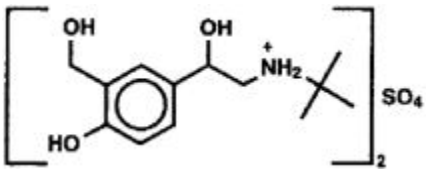
PROVENTIL® HFA
(albuterol sulfate)
Inhalation Aerosol

FOR ORAL INHALATION ONLY

Prescribing Information

DESCRIPTION

The active component of PROVENTIL® HFA (albuterol sulfate) Inhalation Aerosol is albuterol sulfate, USP racemic α[1] [(*tert*-Butylamino)methyl]-4-hydroxy-*m*-xylene-α,α'-diol sulfate (2:1)(salt), a relatively selective beta$_2$-adrenergic bronchodilator having the following chemical structure:



Albuterol sulfate is the official generic name in the United States. The World Health Organization recommended name for the drug is salbutamol sulfate. The molecular weight of albuterol sulfate is 576.7, and the empirical formula is $(C_{13}H_{21}NO_3)_2 \cdot H_2SO_4$. Albuterol sulfate is a white to off-white crystalline solid. It is soluble in water and slightly soluble in ethanol. PROVENTIL HFA Inhalation Aerosol 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), ethanol, and oleic acid.

Each actuation delivers 120 mcg albuterol sulfate, USP from the valve and 108 mcg albuterol sulfate, USP from the mouthpiece (equivalent to 90 mcg of albuterol base from the mouthpiece). Each canister provides 200 inhalations. 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 four “test sprays” into the air, away from the face.

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 on 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 section.)

Activation of beta$_2$-adrenergic receptors on airway smooth muscle leads to the activation of adenylcyclase and to an increase in the intra-cellular concentration of cyclic-3',5'-adenosine monophosphate (cyclic AMP). This increase of cyclic AMP leads to the activation of protein kinase A, which inhabits 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 bronchoconstricor 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 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% 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$_2$-agonist and methylxanthines were 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 (380-1300 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 (Tmax) 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 In a single-dose bioavailability study which enrolled six healthy, male volunteers, transient low albuterol levels (close to the lower limit of quantitation) were observed after administration of two puffs from both PROVENTIL® HFA Inhalation Aerosol and a CFC 11/12 propelled albuterol inhaler. No formal pharmacokinetic analyses were possible for either treatment, but systemic albuterol levels appeared similar.

Clinical Trials In a 12-week, randomized, double-blind, double-dummy, active- and placebo-controlled trial, 565 patients with asthma were evaluated for the bronchodilator efficacy of PROVENTIL HFA Inhalation Aerosol (193 patients) in comparison to a CFC 11/12 propelled albuterol inhaler (186 patients) and an HFA-134a placebo inhaler (186 patients).

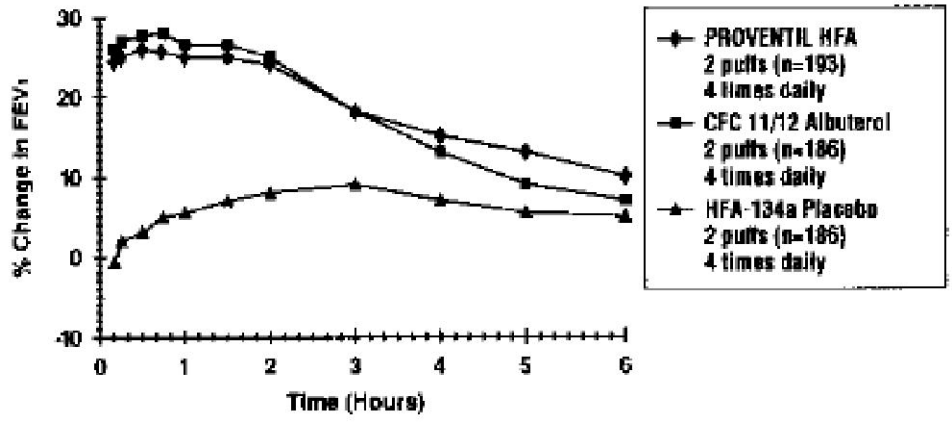
Serial FEV_1 measurements (shown below as percent change from test-day baseline) demonstrated that two inhalations of PROVENTIL HFA Inhalation Aerosol produced significantly greater improvement in pulmonary function than placebo and produced outcomes which were clinically comparable to a CFC 11/12 propelled albuterol inhaler.

The mean time to onset of a 15% increase in FEV_1 was 6 minutes and the mean time to peak effect was 50 to 55 minutes. The mean duration of effect as measured by a 15% increase in FEV_1 was 3 hours. In some patients, duration of effect was as long as 6 hours.

In another clinical study in adults, two inhalations of PROVENTIL HFA Inhalation Aerosol taken 30 minutes before exercise prevented exercise-induced bronchospasm as demonstrated by the maintenance of FEV_1 within 80% of baseline values in the majority of patients.

In a 4-week, randomized, open-label trial, 63 children, 4 to 11 years of age, with asthma were evaluated for the bronchodilator efficacy of PROVENTIL HFA Inhalation Aerosol (33 pediatric patients) in comparison to a CFC 11/12 propelled albuterol inhaler (30 pediatric patients).

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



Serial FEV_1 measurements as percent change from test-day baseline demonstrated that two inhalations of PROVENTIL HFA Inhalation Aerosol produced outcomes which were clinically comparable to a CFC 11/12 propelled albuterol inhaler.

The mean time to onset of a 12% increase in FEV_1 for PROVENTIL HFA Inhalation Aerosol was 7 minutes and the mean time to peak effect was approximately 50 minutes. The mean duration of effect as measured by a 12% increase in FEV_1 was 2.3 hours. In some pediatric patients, duration of effect was as long as 6 hours.

In another clinical study in pediatric patients, two inhalations of PROVENTIL HFA Inhalation Aerosol taken 30 minutes before exercise provided comparable protection against exercise-induced bronchospasm as a CFC 11/12 propelled albuterol inhaler.

INDICATIONS AND USAGE

PROVENTIL® HFA Inhalation Aerosol is indicated in adults and children 4 years of age and older for the treatment or prevention of bronchospasm with reversible obstructive airway disease and for the prevention of exercise-induced bronchospasm.

CONTRAINDICTIONS

PROVENTIL® HFA Inhalation Aerosol is contraindicated in patients with a history of hypersensitivity to albuterol or any other PROVENTIL HFA components.

WARNINGS

1. Paradoxical Bronchospasm: Inhaled albuterol sulfate can produce paradoxical bronchospasm that may be life threatening. If paradoxical bronchospasm occur, PROVENTIL® HFA Inhalation Aerosol 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.

2. 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 PROVENTIL HFA Inhalation Aerosol than usual, this may be a marker of destabilization of asthma

and requires re-evaluation of the patient and treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, eg, corticosteroids.

3. 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, eg, corticosteroids, to the therapeutic regimen.

4. Cardiovascular Effects: PROVENTIL HFA Inhalation Aerosol, like other beta-adrenergic agonist, 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 PROVENTIL HFA Inhalation Aerosol 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 QT_C interval, and ST segment depression. The clinical significance of these findings is unknown. Therefore, PROVENTIL HFA Inhalation Aerosol, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

5. 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.

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

PRECAUTIONS

General Albuterol sulfate, as with all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders,

hyperthyroidism, or diabetes mellitus; and in patients who are unusually responsive to sympathomimetic amines. Clinically significant changes in systolic and diastolic blood pressure have been seen 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 four “test sprays” into the air, away from the face.

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

The mouthpiece should be cleaned (with the canister removed) by running warm water through the top and bottom for 30 seconds at least once a week. The mouthpiece 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 thoroughly air dry the mouthpiece.

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

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

The action of PROVENTIL® HFA Inhalation Aerosol should last up to 4 to 6 hours. PROVENTIL HFA Inhalation Aerosol should not be used more frequently than recommended. Do not increase the dose or frequency of doses of PROVENTIL HFA Inhalation Aerosol without consulting your physician. If you find that treatment with PROVENTIL HFA Inhalation Aerosol becomes less effective for symptomatic relief, your symptoms become worse, and/or you need to use the product more frequently than usual, medical attention should be sought immediately. While you are taking PROVENTIL HFA Inhalation Aerosol, 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, or nervousness. If you are pregnant or nursing, contact your physician about use of PROVENTIL HFA Inhalation Aerosol. Effective and safe use of PROVENTIL HFA Inhalation Aerosol includes an understanding of the way that it should be administered. Use PROVENTIL HFA Inhalation Aerosol only with the actuator supplied with the product. Discard the canister after 200 sprays have been used.

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

Drug Interactions

1. Beta-Blockers: Beta-adrenergic-receptor blocking agents not only block the pulmonary effect of beta-agonists, such as PROVENTIL HFA Inhalation Aerosol, but may produce severe bronchospasm in asthmatic patients. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, eg, 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.

2. Diuretics: The ECG changes and/or hypokalemia which 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.

3. Albuterol-Digoxin: Mean decreases of 16% and 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.

4. Monoamine Oxidase Inhibitors or Tricyclic Antidepressants: PROVENTIL HFA Inhalation Aerosol 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 cardiovascular system may be potentiated.

Carcinogenesis, Mutagenesis, and 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 the above dietary doses of 2 mg/kg (approximately 15 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 nonselective 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 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 (37%) fetuses when albuterol sulfate was administered orally at 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 SPRAGUE-DAWLEY rats, the albuterol sulfate/HFA-134a formulation did not exhibit any teratogenic effects at 10.5 mg/kg (approximately 70 times 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 PROVENTIL HFA Inhalation Aerosol or albuterol sulfate in pregnant women. PROVENTIL HFA Inhalation Aerosol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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

Use in Labor and Delivery

Because of the potential for beta-agonist interference with uterine contractility, use of PROVENTIL HFA Inhalation Aerosol for relief of bronchospesm 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 pulmonary edema, have been reported during the 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 PROVENTIL HFA Inhalation Aerosol are excreated in human milk.

Because of the potential for tumorigenicity shown for albuterol in animal studies and lack of experience with the use of PROVENTIL HFA Inhalation Aerosol 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.

Pediatrics

The safety and effectiveness of PROVENTIL HFA Inhalation Aerosol in pediatric patients below the age of 4 years have not been established.

Geriatrics

PROVENTIL HFA Inhalation Aerosol has not been studied in a geriatric population. As with other $beta_2$-agonists, special caution should be observed when using PROVENTIL HFA Inhalation Aerosol in elderly patients who have concomitant cardiovascular disease that could be adversely affected by this class of drug.

ADVERSE REACTIONS

Adverse reaction information concerning PROVENTIL® HFA Inhalation Aerosol is derived from a 12-week, double-blind, double-dummy study which compared PROVENTIL HFA Inhalation Aerosol, a CFC 11/12 propelled albuterol inhaler, and an HFA-134a placebo inhaler in 565 asthmatic patients. The following table lists the incidence of all adverse events (whether considered by the investigator drug related or unrelated to drug) from this study which occurred at a rate of 3% or greater in the PROVENTIL HFA Inhalation Aerosol treatment group and more frequently in the PROVENTIL HFA Inhalation Aerosol treatment group than in the placebo group. Overall, the incidence and nature of the adverse reactions reported for PROVENTIL HFA Inhalation Aerosol and a CFC 11/12 propelled albuterol inhaler were comparable.

Adverse Experience Incidences (% of patients) in a Large 12-week Clinical Trial*

Body System/ Adverse Event (Preferred Term)		PROVENTIL® HFA Inhalation Aerosol (N=193)	CFC 11/12 Propelled Albuterol Inhaler (N=186)	HFA-134a Placebo Inhaler (N=186)
Application Site Disorders	Inhalation Site Sensation	6	9	2
	Inhalation Taste Sensation	4	3	3
Body as a Whole	Allergic Reaction/Symptoms	6	4	<1
	Back Pain	4	2	3
	Fever	6	2	5
Central and Peripheral Nervous System	Tremor	7	8	2
Gastrointestinal System	Nausea	10	9	5
	Vomiting	7	2	3
Heart Rate and Rhythm Disorder	Tachycardia	7	2	<1
Psychiatric Disorders	Nervousness	7	9	3
Respiratory System Disorders	Respiratory Disorder (unspecified)	6	4	5
	Rhinitis	16	22	14
	Upper Resp Tract Infection	21	20	18
Urinary System Disorder	Urinary Tract Infection	3	4	2

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

Adverse events reported by less than 3% of the patients receiving PROVENTIL HFA Inhalation Aerosol, and by a greater proportion of PROVENTIL HFA Inhalation Aerosol patients than placebo patients, which have the potential to be related to PROVENTIL HFA Inhalation Aerosol include: dysphonia, increased sweating, dry mouth, chest pain, edema, rigors, ataxia, leg cramps, hyperkinesia, eructation, flatulence, tinnitus, diabetes mellitus, anxiety, depression, somnolence, rash. Palpitation and dizziness have also been observed with PROVENTIL HFA Inhalation Aerosol.

Adverse events reported in a 4-week pediatric clinical trail comparing PROVENTIL HFA Inhalation Aerosol and a CFC 11/12 propelled albuterol inhaler occurred at a low incidence rate and were similar to those seen in the adult trials.

In small, cumulative dose studies, tremor, nervousness, and headache appeared to be dose related.

Rare cases of urticaria, angioedema, rash, bronchospasm, and oropharyngeal edema have been reported after the use of inhaled albuterol. In addition, albuterol, like other sympathomimetic agents, can cause adverse reactions such as hypertension, angina, vertigo, central nervous system stimulation, insomnia, headache, and drying or irritation of the oropharynx.

OVERDOSE

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, eg, 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, and insomnia.

Hypokalemia may also occur. As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of PROVENTIL® HFA Inhalation Aerosol. Treatment consists of discontinuation of PROVENTIL HFA Inhalation Aerosol 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 PROVENTIL HFA Inhalation Aerosol.

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

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 two inhalations repeated every 4 to 6 hours. More frequent administration or a larger number of inhalations is not recommended. In some patients, one inhalation every 4 hours may be sufficient. Each actuation of PROVENTIL® HFA Inhalation Aerosol delivers 108 mcg of albuterol sulfate (equivalent to 90 mcg of albuterol base) from the mouthpiece. 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 four “test sprays” into the air, away from the face.

Exercise Induced Bronchospasm Prevention: The usual dosage for adults and children 4 years of age and older is two inhalations 15 to 30 minutes before exercise.

To maintain proper use of this product, it is important that the mouthpiece 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 PRECAUTIONS, Information for Patients section). Keeping the plastic mouthpiece clean is very important to prevent medication build-up and blockage. The inhaler may cease to deliver medication if not properly cleaned and air dried thoroughly. If the mouthpiece becomes blocked, washing the mouthpiece will remove the blockage.

If a previously effective dose 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, eg, corticosteroids.

HOW SUPPLIED

PROVENTIL® HFA (albuterol sulfate) Inhalation Aerosol is supplied as a pressurized aluminum canister with a yellow plastic actuator and orange dust cap each in boxes of one. Each actuation delivers 120 mcg of albuterol sulfate from the valve and 108 mcg of albuterol sulfate from the mouthpiece (equivalent to 90 mcg of albuterol base). Canisters with a labeled net weight of 6.7 g contain 200 inhalations (NDC 0085-1132-01).

Rx only. Store between 15°-25°C (59°-77°F). For best results, canister should be at room temperature before use.

SHAKE WELL BEFORE USING.

The yellow actuator supplied with PROVENTIL HFA Inhalation Aerosol should not be used with any other product canister, and actuator from other products should not be used with a PROVENTIL HFA Inhalation Aerosol 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 the labeled number of actuations have been used.

WARNING: Avoid spraying in eyes. Contents under pressure. Do not puncture or incinerate. Exposure to temperatures above 120°F may cause bursting. Keep out of reach of children.

PROVENTI®L HFA Inhalation Aerosol does not contain chlorfluorocarbons (CFCs) as the propellant.

Developed and Manufactured by

3M Health Care Limited

Loughborough UK

or

3M Drug Delivery Systems

Northridge, CA 91324

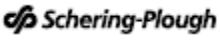
for

Schering Corporation,

a subsidiary of

Schering-Plough Corporation,

Kenilworth, NJ 07033 USA



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Rev. 02/09

Attention Health Care Professional

Detach Patient's Instructions for Use from package insert and dispense with the product.

PROVENTIL® HFA

(albuterol sulfate)

Inhalation Aerosol

FOR ORAL INHALATION ONLY

Patient's Instructions for Use

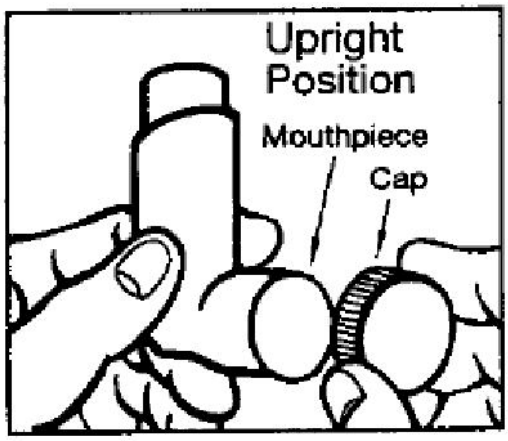

Figure 1

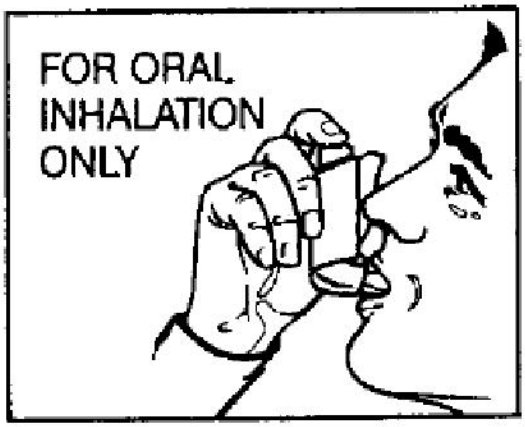

Figure 2

Before using your PROVENTIL® HFA (albuterol Sulfate) Inhalation Aerosol, read complete instructions carefully. Children should use PROVENTIL HFA Inhalation Aerosol under adult supervision, as instructed by the patient's doctor

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

1. SHAKE THE INHALER WELL immediately before each use. **Then remove the cap from the mouthpiece** (see Figure 1). **Check mouthpiece for foreign objects prior to use.** Make sure the canister is fully inserted into the actuator.
2. As with all aerosol medications, 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. Prime by releasing four “test sprays” into the air, away from your face.
3. BREATH 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 its upright position (see Figure 2) and closing the lips around it.
4. WHILE BREATHING IN DEEPLY AND SLOWLY THROUGH THE MOUTH, FULLY DEPRESS THE TOP OF THE METAL CANISTER with your index finger (see Figure 2).
5. HOLD YOUR BREATH AS LONG AS POSSIBLE, up to 10 seconds. Before breathing out, remove the inhaler from your mouth and release your finger from the canister.
6. If your physician has prescribed additional puffs, wait 1 minute, shake the inhaler again, and repeat steps 3 through 5. Replace the cap after use.
7. KEEPING THE PLACTIC MOUTHPIECE CLEAN IS EXTREMELY IMPORTANT TO PREVENT MEDICATION BUILD-UP AND BLOCKAGE. THE MOUTHPIECE SHOULD BE WASHED, SHAKEN

TO REMOVE EXCESS WATER, AND AIR DRIED THOROUGHLY AT LEAST ONCE A WEEK. INHALER MAY STOP SPRAYING IF NOT PROPERLY CLEANED.

Routine cleaning instructions:

Step 1. To clean, remove the canister and mouthpiece cap. Wash the mouthpiece through the top and bottom with warm running water for 30 seconds at lease once a week (see Figure A). **Never immerse the metal canister in water.**

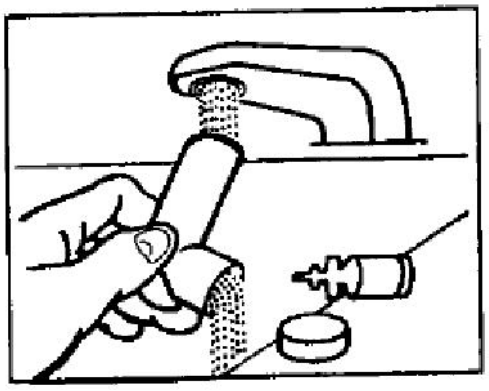

Figure A

Wash mouthpiece under warm running water.

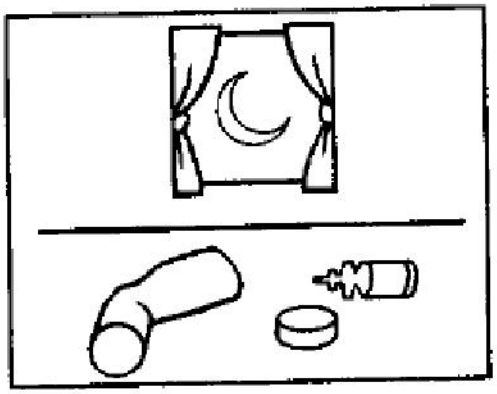

Figure B

Allow mouthpiece to dry, such as overnight.

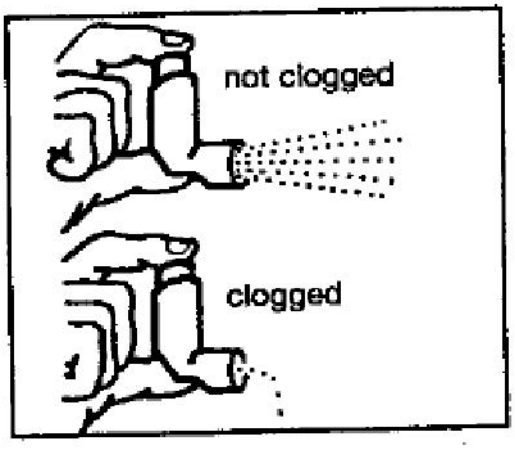

Figure C

When blocked, little or no medicine comes out.

Step 2. To dry, shake off excess water and let the mouthpiece air dry thoroughly, such as overnight (see Figure B). When the mouthpiece is dry, replace the canister and the mouthpiece cap. Blockage from medication buildup is more likely to occur if the mouthpiece is not allowed to air dry thoroughly.

IF YOUR INHALER HAS BECOME BLOCKED (little or no medication coming out of the mouthpiece, see Figure C), wash the mouthpiece as described in Step 1 and air dry thoroughly as described in Step 2.

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

8. The correct amount of medication in each inhalation cannot be assured after 200 actuations, even though the canister is not completely empty. The canister should be discarded when the labeled number of actuations have been used. Before you reach the specific number of actuations, you should consult your physician to determine whether a

refill is needed. Just as you should not take extra doses without consulting your physician, you also should not stop using PROVENTIL HFA Inhalation Aerosol without consulting your physician.

You may notice a slightly different taste or spray force than you are used to with PROVENTIL HFA Inhalation Aerosol, compared to other albuterol inhalation aerosol products.

DOSAGE:

Use only as directed by your physician.

WARNINGS:

The action of PROVENTIL® HFA Inhalation Aerosol should last up to 4 to 6 hours. PROVENTIL HFA Inhalation Aerosol should not be used more frequently than recommended. Do not increase the number of puffs or frequency of doses of PROVENTIL HFA Inhalation Aerosol without consulting your physician. If you find that treatment with PROVENTIL HFA Inhalation Aerosol becomes less effective for symptomatic relief, your symptoms become worse, and/or you need to use the product more frequently than usual, medical attention should be sought immediately. While you are taking PROVENTIL HFA Inhalation Aerosol, other inhaled drugs should be taken only as directed by your physician. If you are pregnant or nursing, contact your physician about the use of PROVENTIL HFA Inhalation Aerosol.

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

For best results, use at room temperature. Avoid exposing product to extreme heat and cold.

Shake well before use.

Contents Under Pressure.

Do not puncture. Do not store near hear or open flame. Exposure to temperatures above 120°F may cause bursting. Never throw container into fire or incinerator. Store between 15° - 25°C (59° - 77°F). Avoid spraying in eyes. Keep out of reach of children.

Further Information: Your PROVENTIL® HFA (albuterol sulfate) Inhalation Aerosol does not contain chlorofluorocarbons (CFCs) as the propellant. Instead, the inhaler contains a hydrofluoroalkane (HFA-134a) as the propellant.

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