate the efficacy and safety of switching patients from CFC 11/12-propelled albuterol to VENTOLIN HFA. During the 3-week run-in phase of the study, all patients received CFC 11/12-propelled albuterol. During the double-blind treatment phase, VENTOLIN HFA (91 patients) was compared to CFC 11/12-propelled albuterol (100 patients) and an HFA-134a placebo inhaler (95 patients) in adolescent and adult patients with mild to moderate asthma. Serial FEV_1 measurements demonstrated that 2 inhalations of VENTOLIN HFA produced significantly greater improvement in pulmonary function than placebo. The switching from CFC 11/12-propelled albuterol inhaler to VENTOLIN HFA did not reveal any clinically significant changes in the efficacy profile.

In the 2 adult studies, the efficacy results from Ventolin HFA were significantly greater than placebo and were clinically comparable to those achieved with albuterol CFC 11/12-propelled albuterol, although small numerical differences in mean FEV_1 response and other measures were observed. Physicians should recognize that individual responses to beta-adrenergic agonists

administered via different propellants may vary and that equivalent responses in individual patients should not be assumed.

In a 2-week, randomized, double-blind study, VENTOLIN HFA was compared to CFC 11/12-propelled albuterol and an HFA-134a placebo inhaler in 135 pediatric patients (4 to 11 years old) with mild to moderate asthma. Serial pulmonary function measurements demonstrated that two inhalations of VENTOLIN HFA produced significantly greater improvement in pulmonary function than placebo and that there were no significant differences between the groups treated with VENTOLIN HFA and CFC 11/12-propelled albuterol. In the responder population treated with VENTOLIN HFA, the mean time to onset of a 15% increase in peak expiratory flow rate (PEFR) over the pretreatment value was 7.8 minutes, and the mean time to peak effect was approximately 90 minutes. The mean duration of effect as measured by a 15% increase in PEFR over the pretreatment value was greater than 3 hours. In some patients, duration of effect was as long as 6 hours.

One controlled clinical study in adult patients with asthma (n = 24) demonstrated that 2 inhalations of VENTOLIN HFA taken approximately 30 minutes prior to exercise significantly prevented exercise-induced bronchospasm (as measured by maximum percentage fall in FEV_1 following exercise) compared to an HFA-134a placebo inhaler. In addition, VENTOLIN HFA was shown to be clinically comparable to a CFC 11/12-propelled albuterol inhaler for this indication.

Some patients who participated in these clinical trials were using concomitant steroid therapy.

INDICATIONS AND USAGE: VENTOLIN HFA is indicated for the treatment or prevention of bronchospasm in adults and children 4 years of age and older with reversible obstructive airway disease and for the prevention of exercise-induced bronchospasm in patients 4 years of age and older.

CONTRAINDICATIONS: VENTOLIN HFA is contraindicated in patients with a history of hypersensitivity to albuterol or any other components of VENTOLIN HFA.

WARNINGS:

Paradoxical Bronchospasm: Inhaled albuterol sulfate can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs, VENTOLIN HFA 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 canister.

Cardiovascular Effects: VENTOLIN HFA, like all other beta-adrenergic agonists, can produce clinically significant cardiovascular effects in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of VENTOLIN HFA 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 HFA, 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 HFA 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, to the therapeutic regimen.

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

Do Not Exceed Recommended Dose: Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma. The exact cause of death is unknown, but cardiac arrest following an unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected.

PRECAUTIONS:

General: Albuterol sulfate, 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: See illustrated Patient's Instructions for Use. SHAKE WELL BEFORE USING. Patients should be given the following information:

It is recommended to prime the inhaler before using for the first time and in cases where the inhaler has not been used for more than 2 weeks by releasing 4 test sprays into the air, away from the face.

KEEPING THE PLASTIC ACTUATOR CLEAN IS VERY IMPORTANT TO PREVENT MEDICATION BUILD-UP AND BLOCKAGE. THE ACTUATOR SHOULD BE WASHED, SHAKEN TO REMOVE EXCESS WATER, AND AIR-DRIED THOROUGHLY AT LEAST ONCE A WEEK. THE INHALER MAY CEASE TO DELIVER MEDICATION IF NOT PROPERLY CLEANED.

The actuator should be cleaned (with the canister removed) by running warm water through the top and bottom for 30 seconds at least once a week. Do not attempt to clean the metal canister or

allow the metal canister to become wet. Never immerse the metal canister in water. The actuator must be shaken to remove excess water, then air-dried thoroughly (such as overnight). Blockage from medication build-up or improper medication delivery may result from failure to clean and thoroughly air-dry the actuator.

If the actuator should become blocked (little or no medication coming out of the mouthpiece), the blockage may be removed by washing the actuator as described above.

If it is necessary to use the inhaler before it is completely dry, shake excess water off the plastic actuator, replace canister, shake well, test spray twice away from face, and take the prescribed dose. After such use, the actuator should be rewashed and allowed to air-dry thoroughly.

The action of VENTOLIN HFA should last up to 4 to 6 hours. VENTOLIN HFA should not be used more frequently than recommended. Do not increase the dose or frequency of doses of VENTOLIN HFA without consulting your physician. If you find that treatment with VENTOLIN HFA 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 VENTOLIN HFA, other inhaled drugs and asthma medications should be taken only as directed by your physician.

Common adverse effects of treatment with inhaled albuterol include palpitations, chest pain, rapid heart rate, tremor, and nervousness. If you are pregnant or nursing, contact your physician about use of VENTOLIN HFA. Effective and safe use of VENTOLIN HFA includes an understanding of the way that it should be administered.

Use VENTOLIN HFA only with the actuator supplied with the product. Discard the canister after 200 sprays have been used or 3 months after removal from the moisture-protective foil pouch, whichever comes first. Never immerse the canister into water to determine how full the canister is (“float test”).

In general, the technique for administering VENTOLIN HFA to children is similar to that for adults. Children should use VENTOLIN HFA under adult supervision, as instructed by the patient's physician. (See Patient’s Instructions for Use.)

Drug Interactions: Other short-acting sympathomimetic aerosol bronchodilators should not be used concomitantly with albuterol. If additional adrenergic drugs are to be administered by any route, they should be used with caution to avoid deleterious cardiovascular effects.

Monoamine Oxidase Inhibitors or Tricyclic Antidepressants: VENTOLIN HFA 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 HFA, 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 should 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 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 dose-related increase in the incidence of benign leiomyomas of the mesovarium at and above dietary doses of 2.0 mg/kg (approximately 14 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis and approximately 6 times the maximum recommended daily inhalation dose for children 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 1700 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis and approximately 800 times the maximum recommended daily inhalation dose for children on a mg/m^2 basis). In a 22-month study in Golden hamsters, albuterol sulfate showed no evidence of tumorigenicity at dietary doses of up to 50 mg/kg (approximately 225 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis and approximately 110 times the maximum recommended daily inhalation dose for children on a mg/m^2 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 340 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis).

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category C. Albuterol sulfate has been shown to be teratogenic in mice. A study in CD-1 mice given albuterol sulfate 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 for adults on a mg/m^2 basis) and in 10 of 108 (9.3%) fetuses at 2.5 mg/kg (approximately 8 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis). The drug did not induce cleft palate formation at a dose of 0.025 mg/kg (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 subcutaneously with 2.5 mg/kg of isoproterenol (positive control).

A reproduction study in Stride Dutch rabbits revealed cranioschisis in 7 of 19 fetuses (37%) when albuterol sulfate was administered orally at a 50 mg/kg dose (approximately 680 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis).

In an inhalation reproduction study in New Zealand white rabbits, albuterol sulfate/HFA-134a formulation exhibited enlargement of the frontal portion of the fetal fontanelles at and above inhalation doses of 0.0193 mg/kg (less than the maximum recommended daily inhalation dose for adults on a mg/m^2 basis).

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

There are no adequate and well-controlled studies of VENTOLIN HFA or albuterol sulfate in pregnant women. VENTOLIN HFA 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. No consistent pattern of defects can be discerned, and a relationship between albuterol use and congenital anomalies has not been established.

Use in Labor and Delivery: Because of the potential for beta-agonist interference with uterine contractility, use of VENTOLIN HFA 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 $beta_2$-agonists, including albuterol.

Nursing Mothers: Plasma levels of albuterol sulfate and HFA-134a after inhaled therapeutic doses are very low in humans, but it is not known whether the components of VENTOLIN HFA are excreted in human milk. Because of the potential for tumorigenicity shown for albuterol in animal studies and lack of experience with the use of VENTOLIN HFA by nursing mothers, 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. Caution should be exercised when albuterol sulfate is administered to a nursing woman.

Pediatric Use: Results from a 2-week, randomized study in pediatric patients 4-11 years old with mild to moderate asthma have shown that VENTOLIN HFA is safe and effective in this population. Safety and effectiveness in children below 4 years of age have not been established.

Geriatrics: Clinical studies of VENTOLIN HFA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the

dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS: Adverse reaction information concerning VENTOLIN HFA is derived from two 12-week, randomized, double-blind studies in 610 adolescent and adult asthmatic patients that compared VENTOLIN HFA, a CFC 11/12-propelled albuterol inhaler, and an HFA-134a placebo inhaler. The following table lists the incidence of all adverse events (whether considered by the investigator to be related or unrelated to drug) from these studies that occurred at a rate of 3% or greater in the group treated with VENTOLIN HFA and more frequently in the group treated with VENTOLIN HFA than in the HFA-134a placebo inhaler group. Overall, the incidence and nature of the adverse events reported for VENTOLIN HFA and a CFC 11/12-propelled albuterol inhaler were comparable. Results in a 2-week pediatric clinical study (n = 135) showed that the adverse event profile was generally similar to that of the adult.

Adverse Experience Incidence (% of Patients) in 2 Large 12-Week Adolescent and Adult Clinical Trials*

	Percent of Patients		
Adverse Event Type	VENTOLIN HFA (n = 202)	CFC 11/12-Propelled Albuterol Inhaler (n = 207)	Placebo HFA-134a (n = 201)
Ear, nose, and throat			
Throat irritation	10	6	7
Upper respiratory inflammation	5	5	2
Lower respiratory			
Viral respiratory infections	7	4	4
Cough	5	2	2
Musculoskeletal			
Musculoskeletal pain	5	5	4

* This table includes all adverse events (whether considered by the investigator to be drug-related or unrelated to drug) that occurred at an incidence rate of at least 3.0% in the group treated with VENTOLIN HFA and more frequently in the group treated with VENTOLIN HFA than in the HFA-134a placebo inhaler group.

Adverse events reported by less than 3% of the adolescent and adult patients receiving VENTOLIN HFA and by a greater proportion of patients receiving VENTOLIN HFA than receiving HFA-134a placebo inhaler and that have the potential to be related to VENTOLIN HFA include diarrhea, laryngitis, oropharyngeal edema, cough, lung disorders, tachycardia, and extrasystoles. Palpitation and dizziness have also been observed with VENTOLIN HFA.

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

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

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 aerosol medications, cardiac arrest and even death may be associated with abuse of VENTOLIN HFA. Treatment consists of discontinuation of VENTOLIN HFA 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 HFA.

The oral median lethal dose of albuterol sulfate in mice is greater than 2000 mg/kg (approximately 6800 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis and approximately 3200 times the maximum recommended daily inhalation dose for children on a mg/m^2 basis). In mature rats, the subcutaneous median lethal dose of albuterol sulfate is approximately 450 mg/kg (approximately 3000 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis and approximately 1400 times the maximum recommended daily inhalation dose for children on a mg/m^2 basis). In young rats, the subcutaneous median lethal dose is approximately 2000 mg/kg (approximately 14,000 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis and approximately 6400 times the maximum recommended daily inhalation dose for children on a mg/m^2 basis). The inhalation median lethal dose has not been determined in animals.

DOSAGE AND ADMINISTRATION: Adult and Pediatric Asthma: For treatment of acute episodes of bronchospasm or prevention of asthmatic symptoms, the usual dosage for adults and children 4 years of age and older is 2 inhalations repeated every 4 to 6 hours; in some patients, 1 inhalation every 4 hours may be sufficient. More frequent administration or a larger number of inhalations is not recommended. It is recommended to prime the inhaler before using for the first time and in cases where the inhaler has not been used for more than 2 weeks by releasing 4 test sprays into the air, away from the face.

VENTOLIN HFA can also be used to relieve acute symptoms of asthma. The use of VENTOLIN HFA can be continued as medically indicated to control recurring bouts of bronchospasm. If a previously effective dosage regimen fails to provide the usual response, 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.

Safe usage of albuterol for periods extending over several years has been documented.

Exercise-Induced Bronchospasm Prevention: The usual dosage for adults and children 4 years and older is 2 inhalations 15 to 30 minutes before exercise. For treatment, see above.

Cleaning: To maintain proper use of this product, it is important that the actuator be washed and dried thoroughly at least once a week. The inhaler may cease to deliver medication if not properly cleaned and dried thoroughly. **See Information for Patients**. Keeping the plastic actuator clean is very important to prevent medication build-up and blockage. If the actuator becomes blocked with drug, washing the actuator will remove the blockage.

HOW SUPPLIED: VENTOLIN HFA (albuterol sulfate HFA inhalation aerosol) is supplied as a pressurized aluminum canister with a blue plastic actuator and a blue strapcap packaged within a moisture-protective foil pouch, each in boxes of 1 with patient's instructions (NDC 0173-0682-00). The moisture-protective foil pouch also contains a desiccant that should be discarded when the pouch is opened.

Also available is VENTOLIN HFA Refill 18-g canister only packaged within a moisture-protective foil pouch with desiccant with patient's instructions (NDC 0173-0682-01).

It is recommended to prime the inhaler before using for the first time and in cases where the inhaler has not been used for more than 2 weeks by releasing 4 test sprays into the air, away from the face. After priming with 4 actuations, each actuation delivers 120 mcg of albuterol sulfate, USP in 75 mg of suspension from the valve and 108 mcg of albuterol sulfate, USP from the mouthpiece (equivalent to 90 mcg of albuterol base from the mouthpiece). The canister is labeled with a net weight of 18 g and contains 200 metered inhalations.

The blue actuator supplied with VENTOLIN HFA should not be used with any other product canisters, and actuators from other products should not be used with a VENTOLIN HFA canister. The correct amount of medication in each canister cannot be assured after 200 actuations, even though the canister is not completely empty. The canister should be discarded when 200 actuations have been used or 3 months after removal from the moisture-protective foil pouch, whichever comes first. Never immerse the canister into water to determine how full the canister is (“float test”).

Contents Under Pressure: Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 120°F may cause bursting. Never throw container into fire or incinerator. Keep out of reach of children. Avoid spraying in eyes.

Store between 15° and 25°C (59° and 77°F). Store canister with mouthpiece down. For best results, the canister should be at room temperature before use. SHAKE WELL BEFORE USING.

VENTOLIN HFA does not contain chlorofluorocarbons (CFCs) as the propellant.

GlaxoWellcome

Glaxo Wellcome Inc.
Research Triangle Park, NC 27709

US Patent Nos. 5,674,471; 5,676,929; 6,131,566; and 6,119,853

December 5, 2000 RL-867

[The instructions below have been revised to a tear-off rather than a separate leaflet.]

PHARMACIST—DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT.

THIS LEAFLET SHOULD ACCOMPANY EACH VENTOLIN HFA OR REFILL DISPENSED.

Patient's Instructions for Use

Before using your VENTOLIN® HFA (albuterol sulfate HFA inhalation aerosol, read complete instructions carefully.

Please note that CFC indicates that this inhalation aerosol does not contain chlorofluorocarbons (CFCs) as the propellant.

Children should use VENTOLIN HFA under adult supervision, as instructed by the patient's doctor.

The blue actuator supplied with VENTOLIN HFA should not be used with any other product canisters, and actuators from other products should not be used with a VENTOLIN HFA canister. The refill canister is to be used only with the blue VENTOLIN HFA actuator.

SHAKE THE INHALER WELL immediately before each use.

As with all other inhalation aerosol medications, patients should make sure that the canister is seated in the plastic mouthpiece adaptor before each use and the product is primed at specified times. Patients should prime VENTOLIN HFA by activating into the air, away from the eyes and face, 4 times before using for the first time and 4 times when the aerosol has not been used for a period of at least 14 days.

1. REMOVE THE CAP FROM THE MOUTHPIECE (see Figure 1); the strap on the cap will stay attached to the actuator. Inspect the inhaler mouthpiece for the presence of foreign objects before each use, especially if the strap is removed from the actuator and lost or if the cap has not been used to cover the mouthpiece. Make sure the canister is fully and firmly inserted into the actuator. **SHAKE THE INHALER WELL** immediately before each use.

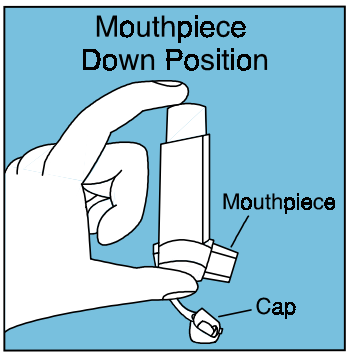


Figure 1

(Text in figure artwork changed from “UPRIGHT POSITION” to “Mouthpiece Down Position”)

2. BREATHE OUT FULLY THROUGH THE MOUTH, expelling as much air from your lungs as possible. Place the mouthpiece fully into the mouth, holding the inhaler in the mouthpiece down position (see Figure 1) and closing the lips around it.

3. WHILE BREATHING IN DEEPLY AND SLOWLY THROUGH THE MOUTH, FULLY DEPRESS THE TOP OF THE METAL CANISTER with your index finger (see Figure 2). Immediately after the puff is delivered, release your finger from the canister and remove the inhaler from your mouth.

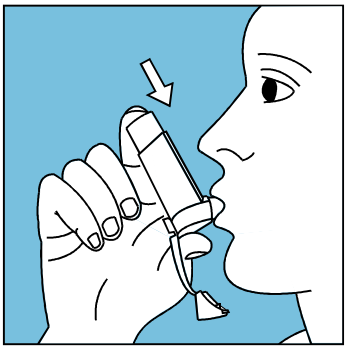


Figure 2

4. HOLD YOUR BREATH AS LONG AS POSSIBLE, up to 10 seconds.

5. If your doctor has prescribed additional puffs, wait 1 minute and **SHAKE** the inhaler again. Repeat steps 2 through 4. Replace the cap after use.

6. KEEPING THE PLASTIC ACTUATOR CLEAN IS VERY IMPORTANT TO PREVENT MEDICINE BUILD-UP AND BLOCKAGE. THE ACTUATOR SHOULD BE WASHED, SHAKEN TO REMOVE EXCESS WATER, AND AIR-DRIED THOROUGHLY AT LEAST ONCE A WEEK. THE INHALER MAY STOP SPRAYING IF NOT PROPERLY CLEANED.

Routine cleaning instructions:

Step 1. To clean, remove the canister and mouthpiece cap; the strap on the cap will stay attached to the actuator. Wash the actuator through the top and bottom with warm running warm water for 30 seconds at least once a week (see Figure 3). **Do not attempt to clean the metal canister or allow the metal canister to become wet. Never immerse the metal canister in water.**

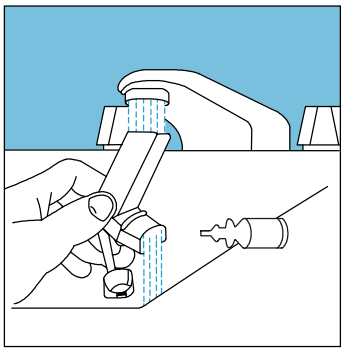


Figure 3

Step 2. To dry, shake off excess water and let the actuator air-dry thoroughly, such as overnight (see Figure 4). When the actuator is dry, replace the canister and the mouthpiece cap; make sure the canister is fully and firmly inserted into the actuator. Blockage from medicine build-up is more likely to occur if the actuator is not allowed to air-dry thoroughly.

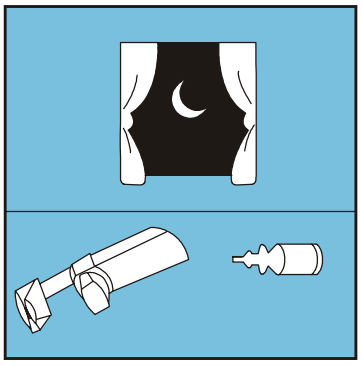


Figure 4

IF THE ACTUATOR BECOMES BLOCKED (little or no medicine coming out of the mouthpiece, see Figure 5), wash the actuator as described in Step 1 and air-dry thoroughly as described in Step 2.

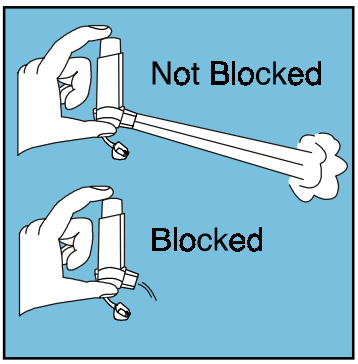


Figure 5

IF YOU NEED TO USE YOUR INHALER BEFORE IT IS COMPLETELY DRY, SHAKE EXCESS WATER off the plastic actuator**,** replace the canister, **shake well**, and test spray twice into the air, away from your face, to remove most of the water remaining in the actuator. Then take your dose as prescribed. **After such use, rewash and air-dry thoroughly as described in Steps 1 and 2.**

7. DISCARD THE CANISTER AFTER YOU HAVE USED 200 INHALATIONS or 3 months after removal from the moisture-protective foil pouch, whichever comes first. The correct amount of medicine in each inhalation cannot be assured after 200 sprays, even though the canister is not completely empty. Never immerse the canister into water to determine how full the canister is ("float test"). Before you reach 200 sprays, you should consult your doctor to determine whether a refill is needed. Just as you should not take extra doses without consulting your doctor, you also should not stop using VENTOLIN HFA without consulting your doctor.

You may notice a slightly different taste or spray than you are used to with VENTOLIN HFA compared to other albuterol inhalation aerosol products.

DOSAGE: Use only as directed by your doctor.

WARNINGS: The action of VENTOLIN HFA should last up to 4 to 6 hours. VENTOLIN HFA should not be used more frequently than recommended. Do not increase the dose or frequency of VENTOLIN HFA without consulting your doctor. If you find that treatment with VENTOLIN HFA 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 VENTOLIN HFA, other inhaled drugs and asthma medicines should be used only as directed by your doctor. If you are pregnant or nursing, contact your doctor about the use of VENTOLIN HFA.

Adverse effects of treatment with VENTOLIN HFA include palpitations, chest pain, rapid heart rate, tremor, or nervousness. Effective and safe use of VENTOLIN HFA includes an understanding of the way that it should be administered. Use VENTOLIN HFA only with the actuator supplied with the product. The VENTOLIN HFA actuator should not be used with other aerosol medicines.

Contents Under Pressure: Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 120°F may cause bursting. Never throw container into fire or incinerator. Keep out of reach of children. Avoid spraying in eyes.

Store between 15° and 25°C (59° and 77°F). Store canister with mouthpiece down. For best results, the canister should be at room temperature before use. Avoid exposing product to extreme heat and cold. SHAKE WELL BEFORE USING.

Further Information: Your VENTOLIN HFA does not contain chlorofluorocarbons (CFCs) as the propellant. Instead, the inhaler contains a hydrofluoroalkane (HFA-134a) as the propellant.

GlaxoWellcome

Glaxo Wellcome Inc.
Research Triangle Park, NC 27709

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