PRODUCT MONOGRAPH

Pr VENTOLIN HFA

salbutamol pressurised inhalation, suspension
Mfr. Std.

100 mcg salbutamol (as salbutamol sulfate) / metered dose

Bronchodilator

(beta$_2$-adrenergic agonist)

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PrVENTOLIN HFA

salbutamol pressurised inhalation, suspension
Mfr. Std.

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral Inhalation	pressurised inhalation, suspension/ 100 mcg salbutamol (as salbutamol sulfate)	1, 1, 1, 2-tetrafluoroethane (HFA-134a)

INDICATIONS AND CLINICAL USE

Adults and Children (4 years and older):
VENTOLIN HFA (salbutamol pressurised inhalation, suspension) is indicated for:

- the symptomatic relief and prevention of bronchospasm due to bronchial asthma, chronic bronchitis and other chronic bronchopulmonary disorders in which bronchospasm is a complicating factor.
- the prevention of exercise-induced bronchospasm.

Pediatrics (<4 years of age):
The safety and efficacy in children below the age of 4 years has not been established.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container (see DOSAGE FORMS, COMPOSITION AND PACKAGING).
- As a tocolytic in patients at risk of premature labour or threatened abortion.

WARNINGS AND PRECAUTIONS

General

Patients should always carry their VENTOLIN HFA to use immediately if an episode of asthma is experienced. If therapy does not produce a significant improvement or if the patient's condition worsens, medical advice must be sought to determine a new plan of treatment. In the case of acute or rapidly worsening dyspnea, a doctor should be consulted immediately.

Deterioration of Asthma

Asthma may deteriorate over time. If the patient needs to use VENTOLIN HFA more often than usual, this may be a sign of worsening asthma. This requires re-evaluation of the patient and treatment plan and consideration of adjusting the asthma maintenance therapy. If treatment with VENTOLIN HFA alone is not adequate to control asthma, concomitant anti-inflammatory therapy should be part of the treatment regimen. It is essential that the physician instruct the patient in the need for further evaluation if the patient's asthma becomes worse (see DOSAGE AND ADMINISTRATION).

Cardiovascular

In individual patients, any beta$_2$-adrenergic agonist, including salbutamol, may have a clinically significant cardiac effect. Care should be taken with patients suffering from cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias and hypertension. Special care and supervision are required in patients with idiopathic hypertrophic subvalvular aortic stenosis, in whom an increase in the pressure gradient between the left ventricle and the aorta may occur, causing increased strain on the left ventricle.

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.

Endocrine and Metabolism

Metabolic Effects

In common with other beta-adrenergic agents, salbutamol sulfate can induce reversible metabolic changes such as potentially serious hypokalemia, particularly following nebulised or especially infused administration. Particular caution is advised in acute severe asthma since hypokalemia may be potentiated by concomitant treatment with xanthine derivatives, steroids and diuretics and by hypoxia. Hypokalemia will increase the susceptibility of digitalis-treated patients to cardiac arrhythmias. It is recommended that serum potassium levels be monitored in such situations.

Care should be taken with patients with diabetes mellitus. Salbutamol can induce reversible hyperglycemia during nebulised administration or especially during

infusions of the drug. The diabetic patient may be unable to compensate for this and the development of ketoacidosis has been reported. Concurrent administration of corticosteroids can exaggerate this effect.

Care should be taken with patients with hyperthyroidism.

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

Care should be taken in patients who are unusually responsive to sympathomimetic amines.

Neurologic
Care should be taken with patients with convulsive disorders.

Respiratory
As with other inhaled medications, paradoxical bronchospasm may occur characterized by an immediate increase in wheezing after dosing. This should be treated immediately with an alternative presentation or a different fast-acting inhaled bronchodilator to relieve acute asthmatic symptoms. VENTOLIN HFA should be discontinued immediately, the patient assessed and if necessary, alternative therapy instituted (see ADVERSE REACTIONS).

Special Populations

Pregnant Women: Salbutamol has been in widespread use for many years in humans without apparent ill consequence. However, there are no adequate and well-controlled studies in pregnant women and there is little published evidence of its safety in the early stages of human pregnancy. Administration of any drug to pregnant women should only be considered if the anticipated benefits to the expectant woman are greater than any possible risks to the fetus (see TOXICOLOGY, Teratogenicity Studies).

During worldwide marketing experience, rare cases of various congenital anomalies, including cleft palate and limb defects have been reported in the offspring of patients being treated with salbutamol. Some of the mothers were taking multiple medications during their pregnancies. Because no consistent pattern of defects can be discerned, and baseline rate for congenital anomalies is 2-3%, a relationship with salbutamol use cannot be established.

Labour & Delivery: Because of the potential for beta-agonist interference with uterine contractility, use of VENTOLIN HFA for relief of bronchospasm during labour should be restricted to those patients in whom the benefits clearly outweigh the risks.

Nursing Women: Plasma levels of salbutamol sulfate and HFA-134a after inhaled therapeutic doses are very low in humans, but it is not known whether the components are excreted in human milk. Because of the potential for tumorigenicity shown for salbutamol in some animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the benefit of the drug to the mother. It is not known whether salbutamol in breast milk has a harmful effect on the neonate.

Pediatrics (4 to < 12 years): The use of metered-dose inhalers in children depends on the ability of the individual child to learn the proper use of this device. Metered-dose inhalers with spacers are recommended for children under 5 years of age, especially for administration of inhaled corticosteroids. Conversion from a face mask to a mouthpiece is strongly encouraged as soon as the age and the cooperation of the child permit.

During inhalation, children should be assisted or supervised by an adult who knows the proper use of the device.

Rarely, in children, hyperactivity occurs and occasionally, sleep disturbances, hallucination or atypical psychosis have been reported.

Pediatrics (< 4 years of age): The safety and efficacy in children below the age of 4 years has not been established.

Geriatrics: As with other $beta_2$-agonists, special caution should be observed when using VENTOLIN HFA in elderly patients who have concomitant cardiovascular disease that could be adversely affected by this class of drug.

Monitoring and Laboratory Tests
In accordance with the present practice for asthma treatment, patient response should be monitored clinically and by lung function tests.

Monitoring Control of Asthma
Failure to respond for at least three hours to a previously effective dose of VENTOLIN HFA indicates a deterioration of the condition and the physician should be contacted promptly. Patients should be warned not to exceed the recommended dose as there may be adverse effects associated with excessive dosing.

The increasing use of fast-acting, short duration inhaled $beta_2$-adrenergic agonists to control symptoms indicates deterioration of asthma control and the patient's therapy plan should be reassessed. In worsening asthma it is inadequate to increase $beta_2$-agonist use only, especially over an extended period of time. In the case of acute or rapidly worsening dyspnea, a doctor should be consulted immediately. Sudden or progressive deterioration in asthma control is potentially life threatening; the treatment plan must be re-evaluated, and consideration be given to corticosteroid therapy (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

As with other bronchodilator inhalation therapy, the potential for paradoxical bronchospasm should be kept in mind. If it occurs, the preparation should be discontinued immediately and alternative therapy instituted.

Potentially serious hypokalemia may result from beta$_2$-agonist therapy primarily from parenteral and nebulised routes of administration (see WARNINGS and PRECAUTIONS, Endocrine and Metabolism).

Peripheral vasodilation and a compensatory small increase in heart rate may occur in some patients. Cardiac arrhythmias (including atrial fibrillation, supraventricular tachycardia, extrasystoles) have been reported, usually in susceptible patients.

Other adverse reactions associated with salbutamol are nervousness and tremor. In some patients inhaled salbutamol may cause a fine tremor of skeletal muscle, particularly in the hands. This effect is common to all beta$_2$-adrenergic agonists. Adaptation occurs during the first few days of dosing and the tremor usually disappears as treatment continues.

In addition, salbutamol, like other sympathomimetic agents, can cause adverse effects such as drowsiness, flushing, restlessness, irritability, chest discomfort, difficulty in micturition, hypertension, angina, vomiting, vertigo, central nervous system stimulation, hyperactivity in children, unusual taste and drying or irritation of the oropharynx, headache, palpitations, transient muscle cramps, insomnia, nausea, weakness and dizziness.

Immediate hypersensitivity reactions including angioedema, urticaria, bronchospasm, hypotension, rash, oropharyngeal oedema, anaphylaxis and collapse have been reported very rarely.

Rarely, in children, hyperactivity occurs and occasionally, sleep disturbances, hallucination or atypical psychosis have been reported.

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

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, VENTOLIN inhalation aerosol (CFC formulation), and an HFA-134a placebo inhaler.

Table 1 Adverse experience incidence (% of patients) in two large 12-week adolescent and adult clinical trials*

	VENTOLIN HFA n= 202 (% patients)	VENTOLIN (CFC formulation) n= 207 (% patients)	Placebo (HFA-134a) n= 201 (% patients)
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% 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 VENTOLIN inhalation aerosol (CFC formulation) were similar. Results in a 2-week pediatric clinical study (n=35) showed that the adverse event profile was generally similar to that of the adult.

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, cough, lung disorders, tachycardia, and extrasystoles. Palpitation and dizziness have also been observed with VENTOLIN HFA.

DRUG INTERACTIONS

Drug-Drug Interactions

Table 2 Established or Potential Drug-Drug Interactions

Drug type	Ref	Effect	Clinical comment
Monoamine oxidase inhibitors or tricyclic antidepressants	CS	May potentiate action of salbutamol on cardiovascular system.	Salbutamol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants.
Other inhaled sympathomimetic bronchodilators or epinephrine	CS	May lead to deleterious cardiovascular effects.	Other inhaled sympathomimetic bronchodilators or epinephrine should not be used concomitantly with salbutamol. If additional adrenergic drugs are to be administered by any route to the patient using inhaled salbutamol, the adrenergic drugs should be used with caution. Such concomitant use must be individualised and not given on a routine basis. If regular co-administration is required then alternative therapy must be considered.
Beta-blockers	CS	May effectively antagonize the action of salbutamol.	Beta-adrenergic blocking drugs, especially the non-cardioselective ones, such as propranolol, should not usually be prescribed together.
Diuretics	CS	May lead to ECG changes and/or hypokalemia although the clinical significance of these effects is not known.	The ECG changes and/or hypokalemia that may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Caution is advised in the co-administration of beta-agonists with non-potassium sparing diuretics.
Digoxin	CS	May lead to a decrease in serum digoxin levels, although the clinical significance of these findings for patients with obstructive airways disease who are receiving salbutamol and digoxin on a chronic basis is unclear.	Mean decreases of 16-22% in serum digoxin levels were demonstrated after single dose intravenous and oral administration of salbutamol, respectively, to normal volunteers who had received digoxin for 10 days. It would be prudent to carefully evaluate serum digoxin levels in patients who are currently receiving digoxin and salbutamol.

Legend: CS = Class Statement

DOSAGE AND ADMINISTRATION

Dosing Considerations

The dosage should be individualised, and the patient's response should be monitored by the prescribing physician on an ongoing basis.

Increasing demand for VENTOLIN HFA in bronchial asthma is usually a sign of poorly controlled or worsening asthma and indicates that the patient should be re-evaluated, the treatment plan should be reviewed and the regular asthma controller treatment should be optimized. If treatment with VENTOLIN HFA alone is not adequate to control asthma, concomitant anti-inflammatory therapy should be part of the treatment regimen.

If a previously effective dose fails to provide the usual relief, or the effects of a dose last for less than three hours, patients should seek prompt medical advice since this is usually a sign of worsening asthma.

As there may be adverse effects associated with excessive dosing, the dosage or frequency of administration should only be increased on medical advice. However, if a more severe attack has not been relieved by the usual dose, additional doses may be required. In these cases, patients should immediately consult their doctors or the nearest hospital.

Recommended Dose and Dosage Adjustment

	Relief of Acute Episodes of Bronchospasm*	**Prevention of Bronchospasm****	**Prevention of Exercise-induced Bronchospasm**	**Maximum Daily Dose (Total daily dose should not exceed)**
Adults and Adolescents (≥ 12 years)	One to two puffs [100 to 200 mcg salbutamol] as needed.	One to two puffs [100 to 200 mcg salbutamol] every 4 to 6 hours to a maximum of four times per day.	Two puffs [200 mcg salbutamol] 15 minutes before exercise.	Eight puffs [800 mcg salbutamol].
Children (4 to < 12 years)	One puff [100 mcg salbutamol] as needed. May be increased to two puffs (200 mcg salbutamol), if required.	One puff [100 mcg salbutamol] every 4 to 6 hours to a maximum of four times per day.	One puff [100 mcg salbutamol] 15 minutes before exercise. May be increased to two puffs (200 mcg salbutamol), if required.	Four puffs [400 mcg salbutamol].

* If a more severe attack has not been relieved by the usual dose, further inhalations may be needed every 4 to 6 hours. More frequent or a larger number of inhalations is not recommended. In these cases, patients should immediately consult their doctors or the nearest hospital.
**Despite appropriate maintenance therapy, regular use of the VENTOLIN HFA remains necessary for the control of bronchospasm due to bronchial asthma.

Missed Dose
If a single dose is missed, instruct the patient to take the next dose when it is due or if they become wheezy.

Administration
VENTOLIN HFA is administered by the inhaled route only. To ensure administration of the proper dose of the drug, the patient should be instructed by the physician or other health professional in the proper use of the pressurised inhalation, suspension.

Inhaler actuation should be synchronised with inspiration to ensure optimum delivery of drug to the lungs. In patients who find coordination of a pressurised metered dose inhaler difficult, a spacer may be used with VENTOLIN HFA.

The use of open mouth technique to administer VENTOLIN HFA has not been investigated in clinical trials.

Priming: It is recommended to test spray VENTOLIN HFA into the air four times, away from the face, before using for the first time and in cases where the aerosol has not been used for more than 5 days.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Symptoms and signs

The most common signs and symptoms of overdose with salbutamol are transient beta agonist pharmacologically mediated events (see Warning and Precautions and Adverse Reactions). Overdosage may cause tachycardia, cardiac arrhythmia, hypokalemia, hypertension and, in extreme cases, sudden death. Serum potassium levels should be monitored.

Lactic acidosis has been reported in association with high therapeutic doses as well as overdoses of short-acting beta-agonist therapy, therefore monitoring for elevated serum lactate and consequent metabolic acidosis (particularly if there is persistence or worsening of tachypnea despite resolution of other signs of bronchospasm such as wheezing) may be indicated in the setting of overdose.

Treatment

Consideration should be given to discontinuation of treatment and appropriate symptomatic therapy. To antagonise the effect of salbutamol, the judicious use of a cardioselective beta-adrenergic blocking agent (e.g. metoprolol, atenolol) may be considered, bearing in mind the danger of inducing an asthmatic attack. There is insufficient evidence to determine if dialysis is beneficial for overdosage of VENTOLIN HFA.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Salbutamol produces bronchodilation through stimulation of $beta_2$-adrenergic receptors in bronchial smooth muscle, thereby causing relaxation of bronchial muscle fibres. This action is manifested by an improvement in pulmonary function as demonstrated by spirometric measurements. Although $beta_2$-receptors are the predominant adrenergic receptors in bronchial smooth muscle and $beta_1$-receptors are the predominant receptors in the heart, there are also $beta_2$-receptors in the human heart comprising 10% to 50% of the total beta-adrenergic receptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective $beta_2$-agonists may have cardiac effects. At therapeutic doses, salbutamol has little action on the $beta_1$-adrenergic receptors in cardiac muscle.

A measurable decrease in airway resistance is typically observed within 5 to 15 minutes after inhalation of salbutamol. The maximum improvement in pulmonary function usually occurs 60 to 90 minutes after salbutamol treatment, and significant bronchodilator activity has been observed to persist for 3 to 6 hours.

Pharmacokinetics

After inhalation of recommended doses of salbutamol, plasma drug levels are very low. When 100 mcg of tritiated salbutamol aerosol was administered to two normal volunteers, plasma levels of drug-radioactivity were insignificant at 10, 20 and 30 minutes following inhalation. The plasma concentration of salbutamol may be even less as the amount of plasma drug-radioactivity does not differentiate salbutamol from its principal metabolite, a sulfate ester. In a separate study, plasma salbutamol levels ranged from less than 0.5 ng/mL to 1.6 ng/mL in ten asthmatic children one hour after inhalation of 200 micrograms of salbutamol.

Approximately 10% of an inhaled salbutamol dose is deposited in the lungs. Eighty-five per cent of the remaining salbutamol administered from a metered-dose inhaler is swallowed, however, since the dose is low (100 to 200 mcg), the absolute amount swallowed is too small to be of clinical significance. Salbutamol is only weakly bound to plasma proteins. Results of animal studies indicate that following systemic administration, salbutamol does not cross the blood-brain barrier but does cross the placenta using an in vitro perfused isolated human placenta model. It has been found that between 2% and 3% of salbutamol was transferred from the maternal side to the fetal side of the placenta.

Salbutamol is metabolized in the liver. The principal metabolite in humans is salbutamol-o-sulfate, which has negligible pharmacologic activity. Salbutamol may also be metabolized by oxidative deamination and/or conjugation with glucuronide.

Salbutamol is longer acting than isoprenaline 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. Salbutamol and its metabolites are excreted in the urine (>80%) and the feces (5% to 10%). Plasma levels are insignificant after administration of aerosolized salbutamol; the plasma half-life ranges from 3.8 to 7.1 hours.

Propellant HFA-134a is devoid of pharmacological activity except at very high doses in animals (140 to 800 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 CFCs, which have been used extensively in metered-dose inhalers.

In animals and humans, propellant HFA-134a was eliminated rapidly in the breath, with no evidence of metabolism or accumulation in the body. 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.

STORAGE AND STABILITY

Replace the mouthpiece cover firmly and snap it into position. Keep out of the sight and reach of children. Store at a temperature between 15°C and 25°C.

SPECIAL HANDLING INSTRUCTIONS

The contents of VENTOLIN HFA are under pressure. The container may explode if heated. Do not place in hot water or near radiators, stoves or other sources of heat. Even when empty, do not puncture or incinerate container. As with most inhaled medications in aerosol canisters, the therapeutic effect of this medication may decrease when the canister is cold.

DOSAGE FORMS, COMPOSITION AND PACKAGING

VENTOLIN HFA is a pressurized metered dose inhaler (MDI) consisting of an aluminum canister fitted with a metering valve. Each canister is fitted into the supplied blue plastic actuator. A blue dust cap is fitted over the actuator's mouthpiece when not in use. Each depression of the valve delivers 100 mcg of salbutamol (as sulfate).

VENTOLIN HFA contains a micro-crystalline suspension of salbutamol sulfate in propellant HFA-134a (1,1,1,2-tetrafluoroethane). It contains no excipients. Each actuation delivers 100 micrograms of salbutamol (as sulfate). This product does not contain chlorofluorocarbons (CFCs) as the propellant.

VENTOLIN HFA is available in 200 dose formats.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

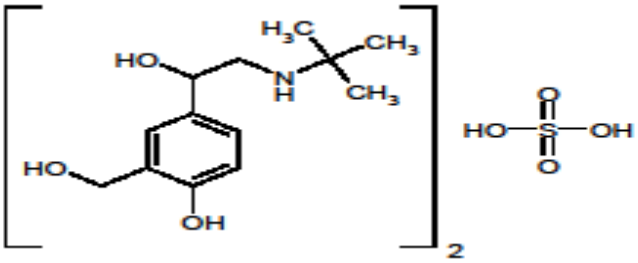
Drug Substance

Proper name: salbutamol sulfate

Chemical name: α^1-[(*tert*-butylamino)methyl]-4-hydroxy-*m*-xylene-α, α'-diol sulfate (2:1) (salt)

Molecular formula and molecular mass: $(C_{13}H_{21}NO_3)_2XH_2SO_4$ 576.7

Structural formula:



Physicochemical properties:

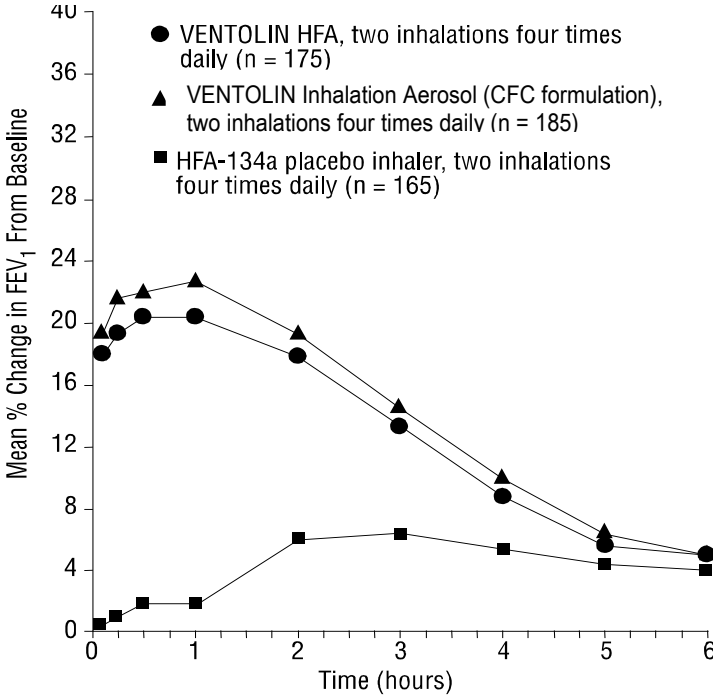
Description	White to almost white powder.
Solubility	Soluble in water and slightly soluble in methanol.
pKa Values	9.4 and 10.0.
Distribution Coefficient	The distribution coefficient between two phases of octanol and water, as determined by HPLC, at pH 9.9 is 0.23.
Melting Point	Approximately 156°C.

CLINICAL TRIALS

In two 12-week, randomized, double-blind studies, VENTOLIN HFA pressurised inhalation, suspension (202 patients) was compared to VENTOLIN inhalation aerosol (CFC formulation) (207 patients) and an HFA-134a placebo inhaler (201 patients) in adolescent and adult patients with mild to moderate asthma. The studies were similar in design.

One study evaluated the safety and efficacy of VENTOLIN HFA in patients with asthma, and the second study evaluated the effects of switching from VENTOLIN inhalation aerosol (CFC formulation) to VENTOLIN HFA. Serial forced expiratory volume in 1 second (FEV_1) measurements (shown below as percent change from test-day baseline at week 12, n = 525) demonstrated that two inhalations of VENTOLIN HFA produced significantly greater improvement in pulmonary function than placebo and produced outcomes that were clinically comparable to VENTOLIN inhalation aerosol (CFC formulation) . Patients taking the HFA-134a placebo inhaler also took VENTOLIN HFA for asthma symptom relief on an as-needed basis. These patients produced similar morning predose baseline FEV_1 values to patients taking VENTOLIN HFA and VENTOLIN inhalation aerosol (CFC formulation) taken four times daily (plus as-needed for asthma symptom relief) throughout the 12-week study period.

FEV_1 as Percent Change From Predose in Two Large, 12-Week Clinical Trials



The median time to onset of a 15% increase in FEV_1 was 4.8 minutes, and the median time to peak effect was 48 to 60 minutes. The mean duration of effect as measured by a 15% increase in FEV_1 was approximately 3 hours. In some patients, duration of effect was as long as 6 hours.

In a 2-week, randomized, double-blind study, VENTOLIN HFA was compared to VENTOLIN inhalation aerosol (CFC formulation) 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 VENTOLIN inhalation aerosol (CFC formulation).

The median time to onset of a 15% increase in peak expiratory flow rate (PEFR) was 5 to 10 minutes, and the median time to peak effect was approximately 60 minutes. The mean duration of effect as measured by a 15% increase in PEFR was 2.5 hours. In some patients, duration of effect was as long as 6 hours.

In a clinical study in adult patients with asthma, two 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 VENTOLIN inhalation aerosol (CFC formulation).

DETAILED PHARMACOLOGY

Animals

In vitro studies and *in vivo* pharmacologic studies have demonstrated that salbutamol has a preferential effect on $beta_2$-adrenergic receptors compared with isoprenaline. While it is recognized that $beta_2$-adrenergic receptors are the predominant receptors in bronchial smooth muscle, recent data indicate that there is a population of $beta_2$-receptors in the human heart existing in a concentration between 10% and 50%. The precise function of these, however, is not yet established.

The pharmacologic effects of beta-adrenergic agonist drugs, including salbutamol, are at least in part attributable to stimulation through beta-adrenergic receptors of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cAMP). Increased cAMP levels are associated with relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

The muscle-relaxing effect of salbutamol was found to be more prolonged than when the effect was induced by isoprenaline. As suggested from the results of experiments in isolated animal tissues, salbutamol has been shown to produce a substantial bronchodilator effect in the intact animal. In the anaesthetised guinea pig, salbutamol

completely prevents acetylcholine-induced bronchospasm at the dose of 100 micrograms/kg intravenously.

Administration of salbutamol aerosol at a dose of 250 micrograms/mL for one minute to guinea pigs prevented acetylcholine-induced bronchospasm without any chronotropic effect. A prolonged bronchodilator effect of salbutamol compared to isoprenaline (in terms of mean times to dyspnea following acetylcholine challenge) was observed following oral administration of salbutamol to conscious guinea pigs. The protective action of salbutamol in this case persisted for up to six hours.

In anaesthetised cats and dogs, salbutamol prevented the bronchospasm elicited by vagal stimulation without any significant effect on heart rate and blood pressure. Comparative tests of salbutamol and isoprenaline in isolated dog papillary muscle, guinea pig atrial muscle and human heart muscle have shown that the effect of salbutamol on $beta_1$-adrenergic receptors in the heart is minimal.

In a number of studies using guinea pig atria, it was found that on a weight-to-weight basis, salbutamol was from 2,000 to 2,500 times less active in terms of inotropic effect and 500 times less active in terms of chronotropic effect than isoprenaline. Compared to orciprenaline, salbutamol was about 40 times less active in terms of inotropic effect and four times less potent in terms of chronotropic effect. Salbutamol has been shown to be one-fifth as potent a vasodilator in skeletal muscle as isoprenaline, as measured by effects on hind limb blood flow in the anaesthetised dog. In the perfused rabbit ear, salbutamol was shown to possess only one-tenth the activity of isoprenaline in terms of vasodilating effect. In dogs, salbutamol was shown to increase coronary blood flow, which was subsequently shown to be the result of a direct coronary vasodilating effect of salbutamol.

In six dogs with right-sided cardiac by-pass, salbutamol, given at the dose of 25 micrograms/kg, improved left ventricular efficiency and increased coronary blood flow. Recent studies in minipigs, rodents, and dogs recorded the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines were administered concurrently. The significance of these findings when applied to humans is currently unknown.

Animal studies show that salbutamol does not pass the blood brain barrier.

TOXICOLOGY

Acute Toxicity

Species (n)	Oral LD_{50}	Intravenous LD_{50}
Mouse (10)	>2000 mg/kg	72 mg/kg
Rat (10)	>2000 mg/kg	60 mg/kg

Rat (n)	Intraperitoneal LD_{50}
Newborn (155)	216 mg/kg
Weanling (100)	524 mg/kg
2 week old (90)	437 mg/kg

The rate of respiration in test animals initially increased, but subsequently became abnormally slow and deep. Death, preceded by convulsions and cyanosis, usually occurred within four hours after drug administration.

Rabbits, cats and dogs survived a single dose of 50 mg/kg salbutamol.

Intermediate (Four Months) Toxicity

Rats received salbutamol twice daily, in oral doses from 0.5 to 25 mg/kg, on an increasing scale. The only significant hematological changes were a small increase in hemoglobin and packed cell volume. BUN and SGOT values were elevated while blood glucose and plasma protein levels remained unchanged. Pituitaries had increased amount of PAS-positive material in the cleft at the higher dose levels.

Salbutamol was given to dogs twice daily, in oral doses from 0.05 to 12.5 mg/kg, on an increasing scale. The rate of increase of hemoglobin and packed cell volume was depressed, particularly at higher doses. Leukocyte count decreased after sixteen weeks of treatment at each dose level. Platelet count was increased after eight weeks at the highest dose. No significant biochemical effects were observed. The only significant histological change was the appearance of corpora amylacea in the stomach which was attributed to altered mucus secretion. Inhalation of 1000 mcg of salbutamol CFC 11/12-propelled aerosol twice daily for three months did not produce any morphological changes in the lungs, trachea, lymph nodes, liver or heart.

Long-Term Toxicity

Fifty female, Charles River CD Albino rats received salbutamol orally at 2, 10 and 50 mg/kg/day for one hundred and four weeks; fifty female Charles River CD Sprague-Dawley-derived rats received 20 mg/kg/day salbutamol orally for fifty weeks, and fifty female Charles River Long-Evans rats received 20 mg/kg/day salbutamol orally for ninety-six weeks. These rat studies demonstrated a dose-related incidence of mesovarian leiomyomas. No similar tumors were seen in mice.

Mutagenicity
In vitro tests involving four micro-organisms revealed no mutagenic activity.

Carcinogenicity
In a two-year study in the rat, salbutamol sulfate caused a significant dose-related increase in the incidence of benign leiomyomas of the mesovarium at doses corresponding to 111, 555, and 2,800 times the maximum human inhalation dose. In another study, the effect was blocked by the co-administration of propranolol. The relevance of these findings to humans is not known. An 18-month study in mice and a lifetime study in hamsters revealed no evidence of tumorigenicity.

Teratogenicity Studies
Salbutamol has been shown to be teratogenic in mice when given in doses corresponding to 14 times the human aerosol dose; when given subcutaneously in doses corresponding to 0.2 times the maximum human (child weighing 21 kg) oral dose; and when given subcutaneously in doses corresponding to 0.4 times the maximum human oral dose.

A reproduction study in CD-1 mice given salbutamol at doses of 0.025, 0.25, and 2.5 mg/kg subcutaneously, corresponding to 1.4, 14, and 140 times the maximum human aerosol dose respectively, 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. No cleft palates were observed at a dose of 0.025 mg/kg salbutamol. Cleft palate occurred in 22 of 72 (30.5%) fetuses treated with 2.5 mg/kg isoprenaline (positive control).

In rats, salbutamol treatment given orally at 0.5. 2.32, 10.75 and 50 mg/kg/day throughout pregnancy resulted in no significant fetal abnormalities. However, at the highest dose level there was an increase in neonatal mortality. Reproduction studies in rats revealed no evidence of impaired fertility.

Salbutamol had no adverse effect when given orally to Stride Dutch rabbits, at doses of 0.5, 2.32 and 10.75 mg/kg/day throughout pregnancy. At a dose of 50 mg/kg/day, which represents 2800 times the maximum human inhalation dose, cranioschisis was observed in 7 of 19 (37%) fetuses.

A reproduction study in New Zealand White rabbits using salbutamol sulfate/HFA-134a formulation, revealed enlargement of the frontal portion of the fontanelles in 6 of 95 (6%) and 15 of 107 (14%) fetuses at 28 and 149 mcg/kg, respectively (approximately 2/5 and 2 times, respectively, the maximum recommended human daily dose on a mg/m^2 basis), giving plasma levels of approximately 12 and 60 ng/mL, respectively.

PART III: CONSUMER INFORMATION

[Pr] VENTOLIN HFA
salbutamol pressurised inhalation, suspension
Mfr. Std.

This leaflet is part III of a three-part "Product Monograph" for VENTOLIN HFA and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about VENTOLIN HFA. Contact your doctor or pharmacist if you have any questions about the drug. Only a doctor can prescribe it for you. Never give it to someone else. It may harm them even if their symptoms are the same as yours.

ABOUT THIS MEDICATION

What the medication is used for:
VENTOLIN HFA is used in Adults and Children 4 years or older to:

- relieve bronchospasm
- prevent bronchospasm
- prevent bronchospasm caused by exercise

Bronchospasm is a sudden worsening of shortness of breath and wheezing.

The safety and effectiveness of VENTOLIN HFA in children under the age of 4 are not known.

What it does:
VENTOLIN HFA is one of a group of medicines called bronchodilators. VENTOLIN HFA relaxes the muscles in the walls of the small air passages in the lungs. This helps to open up the airways and so helps to relieve chest tightness, wheezing and cough so that you can breathe more easily.

When it should not be used:
Do not use VENTOLIN HFA if you are allergic to it or any of the components of its formulation or for the treatment of preterm labour or miscarriage.

What the medicinal ingredient is:
Salbutamol sulfate.

What the nonmedicinal ingredient is:
1, 1, 1, 2-tetrafluoroethane (HFA-134a).

What dosage forms it comes in:
VENTOLIN HFA is a pressurized metered dose inhaler containing 100 mcg of salbutamol per inhalation.
VENTOLIN HFA will deliver at least 200 puffs. However, after 200 puffs, the amount of drug delivered per spray may not be consistent. The canister should be discarded when 200 puffs have been used.

WARNINGS AND PRECAUTIONS

Before you use VENTOLIN HFA, talk to your doctor or pharmacist if:

- You have ever had to stop taking other medications for this illness because you were allergic to them or they caused problems.
- You are having treatment for a thyroid condition.
- You are having treatment for high blood pressure or a heart problem.
- You have diabetes.
- You have a past history of seizures.
- You have low levels of potassium in your blood (hypokalemia), especially if you are taking:
    - Drugs known as xanthine derivatives (such as theophylline)
    - Steroids to treat asthma
    - Water pills (diuretics)
- You are pregnant or intend to become pregnant. Taking VENTOLIN HFA during pregnancy may cause harm to your baby. Your doctor will consider the benefit to you and the risk to your baby of taking VENTOLIN HFA while you're pregnant.
- You are breastfeeding. It is not known if VENTOLIN HFA passes into breast milk.

If the relief of wheezing or chest tightness is not as good as usual, or the effect lasts for less than three hours, tell your doctor as soon as possible. If you notice a sudden worsening of your shortness of breath and wheeze shortly after taking your medicine, tell your doctor as soon as possible. It may be that your chest condition is worsening and you may need to add another type of medicine to your treatment.

You should always carry your VENTOLIN HFA with you to use immediately in case you experience an asthma attack.

Effects on Children:
Children may experience:

- Changes in sleep patterns
- Changes in behaviour such as restlessness, excitability (hyperactivity)
- Seeing or hearing things that are not there

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor, nurse, or pharmacist about all the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.

The following may interact with VENTOLIN HFA:

- Anti-depressants
- Allergy medication
- Blood pressure-lowering drugs, including propranolol
- Diuretics ("water pills")
- Bronchodilators used to open the airway (such as other asthma medication)
- Epinephrine
- Digoxin, a heart medication

PROPER USE OF THIS MEDICATION

VENTOLIN HFA **should only be inhaled**. Do not swallow.

If You Are Also Using an Inhaled Corticosteroid:
- Always use VENTOLIN HFA first
- Wait a few minutes
- Then use your inhaled corticosteroid.

Your doctor may prescribe VENTOLIN HFA regularly every day, or only for when you are wheezy or short of breath, or before you exercise. Use VENTOLIN HFA only as directed by your doctor.

The action of VENTOLIN HFA may last up to 6 hours and should last for at least 4 hours.

You should call your doctor immediately if:
- the effects of one dose last less than 3 hours;
- you notice a sudden worsening of your shortness of breath
- your symptoms gets worse;
- your usual dose does not provide relief of wheezing or chest tightness;
- you need to use VENTOLIN HFA more often than before

These may be signs that your asthma or chest condition is getting worse. Your doctor may want to reassess your treatment plan.

Do not increase the dose or the number of times you use your medicine without asking your doctor, as this may make you feel worse.

If you have to go into hospital for an operation, take your inhaler with you and tell the doctor what medicine(s) you are taking.

If your doctor decides to stop your treatment, do not keep any left over medicine unless your doctor tells you to.

Usual dose:
Adults and Adolescents 12 years or older

- **To relieve bronchospasm:** 1 to 2 puffs as needed. If you have a more severe attack, you can repeat the dose every 4 to 6 hours, and immediately consult your doctor or the nearest hospital.

- **To prevent bronchospasm:** 1 to 2 puffs repeated every 4 to 6 hours to a maximum four times a day.

- **To prevent bronchospasm caused by exercise:** 2 puffs 15 minutes before exercise.

Maximum dose – 8 puffs in a 24 hour period

Children 4-11 years
- **To relieve bronchospasm:** 1 puff as needed The dose may be increased to 2 puffs if required. Follow your doctor's instructions. If you have a more severe attack you can repeat the dose every 4 to 6 hours, and immediately consult your doctor or the nearest hospital.

- **To prevent bronchospasm:** 1 puff repeated every 4 to 6 hours to a maximum four times a day as prescribed by your doctor.

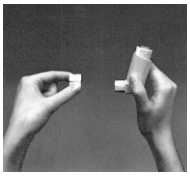
- **To prevent bronchospasm caused by exercise:** 1 puff 15 minutes before exercise. The dose may be increased to 2 puffs if required. Follow your doctor's instructions.

Maximum dose – 4 puffs in a 24 hour period

How to Prime VENTOLIN HFA:
Before using VENTOLIN HFA for the first time, or if your inhaler has not been used for more than 5 days, shake the inhaler well and release four puffs into the air to ensure that it works properly.

How to Use VENTOLIN HFA:
It is extremely important that you use your VENTOLIN HFA properly. This will ensure it is delivered correctly so that you receive maximum benefit. Carefully follow the instructions shown.

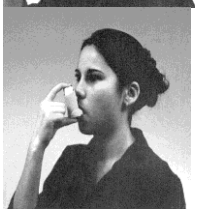
1. To remove the snap-on mouthpiece cover, hold between the thumb and forefinger, squeeze gently and pull apart as shown. Check inside and outside of the inhaler including the mouthpiece for the presence of loose objects.



2. Shake the inhaler well to ensure that any loose objects are removed and the contents of the inhaler are evenly mixed.

3. Hold the inhaler upright between fingers and thumb with your thumb on the base, below the mouthpiece. Breathe out as far as is comfortable.

4. Place the mouthpiece in your mouth between your teeth and close your lips around it, but do not bite it. Just after starting to breathe in through your mouth, press down on the top of the inhaler to release the drug while still breathing in steadily and deeply.



5. While holding your breath, take the inhaler from your mouth and take your finger from the top of the inhaler. Continue holding your breath for as long as is comfortable.

6. If you are to take further puffs, keep the inhaler upright and wait about half a minute before repeating steps 2 through 5.

7. Replace the mouthpiece cover by firmly pushing and snapping the cap into position to keep out dust and lint.

Important: Do not rush steps 3, 4, and 5. It is important that you start to breathe in as slowly as possible just before operating your inhaler. Practice in front of a mirror for the first few times. If you see "mist" coming from the top of your inhaler or the sides of your mouth, you should start again from step 2.

Children - VENTOLIN HFA should be used under the supervision of an adult who understands the proper use of the inhaler, and only as prescribed by the doctor. The adult must encourage the child (as described above) to exhale, and then trigger the spray immediately as inhalation begins. Use of a spacer with the inhaler is recommended for children under 5 years of age. Talk to your doctor if your child has difficulties using the inhaler.

How to clean VENTOLIN HFA :
Your inhaler should be cleaned at least once per week.

1. Pull the metal canister out of the plastic casing of the inhaler and remove the mouthpiece cover.
2. Rinse the plastic casing of the inhaler thoroughly under warm running water and then wash the plastic casing again through the mouthpiece. **Do not put the metal canister into water.**
3. Dry the plastic casing of the inhaler THOROUGHLY inside and out.
4. Replace the canister and mouthpiece cover.
5. After cleansing, release one puff into the air to make sure that the inhaler works.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms. Take this leaflet or your medication with you so that the hospital or poison control centre will know what you have taken.

If you accidentally take a **larger dose than prescribed**, you are more likely to get side effects like a faster heart beat, headaches and feeling shaky or restless. These effects usually wear off within a few hours, but you should tell your doctor as soon as possible.

Missed Dose:
If you forget to inhale a dose, do not worry, just inhale the next dose when it is due or if you become wheezy.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:

Effects on heart
- Hypertension

Effects on nervous system
- Headache
- Feeling a little shaky
- Feeling anxious or irritable
- Feeling tired or weak
- Trouble sleeping (insomnia)
- Hyperactivity in children
- Dizziness, vertigo
- Drowsiness

Effects on muscles and joints
- Muscle cramps
- Muscle pain

Other Effects
- Cough
- Respiratory infections and/or inflammation
- Diarrhea
- Nausea and vomiting
- Chest pain or discomfort
- Flushing
- Difficulty urinating
- Unusual taste in your mouth
- Dry or irritated throat

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	**Faster heart beat** than usual		✓	
Uncommon	**Irregular heart beat** (palpitations)		✓	
Rare	**Low Blood Potassium (hypokalemia):** muscle weakness and muscle spasms		✓	
	Hallucinations in Children: see or hear things that are not there		✓	
Very Rare	**Bronchospasm:** Sudden worsening of shortness of breath and wheezing shortly after using VENTOLIN HFA			✓
	Allergic Reactions: sudden wheeziness and chest pain or tightness; or swelling of eyelids, face, lips, tongue or throat.			✓
	Irregular Heart Beat (atrial fibrillation, supraventricular tachycardia, extrasystoles)		✓	

This is not a complete list of side effects. If you have any unexpected effects after receiving VENTOLIN HFA, contact your doctor or pharmacist.

HOW TO STORE IT

Keep out of sight and reach of children.

After use, replace the mouthpiece cover firmly and snap it into position. Do not use excessive force.

Store at a temperature between 15°C and 25°C. Do not keep any left over medicine unless your doctor tells you to.

Warning: The canister contents are under pressure. The canister may explode if heated. Do not place in hot water or near radiators, stoves or other sources of heat. Even when empty, do not puncture or incinerate canister.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by: Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or calling toll-free at 1-866-234-2345

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

You may need to read this leaflet again. **PLEASE DO NOT THROW IT AWAY** until you have finished your medicine.

This document plus the full product monograph, prepared for health professionals, can be found at:
http://www.gsk.ca;
Or by contacting the sponsor,
GlaxoSmithKline Inc.
7333 Mississauga Road
Mississauga, Ontario
L5N 6L4
1-800-387-7374.

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