

PRODUCT MONOGRAPH

ratio-SALBUTAMOL

salbutamol sulphate respirator solution

1 mg/mL

Bronchodilator
(beta₂-adrenergic stimulant)

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DATE OF PREPARATION:
JULY 24, 2013

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ratio-SALBUTAMOL

salbutamol sulphate Respirator Solution

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral Inhalation	Respirator Solution / 1 mg salbutamol base/mL	Not applicable.

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

INDICATIONS AND CLINICAL USE

Salbutamol (salbutamol sulphate) respirator solutions are indicated for:

- the treatment of severe bronchospasm associated with exacerbations of chronic bronchitis and bronchial asthma. They can be used by "wet" nebulization. When administered through a nebulizer, salbutamol respirator solutions should be used with compressed air or oxygen.

Pediatrics (<5 years of age):

Experience is insufficient for recommending the treatment of children under 5 years of age.

CONTRAINDICATIONS

- Patients with a hypersensitivity to any of the ingredients and in patients with tachyarrhythmia. For a complete listing, see DOSAGE FORMS, COMPOSITION, AND PACKAGING section of the product monograph.

WARNINGS AND PRECAUTIONS

General

Patients should always carry their salbutamol aerosol or dry powder 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.

The application of these inhalation systems in children depends on the ability of the individual child to learn the proper use of the devices. During inhalation, children should be assisted or supervised by an adult who knows the proper use of the devices.

Salbutamol Respirator Solution must only be used by inhalation, to be breathed in through the mouth, and must not be injected or swallowed.

Use of Anti-Inflammatory Agents

In accordance with the present practice for asthma treatment, concomitant anti-inflammatory therapy (eg. corticosteroid) should be part of the regimen if inhaled salbutamol needs to be used on a regular daily basis (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 effects:

In individual patients, any beta₂-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 beta₂-adrenergic agents, salbutamol can induce reversible metabolic changes such as potentially serious hypokalemia, particularly following nebulized 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 nebulized 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.

Lactic acidosis has been reported very rarely in association with high therapeutic doses of intravenous and nebulised short-acting beta-agonist therapy, mainly in patients being treated for an acute asthma exacerbation (see ADVERSE REACTION section). Increase in lactate levels may lead to dyspnea and compensatory hyperventilation, which could be misinterpreted as a sign of asthma treatment failure and lead to inappropriate intensification of short-acting beta-agonist treatment. It is therefore recommended that patients are monitored for the development of elevated serum lactate and consequent metabolic acidosis in this setting.

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, anaphylaxis, and oropharyngeal edema.

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

Neurologic

Care should be taken with patients with convulsive disorders.

Respiratory

With repeated excessive use of sympathomimetic inhalation preparations, some patients have been reported to have developed severe paradoxical bronchospasm, occasionally leading to death. The cause of either the refractory state or death is unknown. However, it is suspected in the fatal episodes that cardiac arrest occurred following the unexpected development of a severe acute asthmatic crisis and subsequent hypoxia. Several cases have been reported in which intermittent positive pressure ventilation in acute asthma attacks was related to lethal episodes of hypoxia and pneumothorax. This method of drug administration may be ineffective in patients with severe obstruction and greatly increased airway resistance, and it may induce severe hypercapnia and hypoxia. During intermittent ventilation therapy, the monitoring of arterial blood gases is highly desirable. It is advisable that in the event of either hypoxia and pneumothorax or paradoxical bronchospasm the use of the preparation should be discontinued immediately and alternate therapy instituted, since in the reported cases the patients did not respond to other forms of therapy until the drug was withdrawn.

Special Populations

Pregnant Women: Salbutamol has been in widespread use for many years in human beings 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 foetus (see TOXICOLOGY, Teratogenicity Studies).

Labour and Delivery: Although there have been no reports concerning the use of inhaled Salbutamol Respirator Solutions formulations during labour and delivery, intravenously administered salbutamol given at high doses may inhibit uterine contractions. While this effect is extremely unlikely as a consequence of using inhaled formulations, it should be kept in mind. Oral salbutamol has been shown to delay preterm labour in some reports but there are no well-controlled studies which demonstrate that it will stop preterm labour or prevent labour at term. When given to pregnant patients for relief of bronchospasm, cautious use of Salbutamol Respirator Solution products is required to avoid interference with uterine contractility.

Nursing Women: Since salbutamol is probably excreted in breast milk and because of its observed tumorigenicity in 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:

ratio-SALBUTAMOL Respirator Solution

ratio-SALBUTAMOL should be used under the supervision of an adult who understands the proper use of the nebulizer and only as presented by the doctor.

Experience is insufficient for recommending the treatment of children under 5 years of age.

Monitoring and Laboratory Tests

The management of asthma should normally follow a stepwise program and 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 salbutamol 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 beta₂-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 beta₂-

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 beta₂-agonist therapy, primarily from parenteral and nebulized routes of administration (see WARNING 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 and extrasystoles) have been reported, usually in susceptible patients.

The most frequent adverse reactions associated with salbutamol inhalation aerosol, dry powder or respirator solution formulations 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 beta₂-adrenergic stimulants. Adaptation occurs during the first few days of dosing and the tremor usually disappears as treatment continues.

Headache, palpitations, transient muscle cramps, insomnia, nausea, weakness and dizziness have been reported as untoward effects following salbutamol administration.

Rarely reported adverse effects include 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.

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

Lactic acidosis has been reported very rarely in patients receiving intravenous and nebulised salbutamol therapy for the treatment of acute asthma exacerbation.

DRUG INTERACTIONS

Drug-Drug Interactions

Table 1 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 individualized and not given on a routine basis. If regular coadministration is required then alternative therapy must be considered.
Beta-blockers	CS	May effectively antagonise 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 coadministration of beta-agonists with non-potassium sparing diuretics.
Digoxin	CS	May lead to decrease in serum digoxin levels. 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.
Ipratropium bromide	CS	Acute angle closure glaucoma has been reported with	A small number of cases of acute angle closure glaucoma

Proper name	Ref	Effect	Clinical comment
		coadministration.	have been reported in patients treated with a combination of nebulized salbutamol and ipratropium bromide. Therefore, a combination of nebulized salbutamol with nebulized anticholinergics should be used cautiously. Patients should receive adequate instruction in correct administration and be warned not to let the solution or mist enter the eye.

Legend: CS=Class Statement

DOSAGE AND ADMINISTRATION

Dosing Considerations

Dosage should be individualized, 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 for relief of symptoms more than twice a day on a regular daily basis or for an extended period of time anti-inflammatory therapy (eg. Corticosteroid) should be part of the regimen.

Increasing demand for Salbutamol (salbutamol sulphate) Respirator Solution preparations 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.

ratio-SALBUTAMOL Respirator Solution may be preferred in the treatment of severe bronchospasm associated with exacerbations of chronic bronchitis and bronchial asthma.

Recommended Dose and Dosage Adjustment

ratio-SALBUTAMOL Respirator Solution:

Adults: In adults, **ratio-SALBUTAMOL** Respirator Solution 0.5 to 1.0 mL (2.5 to 5.0 mg of salbutamol) should be diluted in 2 to 5 mL or more of sterile normal saline. Treatment may be repeated four times a day if necessary.

Children (5 - 12 years): The average dose for a single treatment is 0.25 to 0.5 mL of **ratio-SALBUTAMOL** Respirator Solution (1.25 to 2.5 mg of salbutamol) diluted in 2 to 5 mL or more of sterile normal saline. For more refractory cases, the single dose of **ratio-SALBUTAMOL** Respirator Solution may be increased to 1 mL (5 mg of salbutamol). Treatment may be repeated four times a day if necessary.

If a more severe attack has not been relieved by a treatment, further treatments may be required. In these cases, patients should immediately consult their doctor or the nearest hospital.

Missed Dose

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

Administration

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 nebulizer system.

ratio-SALBUTAMOL Respirator Solution is to be used only under the direction of a physician employing either a respirator or nebulizer. **ratio-SALBUTAMOL** Respirator Solution can be taken by either the nebulization or intermittent positive pressure ventilation method. When used in a nebulizer, a mouthpiece or a face mask may be applied. The nebulizer should be connected to a compressed air or oxygen pump. Gas flow should be in the range of 6 to 10 L/minute. With an average volume of 3 mL, a single treatment lasts approximately 10 minutes. It is advisable to prepare one dose at a time or to utilize the Unit Dose (**ratio-SALBUTAMOL** NEBULES P.F.) presentation. When administered through intermittent positive pressure ventilation, the inspiratory pressure is usually 10-20 cm H₂O and the duration of administration varies from 5 to 20 minutes, depending upon the patient and the control of the apparatus. This length of administration provides a more gradual and more complete lysis of bronchospasm. In several cases it has been reported that the use of intermittent positive pressure ventilation in acute asthma attacks was related to lethal episodes of hypoxia and pneumothorax. This method of drug administration may be ineffective in patients with severe obstruction and may greatly increase airway resistance and possibly induce severe hypercapnia and hypoxia. It is highly desirable to monitor arterial blood gases during intermittent positive pressure ventilation therapy.

In hospitals, **ratio-SALBUTAMOL** Respirator Solution, diluted (1:5 or 1:10) with sterile normal saline, should be used within 24 hours from time of dilution when stored at room temperature or within 48 hours when stored under refrigeration.

Cleansing and maintenance of the nebulizer must be carefully exercised by strict adherence to the manufacturer's instructions.

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.

During continuous administration of salbutamol Respirator Solution, any signs of overdosage can usually be counteracted by withdrawal of the drug.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Salbutamol produces bronchodilation through stimulation of beta₂-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 beta₁-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.

Five asthmatic patients were given tritium-labelled salbutamol from the nebulizer of an intermittent positive pressure ventilator. In all patients, there was a rapid initial rise in plasma concentration of total radioactivity. In four of the five patients, there was a

further rise in plasma concentration to a peak at 2 to 4 hours. All patients showed an improvement in FEV₁ with peak improvement at 30 minutes to 2 hours. An average of 12.5% of the initial dose was recovered in the urine. Of the radioactivity recovered, 88% was recovered in the first 24 hours. The metabolite in the urine was the same as that in the plasma. During the first 2 hours, the ratio of free salbutamol to metabolite average 2:1, whereas by 8 hours, the ratio was 9:11, and thereafter this reversed ratio was maintained.

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 salbutamo-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.

STORAGE AND STABILITY

Keep out of the reach of children.

ratio-SALBUTAMOL Respirator Solution : Store between 15 to 25°C. Protect from light. Discard if not used within one month of opening.

Reconstituted ratio-SALBUTAMOL Respirator Solution

In hospitals, **ratio-SALBUTAMOL** Respirator Solution, diluted (1:5 or 1:10), with sterile normal saline, should be used within 24 hours from time of dilution when stored at room temperature or within 48 hours when stored under refrigeration. Instructions for the dilution of **ratio-SALBUTAMOL** Respirator Solution are given below in Table 2.

In the home, the unit dose preparation (**ratio-SALBUTAMOL** NEBULES P.F.), which is pre-diluted and ready to use, is the most convenient preparation. However, if the standard **ratio-SALBUTAMOL** Respirator Solution is used, it may be diluted with sterile normal saline immediately before use. Any unused solution in the nebulizer should be discarded.

Table 2 **Dilution Table for ratio-SALBUTAMOL Respirator solution**

Dose (mg) of Salbutamol (per treatment)	Volume (mL) of Salbutamol respirator Solution (per treatment)	Volume* (mL) of Sterile Normal Saline to be added as diluent
1.25	0.25	2 - 5 mL or more
2.5	0.50	2 - 5 mL or more
5	1.00	2 - 5 mL or more

*Approximate volumes only are given. Actual volume of diluent used may vary according to the type of nebulizer and individual patient needs.

DOSAGE FORMS, COMPOSITION AND PACKAGING

ratio-SALBUTAMOL Respirator Solution.

ratio-SALBUTAMOL Respirator Solution contains salbutamol sulphate, equivalent to 5 mg of salbutamol base per mL. It is an isotonic solution adjusted to pH 3.4 to 4.4 and preserved with benzalkonium chloride 0.01% w/v. It also contains dilute sulphuric acid and Water for Injection. Available in 10 mL bottles.

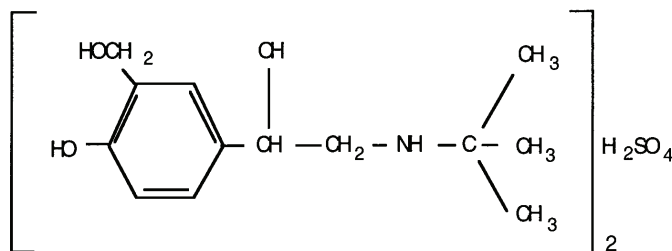
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substances

Proper name:	salbutamol sulphate
Chemical name:	α^1 -[tert-butylamino)methyl]-4-hydroxy-m-xylene-a, a'-diol sulphate (2:1) salt
Molecular Formula and molecular mass:	(C ₁₃ H ₂₁ NO ₃) ₂ H ₂ SO ₄ , 576.7

Structural Formula:



Physicochemical properties:

Descriptions: White to almost white powder. It is odourless or almost odourless.

Solubility: Soluble in 4 parts of water; slightly soluble in ethanol (96%), in chloroform and in ether.

pH value: 4.3.

pKa values: 9.3 and 10.3.

Distribution Coefficient: The distribution coefficient of salbutamol between two phases of octanol and water, as determined by HPLC, is log D=-0.5 at pH 7.42 at room temperature.

Melting Point: Approximately 155°C, with decomposition.

CLINICAL TRIALS

In controlled clinical trials, the onset of improvement in pulmonary function was within 15 minutes, as determined by both maximum mid-expiratory flow rate (MMEF) and FEV₁. MMEF measurements also showed that near maximum improvement in pulmonary function generally occurs within 60 to 90 minutes following two inhalations of salbutamol and that clinically significant improvement generally continues for three to four hours in most patients. In clinical trials some patients with asthma showed a therapeutic response (defined as maintaining FEV₁ values 15% or more above baseline) that was still apparent at six hours. Continued effectiveness of salbutamol was demonstrated over a 13-week period in these same trials.

In clinical studies, two inhalations of salbutamol taken approximately 15 minutes before exercise prevented exercise-induced bronchospasm, as demonstrated by the maintenance of FEV₁ within 80% of baseline values in the majority of patients. One of these studies also evaluated the duration of the prophylactic effect to repeated exercise challenges which was evident at four hours in the majority of patients and at six hours in approximately one third of the patients.

The ability of salbutamol to produce bronchodilation in humans has been demonstrated in many spirometric and plethysmographic studies. Following a challenge with acetylcholine aerosol, in a study examining the effects of salbutamol in airway resistance following challenge testing in 12 patients, the mean airway resistance increased 250%. After salbutamol aerosol (200 micrograms), the mean airway resistance decreased to 78% of the initial value. Challenges with grass pollen or house dust aerosols in five and eight patients, respectively, increased activity resistance 265% and 255%, respectively. Administration of salbutamol decreased airway resistance to initial levels.

Controlled clinical studies and other clinical experience have shown that inhaled salbutamol, like other beta-adrenergic agonist drugs, can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms, and/or ECG changes.

When salbutamol was administered as a metered-dose inhaler preparation to six normal volunteers, at doses of three or seven inhalations of 100 micrograms, it was observed that three inhalations of salbutamol did not alter serum potassium while seven inhalations resulted in a decrease in serum potassium from 4.4 to 3.8 mEq/L. Thus, recommended doses of salbutamol aerosol (two inhalations) would not be expected to alter serum potassium levels.

A double-blind placebo controlled comparison of the bronchodilator effects of salbutamol, inhaled either as a dry powder or as a conventional aerosol, was carried out in 20 adult patients with chronic bronchial asthma. All treatments were significantly better than placebo. There was no significant difference between responses to any of the three dry powder doses (100 mcg, 200 mcg, 300 mcg) but the average response to

200 mcg aerosol was significantly greater than that to 200 mcg dry powder.

Salbutamol dry powder (400 mcg) and conventional aerosol (200 mcg) were administered to 10 adult asthmatics. There was no statistically significant difference between the improvement in FEV₁ obtained 10 minutes after administration of either the dry powder or the aerosol formulation.

Salbutamol was administered as a dry powder (50 mcg, 100 mcg, 200 mcg, 400 mcg) and as an aerosol (200 mcg) to 10 adult asthmatics. The greatest responses were obtained with salbutamol 400 mcg administered as a dry powder. No effect on blood pressure or pulse rate was observed.

Daily improvement in PEFr in response to single doses of inhaled salbutamol (200 mcg dry powder and 100 mcg conventional aerosol) was measured in nine asthmatic children (aged 5-13 years) for six weeks. The order of administration of powder and aerosol was reversed at the end of three weeks. There was no statistically significant difference between the increase in PEFr 5 minutes after either 200 mcg dry powder or after 100 mcg aerosol. The total mean increases in PEFr 10 minutes after inhalation of powder and aerosol (weeks 1-3) and inhalation of aerosol and powder (weeks 4-6) were not significantly different.

In a double-blind placebo-controlled study, salbutamol (200 mcg) completely prevented exercise-induced bronchospasm in three of five children, and greatly reduced the effects in the other two patients.

Administration of 10 mg salbutamol as a 0.5% solution through IPPV from a Bennett ventilator, given in a 3 minute period, resulted in a 40% increase of FEV₁ with maximum effect in about 90 minutes. The average duration of effect was 3 hours. The heart rate had an average increase of 9 beats/minute, peaking after 25 minutes, and lasting for about 36 minutes. No ECG changes were observed.

Salbutamol solution 0.5% was self-administered at home via a portable nebulizer, without IPPV, by 28 adult patients with severe chronic asthma. The dose was 0.5 mL (2.5 mg salbutamol) in 4.5 mL normal saline, 2 to 4 times daily, and the duration of treatment period ranged from 0.9 to 2.7 years (mean 1.7 years). For each patient the treatment period was compared retrospectively with a control period of the same duration preceding nebulizer therapy. No statistically significant differences between treatment and control periods were found for pulmonary function tests performed before and after 5 puffs of a salbutamol pressurized aerosol, or for number of out-patient emergency department visits, hospitalizations, sick leaves, and days hospitalized. However, there were significant reductions during the treatment period in the duration of sick leaves and medical ward treatments, while half of the patients reported that it was easier to sleep and two-thirds said it was easier to exercise.

In 10 pediatric studies, a total of 189 patients up to 14 years of age were treated with salbutamol solution 0.5% administered via a portable nebulizer. In most cases, the

dose was between 0.5 mL and 1.0 mL per treatment, diluted with normal saline, bringing the total volume to 2.0 mL. Children with asthma had very good results from the treatment, while children with bronchitis or bronchiolitis did not respond well. Salbutamol was very well tolerated in these studies. One author reported 2 cases of skeletal muscle tremor, but drew attention to the fact that both patients received concurrent oral bronchodilator. Otherwise, the only reported side effect was occasional mild tachycardia.

Prolonged use of Salbutamol (salbutamol sulphate) in most patients caused no significant changes in ECG pattern, blood sugar, liver and kidney functions and hematological values.

The hemodynamic effects of intravenous salbutamol were studied in patients with mitral valve disease. At the dose of 1 mcg/kg, salbutamol reduced mean aortic pressure by 7 mmHg, increased the cardiac output by 0.6 L/minute and reduced systemic vascular resistance by 7 units. It caused no change in left ventricular ejection time. At the dose of 2 mcg/kg, salbutamol increased the mean oxygen uptake by 21 mL/minute, narrowing the mean arteriovenous oxygen difference by 10 mL/minute. Salbutamol has no effect on the pulmonary ventilation/perfusion ratio, therefore, unlike isoprenaline, it does not increase hypoxia during acute asthmatic attacks.

DETAILED PHARMACOLOGY:

Animal Pharmacology

In vitro studies and in vivo pharmacologic studies have demonstrated that salbutamol has a preferential effect on beta₂-adrenergic receptors compared with isoprenaline. While it is recognized that beta₂-adrenergic receptors are the predominant receptors in bronchial smooth muscle, recent data indicate that there is a population of beta₂-receptors in the human heart existing in a concentration between 10% and 50%. The precise function of these, 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 adenylyl 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 microgram/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 beta₁-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 LD₅₀
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 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 inhalational 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 inhalational dose, and 78 times the maximum human oral dose cranioschisis was observed in 7 of 19 (37%) fetuses.

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 95. Pr^{VENTOLIN}® Product Monograph GlaxoSmithKline Inc., Date of Revision October 3, 2007

PART III: CONSUMER INFORMATION

ratio-SALBUTAMOL salbutamol sulphate respirator solution

This leaflet is part III of a three-part "Product Monograph" for **ratio-SALBUTAMOL** Respirator Solution and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about **ratio-SALBUTAMOL** Respirator Solution. Please read this insert carefully before you start your medicine. Contact your doctor or pharmacist if you have any questions about the drug. This medicine is for you only. Only your doctor can prescribe it for you. Never give it to someone else. It may harm them even if his/her symptoms are the same as yours.

ABOUT THIS MEDICATION

What the medication is used for:

Your doctor has prescribed a medicine called **ratio-SALBUTAMOL** Respirator Solution (salbutamol sulphate) to 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** Respirator Solution if:

- you are allergic to it or any of the components of its formulation (see What the important nonmedicinal ingredients are).
- your heart beats faster than normal.

What the medicinal ingredient is:

ratio-SALBUTAMOL Respirator Solution contains the active ingredient, salbutamol sulphate.

What the important nonmedicinal ingredients are:

Benzalkonium chloride, dilute sulphuric acid and water.

What dosage forms it comes in:

ratio-SALBUTAMOL Respirator Solution contains 1 mg per mL.

WARNINGS AND PRECAUTIONS

Before you use **ratio-SALBUTAMOL** Respirator Solution talk to your doctor or pharmacist if:

- You have ever had to stop taking another medicine for

this illness because you were allergic to it or because it 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 are pregnant or breastfeeding.

Rare cases of lactic acidosis (too much lactic acid in the blood) have been reported in patients receiving high doses of **ratio-SALBUTAMOL** Respirator Solution. If you suffer symptoms (see Serious Side Effects Table), contact your doctor immediately.

If the relief of wheezing or chest tightness is not as good as usual, 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.

Your doctor may decide not to prescribe this medicine during the first 3 months of pregnancy, nor if you are breast feeding a baby. However, there may be circumstances when your doctor advises you differently.

Children

ratio-SALBUTAMOL Respirator Solution should be used under the supervision of an adult who understands the proper use of the nebulizer and only as prescribed by the doctor.

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

Please follow these instructions carefully. It is important that you use your **ratio-SALBUTAMOL** Respirator Solution properly to ensure that you receive the maximum benefit from your medicine.

ratio-SALBUTAMOL Respirator Solution contains salbutamol 5 mg per mL. For proper administration, 1 mL of solution is usually diluted with 2 to 5 mL of sterile normal saline.

In the home, **ratio-SALBUTAMOL** Respirator Solution may be diluted immediately before use. Pre-diluted

solutions of **ratio-SALBUTAMOL** Respirator Solution should not be stored.

Before starting treatment with this drug, be sure that you are fully familiar with the proper use and care of your nebulizer.

1. When preparing the solution for inhalation, use a graduated syringe to draw up **ratio-SALBUTAMOL** Respirator Solution from the bottle at the dose directed by your physician. **Note:** Close the **ratio-SALBUTAMOL** bottle as soon as the solution is drawn into the syringe. Keep the bottle closed at all times and do not open it unnecessarily. Discard unused, diluted **ratio-SALBUTAMOL** Respirator Solution after each use.
2. Inject the solution into the nebulizer through the appropriate opening.
3. Draw into the syringe the amount of diluting fluid (sterile normal saline) directed by your physician and add it to the nebulizer.
4. Gently shake the nebulizer and connect it with the mouthpiece or face mask.
5. Connect the apparatus to the air pump or oxygen and start the treatment.
6. Breathe calmly and evenly as much as possible until no more mist is formed in the nebulizer chamber. At this point, treatment is finished.
7. Any unused solution in the respirator should be discarded.

Care of the **ratio-SALBUTAMOL** Respirator Solution and Nebulizer

Cleaning: after each use, clean the syringe and nebulizer as instructed in the nebulizer manual or as follows:

To clean the nebulizer:

1. Disassemble the supply tube and the nebulizer.
2. Wash in warm detergent solution. Rinse the tube with water.
3. To wash the suction tubes:
 - a. Place 3 mL of detergent solution in the vial, assemble the unit and operate for 2 minutes.
 - b. Disassemble and rinse the vial with warm water, place 3 mL of warm water in the vial, assemble the unit and operate for 2 minutes.
 - c. Disassemble and rinse with warm water.
4. To dry the external passage:
 - a. Connect the nebulizer tube to the pump with the supply tube.
 - b. Turn the pump and blow air through for 1 minute.
5. If there is evidence of clogging, clean the openings and tube connectors with the detergent, then rinse with water.
6. Reassemble.

To clean the syringe:

1. Clean the syringe and needle several times in detergent solution by alternatively drawing up and expelling the detergent solution.
2. Repeat using a rinse of warm water.
3. Dry the needle by drawing air into the syringe several times, by moving the plunger back and forth in the barrel of the syringe. Remove the needle.
4. Remove the plunger from the syringe, allow to air dry.
5. Keep unassembled needle, plunger and barrel of syringe wrapped in clean tissue, stored in a refrigerator along with the **ratio-SALBUTAMOL** bottle.

Discard any solution left in the nebulizer after you finish treatment, clean and dry the nebulizer as instructed by the nebulizer manual.

Follow all the instructions of the nebulizer and air pump manufacturers for the proper care and maintenance of the apparatus.

Do not swallow or inject **ratio-SALBUTAMOL** Respirator Solution. The solution is inhaled into your lungs using a nebulizer.

Usual dose:

Use your **ratio-SALBUTAMOL** Respirator Solution only as directed by your doctor. He will tell you how often, and how much to take for a treatment. If you are not sure how much or when to take your medicine, ask your doctor or pharmacist.

The action of **ratio-SALBUTAMOL** Respirator Solution may last for up to 6 hours and should last at least 4 hours.

Call your doctor immediately if the effect of your usual dose lasts for less than 3 hours or if you suddenly get worse shortness of breath and you wheeze after using your ratio-SALBUTAMOL Respirator Solution. Do not increase the dose or how often you take your medicine without informing your doctor. If symptoms get worse, tell your doctor as soon as possible.

When using **ratio-SALBUTAMOL** Respirator Solution, other medicines (including asthma medicines) should only be used when prescribed by your doctor.

If you regularly use ratio-SALBUTAMOL Respirator Solution two or more times a day, and take no other asthma medication, you should talk to your doctor who may want to reassess your treatment plan.

Adults: **ratio-SALBUTAMOL** Respirator Solution 0.5 to 1.0 mL (2.5 to 5.0 mg of salbutamol) should be diluted in 2 to 5 mL or more of sterile normal saline. Treatment may be repeated four times a day if necessary.

Children: (5 - 12 years): The average dose for a single treatment is 0.25 to 0.5 mL of ratio-SALBUTAMOL Respirator Solution (1.25 to 2.5 mg of salbutamol) diluted in 2 to 5 mL or more of sterile normal saline. For more refractory cases, the single dose of **ratio-SALBUTAMOL** Respirator Solution may be increased to 1 mL (5 mg salbutamol). Treatment may be repeated four times a day if necessary.

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** overdosage, tell your doctor without delay or contact your nearest hospital emergency department or poison control 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, inhale the next dose at the time you would normally take it or inhale a dose sooner than when it is due 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** Respirator Solution. Muscle cramps can occur although these are quite rare. These effects usually wear off with continued treatment. Tell your doctor but do not stop using the medicine unless told to do so. If your heart beat feels irregular, tell your doctor as soon as possible.

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

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	
Very Rare	Increased wheezing or tightness in the chest or difficulty in breathing (sign of bronchospasm).			x
	<i>Allergic reactions (Hypersensitivity)</i> Swelling of the eyelids, face, lips tongue or throat, accompanied by difficulty in breathing, speaking or			x

	swallowing (signs of angioedema). Skin rash, skin eruption or other effect on the skin or eyes, itching or fever. Fainting when the blood pressure is too low (sign of hypotension).			
	Deep and rapid breathing, vomiting, abdominal pain, weight loss, fatigue, malaise (sign of lactic acidosis too much lactic acid in the blood)			x

* If you think you have these side effects, it is important that you seek medical advice from your doctor immediately.

HOW TO STORE IT

Keep your ratio-SALBUTAMOL Respirator Solution in a safe place where children cannot reach them. Your medicines may harm children.

Keep the **ratio-SALBUTAMOL** Respirator Solution in a dry place and store them between 15°C to 25°C. Protect from light. One month after opening the bottle, throw away any solution which is left over.

MORE INFORMATION

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

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701D
Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

This document plus the full product monograph, prepared for health professionals or by contacting the sponsor, Teva Canada Limited, at:

1-800-268-4127 ext. 1255005 (English)

1-877-777-9117 (French)

or druginfo@tevacanada.com

This leaflet was prepared by Teva Canada Limited.

Last revised: July 24, 2013