PRODUCT MONOGRAPH

Pr ratio-SALBUTAMOL HFA

salbutamol sulphate inhalation aerosol

(100 micrograms salbutamol/metered dose)

Bronchodilator
beta$_2$-adrenergic stimulant

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salbutamol sulphate inhalation aerosol

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral inhalation	Inhalation aerosol: 100 mcg salbutamol	1,1,1,2-tetrafluoroethane (HFA-134a)

For a complete listing see Dosage Forms, Composition and Packaging section.

INDICATIONS AND CLINICAL USE

ratio-SALBUTAMOL HFA (salbutamol sulphate) inhalation aerosol 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. For a complete listing, see the Dosage Forms, Composition and Packaging section of the Product Monograph.

WARNINGS AND PRECAUTIONS

General

Patients should always carry their **ratio-SALBUTAMOL HFA** (salbutamol sulphate) inhalation aerosol 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.

Use of Anti-Inflammatory Agents

In accordance with the present practice for asthma treatment, concomitant anti-inflammatory therapy (eg. corticosteroids) should be part of the regimen if **ratio-SALBUTAMOL HFA** needs to be used more than 3 times a week (not including its use to prevent exercise-induced bronchospasm) (see **DOSAGE AND ADMINISTRATION**). It is essential that the physician instruct the patient in the need for further evaluation if the patient's asthma becomes worse.

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 sulphate 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 sulphate, 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
ratio-SALBUTAMOL HFA can produce paradoxical bronchospasm, which may be life-threatening. If paradoxical bronchospasm occurs, **ratio-SALBUTAMOL 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.

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 and Delivery: Because of the potential for beta-agonist interference with uterine contractility, use of **ratio-SALBUTAMOL 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: 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.

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 **ratio-SALBUTAMOL 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 **ratio-SALBUTAMOL HFA** indicates a deterioration of the condition and the physician should be contacted promptly. Patients should be warned not to exceed the recommended dose.

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 stimulants. 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.

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 form clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

Adverse reaction information concerning **ratio-SALBUTAMOL HFA** (salbutamol sulphate) inhalation aerosol is derived from two 12-week, randomized, double-blind studies in 610 adolescent and adult asthmatic patients that compared **ratio-SALBUTAMOL HFA**, **ratio-SALBUTAMOL** 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*

	ratio-SALBUTAMOL HFA n=202 (% patients)	**ratio-SALBUTAMOL (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 3.0% in the group treated with **ratio-SALBUTAMOL HFA** and more frequently in the group treated with **ratio-SALBUTAMOL HFA** than in the HFA-134a placebo inhaler group.

Overall, the incidence and nature of the adverse events reported for **ratio-SALBUTAMOL HFA** and **ratio-SALBUTAMOL** 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 **ratio-SALBUTAMOL HFA** and by a greater proportion of patients receiving **ratio-SALBUTAMOL HFA** than receiving HFA-134a placebo inhaler and that have the potential to be related to **ratio-SALBUTAMOL HFA** include diarrhea, laryngitis, cough, lung disorders, tachycardia, and extrasystoles. Palpitation and dizziness have also been observed with **ratio-SALBUTAMOL HFA**.

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

DRUG INTERACTIONS

Drug-Drug Interactions

Table 2- Established or Potential Drug-Drug Interactions

Proper name	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.

In accordance with current Canadian asthma guidelines, if salbutamol is required more than three times a week (not including its use to prevent exercise-induced bronchospasm), anti-inflammatory therapy (eg. corticosteroids) should be part of the regimen.

Increasing demand for **ratio-SALBUTAMOL HFA** (salbutamol sulphate) inhalation aerosol in bronchial asthma is usually a sign of worsening asthma and indicates that the treatment plan should be reviewed.

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

	Acute Symptoms	**Intermittent and Long-term Treatment***	**Prevention of Exercice-induced Asthma**	**Maximum Daily Dose (Total daily dose should not exceed)**
Adult	One to two puffs of [100 to 200 mcg salbutamol (as sulphate)]	One to two puffs [100 to 200 mcg salbutamol (as sulphate)] four times daily.	Two puffs [200 mcg salbutamol (as sulphate)] before exercise.	Eight puffs [800 mcg salbutamol (as sulphate)].
Children (4 years or older)	One puff [100 mcg of salbutamol (as sulphate)]. May be increased to two puffs (200 mcg salbutamol) if required.	One puff [100 mcg salbutamol (as sulphate)] four times daily.	One puff [100 mcg salbutamol (as sulphate)] before exercise. May be increased to two puffs (200 mcg salbutamol) if required.	Four puffs [400 mcg salbutamol (as sulphate)].

*Despite appropriate anti-inflammatory therapy (eg. corticosteroids), regular daily use of the **ratio-SALBUTAMOL HFA** remains necessary for the control of bronchospasm.

It is recommended to test spray **ratio-SALBUTAMOL HFA** into the air four times before using for the first time and in cases where the aerosol has not been used for more than 4 weeks.

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
ratio-SALBUTAMOL 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 inhalation aerosol.

Inhaler actuation should be synchronised with inspiration to ensure optimum delivery of drug to the lungs.

The use of open mouth technique to administer **ratio-SALBUTAMOL HFA** has not been investigated in clinical trials.

OVERDOSAGE

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.

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 ratio-SALBUTAMOL HFA (salbutamol sulphate) inhalation aerosol.

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.

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. 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 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 sulphate 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-sulphate, 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 reach of children. Store at a temperature between 15°C and 25°C.

SPECIAL HANDLING INSTRUCTIONS

The contents of **ratio-SALBUTAMOL HFA** (salbutamol sulphate) inhalation aerosol 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.

DOSAGE FORMS, COMPOSITION AND PACKAGING

ratio-SALBUTAMOL HFA (salbutamol sulphate) inhalation aerosol 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 sulphate).

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

ratio-SALBUTAMOL HFA is available in 200 dose formats.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

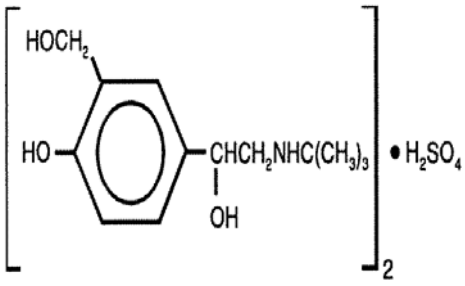
Drug Substance

Proper name: salbutamol sulphate

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

Molecular formula and molecular mass: $(C_{13}H_{21}NO_3)_2.H_2SO_4$ and 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.

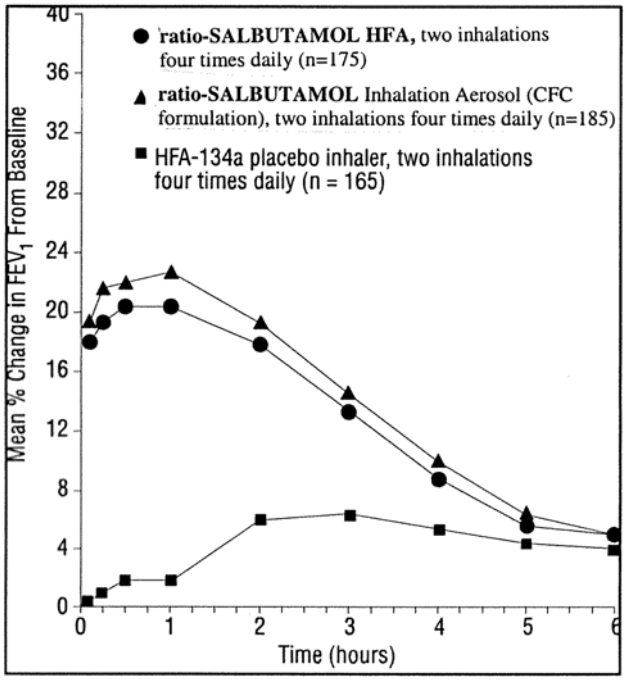
Melting Point: Approximately 156 °C.

CLINICAL TRIALS

In two 12-week, randomized, double-blind studies, **ratio-SALBUTAMOL HFA** (salbutamol sulphate) inhalation aerosol (202 patients) was compared to **ratio-SALBUTAMOL** 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 **ratio-SALBUTAMOL HFA** in patients with asthma, and the second study evaluated the effects of switching from **ratio-SALBUTAMOL** inhalation aerosol (CFC formulation) to **ratio-SALBUTAMOL 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 **ratio-SALBUTAMOL HFA** produced significantly greater improvement in pulmonary function than placebo and produced outcomes that were clinically comparable to **ratio-SALBUTAMOL** inhalation aerosol (CFC formulation) . Patients taking the HFA-134a placebo inhaler also took **ratio-SALBUTAMOL HFA** for asthma symptom relief on an as-needed basis. These patients produced similar morning predose baseline FEV_1 values to patients taking **ratio-SALBUTAMOL HFA** and **ratio-SALBUTAMOL** 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, **ratio-SALBUTAMOL HFA** was compared to **ratio-SALBUTAMOL** 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 **ratio-SALBUTAMOL HFA** produced significantly greater improvement in pulmonary function than placebo and that there were no significant differences between the groups treated with **ratio-SALBUTAMOL HFA** and **ratio-SALBUTAMOL** 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 **ratio-SALBUTAMOL 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 **ratio-SALBUTAMOL HFA** was shown to be clinically comparable to **ratio-SALBUTAMOL** 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	72 mg/kg
Rat (10)	>2000	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 sulphate 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.

REFERENCES

1. Alexander DJ, Libretto SE. An overview of the toxicology of HFA-134a (1,1,1,2-tetrafluoroethane). Human & Exper Toxicol 1995; 14(9): 715-20.

2. Global Strategy for Asthma Management and Prevention NHLBI/WHO Workshop Report M1. National Institutes of Health, Publication Number 95-3659 1995

3. Leaf A. Ozone depletion and public health. Hosp Pract (Off Ed) 1994; 29(6):9-10.

4. Libretto Se. A review of the toxicology of salbutamol (albuterol). Arch Toxicol 1994; 68:213-216.

5. Salbutamol: A review. Drugs 1971; 4:274-302.

6. The Canadian Asthma Consensus Conference. Can Resp J 1996; 3(2): 89-100.

7. Ventresca GP. Clinical pharmacology of HFA 134a. J Aerosol Med 1995; 8Supp 1: S35-S39.

8. Woodcock A. Continuing patient care with metered-dose inhalers. J Aerosol Med 1995; 8 Suppl 2:S5-10.

9. Draft Product Monograph for Ventolin HFA dated October 3, 2007

PART III: CONSUMER INFORMATION

ratio-SALBUTAMOL HFA
salbutamol sulphate Inhalation Aerosol

This leaflet is part III of a three-part "Product Monograph" for **ratio-SALBUTAMOL HFA** and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about **ratio-SALBUTAMOL 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:

Your doctor has prescribed a medicine called **ratio-SALBUTAMOL HFA** for you. It is used to help breathing problems in:
- Asthma
- Other chest illnesses.

What it does:
Salbutamol is one of a group of medicines called bronchodilators. Salbutamol 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 **ratio-SALBUTAMOL HFA** if you are allergic to it or any of the components of its formulation (see what the important non medicinal ingredients are)

What the medicinal ingredient is:
ratio-SALBUTAMOL HFA contains the active ingredient, salbutamol sulphate**.**

What the important nonmedicinal ingredients are:
ratio-SALBUTAMOL HFA is suspensed in a CFC-free propellant, HFA (Hydro Fluoro Alkane).

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

What dosage forms it comes in:
ratio-SALBUTAMOL HFA is a pressurized metered dose inhaler containing 100 mcg of salbutamol per inhalation. **ratio-SALBUTAMOL 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 **ratio-SALBUTAMOL 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.
- if you have diabetes.
- if you have a past history of seizures.

If you notice that your shortness of breath or wheeze is becoming worse, tell your doctor as soon as possible. If the relief of wheezing or chest tightness is not as good as usual, 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.

Your doctor may decide not to prescribe this medicine during the first three months of pregnancy, or if you are breast feeding a baby. However, there may be circumstances when your doctor advises you differently.

INTERACTIONS WITH THIS MEDICATION

Make sure that your doctor knows what other medicines you are taking (such as those for depression, allergies, other airway-opening medications (e.g. other asthma medications), blood pressure and heart medications, and water pills (diuretics), etc.), including those you can buy without a prescription as well as herbal and alternative medicines.

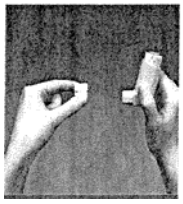
PROPER USE OF THIS MEDICATION

Carefully follow the instructions shown. If you have any problems, tell your doctor or pharmacist.

It is extremely important that you use your **ratio-SALBUTAMOL HFA** properly to ensure that your medicine is delivered correctly so that you receive maximum benefit.

Before using **ratio-SALBUTAMOL HFA** for the first time, or if your inhaler has not been used for more than 4 weeks, shake the inhaler and release four puffs into the air to ensure that it works properly.

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 thumbon 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.

If your doctor has given you different instructions for using your inhaler, please follow them carefully. Tell your doctor if you have any difficulties.

Children - ratio-SALBUTAMOL 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.

Cleaning:
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. Wipe the plastic casing and mouthpiece with a damp cloth. **Do not put the metal canister into water.**
3. Leave the casing and mouthpiece cover to dry in a warm place. Avoid excessive heat.
4. Replace the canister and mouthpiece cover.
5. After cleansing, release one puff into the air to make sure that the inhaler works.

Usual dose:
Use your **ratio-SALBUTAMOL HFA** only as directed by your doctor. He will tell you how often, and how many puffs to take for a treatment. If you are not sure how much or when to take your medicine, ask your doctor or pharmacist. Your doctor may have told you to use your inhaler regularly every day, or only when you are wheezy or short of breath.

The action of **ratio-SALBUTAMOL HFA** may last up to 6 hours and should last for at least 4 hours. **Call your doctor immediately if the effect lasts for less than 3 hours or if you notice a sudden worsening of your shortness of breath. Do not increase the dose or the number of times you use your medicine without asking your doctor. If symptoms get worse or you require your inhaler more than before, tell your doctor as soon as possible.**

If you regularly use ratio-SALBUTAMOL HFA more than 3 times a week, and take no other asthma medication, you should talk to your doctor who may want to reassess your treatment plan.

Unless your doctor has recommended otherwise, do not take more than 8 puffs in a day (24 hours). Unless your doctor has recommended otherwise, children should not take more than 4 puffs in a day.

If you have to go into hospital for an operation, take your inha ler 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.

Do not take more doses or use your inhaler more often than your doctor advises.

Overdose:
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.

In the event of an excessive overdose, tell your doctor without delay or contact your nearest hospital emergency department or poison centre. Take this leaflet or your medication with you so that the hospital or poison control centre will know what you have taken.

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

Very occasionally, some people feel a little shaky or have a headache or notice that their heart is beating a little faster and/or more forcefully than usual after using **ratio-SALBUTAMOL HFA.** Muscle cramps can occur, although these are quite rare. These effects usually wear off within a few hours, but you should tell your doctor as soon as possible. If you have chest pain, if your heart beat feels irregular, or feel unwell in any other way or have any symptoms that you do not understand, you should contact your doctor immediately.

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

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

If you notice a sudden worsening of your shortness of breath and wheeze shortly after using your **ratio-SALBUTAMOL HFA**, tell your doctor as soon as possible.

Some people can be allergic to medicines. If you have any of the following symptoms soon after taking **ratio-SALBUTAMOL HFA, stop** taking this medicine and tell your doctor immediately.

- Sudden wheeziness and chest pain or tightness.
- Swelling of eyelids, face, lips, tongue or throat.
- Lumpy skin rash or "hives" anywhere on the body.

HOW TO STORE IT

Keep your medicine in a safe place where children cannot reach it. Your medicine may harm them.

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 container.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs . If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

Toll-free telephone: 866-234-2345
Toll-free fax 866-678-6789
Email: cadrmp@hc-sc.gc.ca
Regular mail: National AR Centre
Marketed Health Products Safety and Effectiveness
Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

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:

ratiopharm inc.
17 800 Lapointe, Mirabel
Quebec, Canada, J7J 1P3
1-800-337-2584

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