PRODUCT MONOGRAPH

ratio-SALBUTAMOL

salbutamol sulphate respirator solution

5 mg/mL

Bronchodilator
(beta$_2$-adrenergic agonist)

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ratio-SALBUTAMOL

salbutamol sulphate
Respirator Solution

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral Inhalation	Respirator Solution / 5 mg salbutamol base/mL	Benzalkonium chloride, dilute sulphuric acid and water.

INDICATIONS AND CLINICAL USE

Adults and Children (5 years and older):
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 who are hypersensitive to this drug or to any ingredient in the formulation or component of the container and in patients with tachyarrhythmias (see DOSAGE FORMS, COMPOSITION, AND PACKAGING).
- As a tocolytic in patients at risk of premature labour or threatened abortion.

WARNINGS AND PRECAUTIONS

General

Patients should always carry their 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.

A small number of cases of acute angle closure glaucoma have been reported in patients treated with a combination of nebulized salbutamol and ipratropium bromide. A combination of nebulized salbutamol with nebulized anticholinergics should therefore be used cautiously. Patients should receive adequate instruction in correct administration and be warned not to let the solution or mist enters the eye.

Use of Anti-Inflammatory Agents

In accordance with the present practice for asthma treatment, concomitant anti-inflammatory therapy (e.g. 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

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 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 nebulized 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, hypotension, 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
As with other inhaled medications, paradoxical bronchospasm may occur characterized by an immediate increase in wheezing after dosing. This should be treated immediately with an alternative presentation or a different fast-acting inhaled bronchodilator to relieve acute asthmatic symptoms. ratio-SALBUTAMOL Respirator Solution should be discontinued immediately, the patient assessed and if necessary, alternative therapy instituted (see ADVERSE REACTIONS). 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 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: Although there have been no reports concerning the use of inhaled salbutamol 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 ratio-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 (5 – 12 years):
ratio-SALBUTAMOL Respirator Solution
ratio-SALBUTAMOL Respirator Solution should be used under the supervision of an adult who understands the proper use of the nebulizer and/or respirator (as well as ratio-SALBUTAMOL Respirator Solution), and only as presented by the doctor.

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

Pediatrics (< 5 years of age):
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 as there may be adverse effects associated with excessive dosing.

The increasing use of fast acting, short duration inhaled beta$_2$-adrenergic agonists to control symptoms indicates deterioration of asthma control and the patient's therapy plan should be reassessed. In worsening asthma, it is inadequate to increase beta$_2$-agonist use only, especially over an extended period of time. In the case of acute or rapidly worsening dyspnea, a doctor should be consulted immediately. Sudden or progressive deterioration in asthma control is potentially life threatening; the treatment plan must be re-evaluated, and consideration be given to corticosteroid therapy (see DOSAGE AND ADMINISTRATION).

Geriatrics: As with other beta$_2$-agonists, special caution should be observed when using ratio-SALBUTAMOL Respirator Solution in elderly patients who have concomitant cardiovascular disease that could be adversely affected by this class of drug.

ADVERSE REACTIONS

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

Adverse Drug Reaction Overview

Adverse events are listed below; frequencies are defined as: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10,000 and <1/1000) and very rare (<1/10,000) including isolated reports. Very common and common events were generally determined from clinical trial data. Rare, very rare and unknown events were generally determined from spontaneous data.

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 nebulized 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 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

beta$_2$-adrenergic agonists. 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.

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

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

DRUG INTERACTIONS

Drug-Drug Interactions

Table 1 Established or Potential Drug-Drug Interactions

Drug type	Ref	Effect	Clinical comment
Monoamine oxidase inhibitors or tricyclic antidepressants.	CS	May potentiate action of salbutamol on cardiovascular system.	Salbutamol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants.
Other inhaled sympathomimetic bronchodilators or epinephrine.	CS	May lead to deleterious cardiovascular effects.	Other inhaled sympathomimetic bronchodilators or epinephrine should not be used concomitantly with salbutamol. If additional adrenergic drugs are to be administered by any route to the patient using inhaled salbutamol, the adrenergic drugs should be used with caution. Such concomitant use must be individualized and not given on a routine basis. If regular coadministration 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

Drug type	Ref	Effect	Clinical comment
			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 coadministration.	A small number of cases of acute angle closure glaucoma 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 enters the eye.

Legend: CS=Class Statement

DOSAGE AND ADMINISTRATION

Dosing Considerations

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

In patients with asthma, 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 (e.g. corticosteroids) 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 and Adolescents ≥ 13 years of age: 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 or respirator 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. The solution must not be injected or swallowed. When used in a nebulizer delivery may be by a mouthpiece, a face mask, T piece or via an endotracheal tube. 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 of ratio-SALBUTAMOL Respirator Solution or to utilize the Unit Dose (ratio-SALBUTAMOL NEBULES P.F.) presentation.

When ratio-SALBUTAMOL is administered through intermittent positive pressure ventilation, the inspiratory pressure is usually 10-20 cm H_2O 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. When there is a risk of anoxia through hypoventilation, oxygen should be added to the inspired air.

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. As many nebulizers operate on a continuous flow basis, it is likely that nebulized drug will be released in the local environment. ratio-SALBUTAMOL Respirator Solution should therefore be administered in a well ventilated room, particularly in hospitals when several patients may be using nebulizers at the same time.

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

OVERDOSAGE

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

Symptoms and signs
The most common signs and symptoms of overdose with salbutamol are transient beta agonist

pharmacologically mediated events (see Warning and Precautions and Adverse Reactions). Overdosage may cause tachycardia, cardiac arrhythmia, hypokalemia, hypertension and, in extreme cases, sudden death. Serum potassium levels should be monitored.

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

Treatment

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

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

Pharmacokinetics

After inhalation of recommended doses of salbutamol, plasma drug levels are very low. When 100 mcg of tritiated salbutamol aerosol was administered to two normal volunteers, plasma levels of drug-radioactivity were insignificant at 10, 20 and 30 minutes following inhalation. The plasma concentration of salbutamol may be even less as the amount of plasma drug-radioactivity does not differentiate salbutamol from its principal metabolite, a 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 FEV_1 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 percent 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.

STORAGE AND STABILITY

Keep out of the sight and 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.

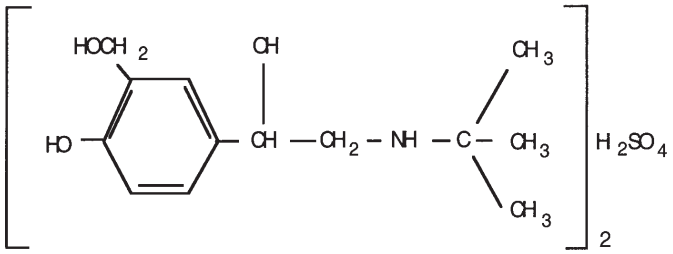
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug 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:	$(C_{13}H_{21}NO_3)_2\ H_2SO_4$, 576.7

Structural formula:



Physicochemical properties:

Description:	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^{o}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 FEV_1. 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 FEV_1 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 FEV_1 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 FEV_1 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 FEV_1 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.

DETAILED PHARMACOLOGY

Clinical Pharmacology

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 l 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.

Animal Pharmacology

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 anaesthetized 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 anaesthetized 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 anaesthetized dog. In the perfused rabbit ear, salbutamol was shown to possess only one-tenth the activity of isoprenaline in terms of vasodilating effect. In dogs, salbutamol was shown to increase coronary blood flow, which was subsequently shown to be the result of a direct coronary vasodilating effect of salbutamol.

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

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

TOXICOLOGY

Acute Toxicity

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

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

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

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

Intermediate (Four Months) Toxicity

Rats received salbutamol twice daily, in oral doses from 0.5 to 25 mg/kg, on an increasing scale. The only significant hematological changes were a small increase in hemoglobin and packed cell

volume. BUN and SGOT values were elevated while blood glucose and plasma protein levels remained unchanged. Pituitaries had increased amount of PAS-positive material in the cleft at the higher dose levels.

Salbutamol was given to dogs twice daily, in oral doses from 0.05 to 12.5 mg/kg, on an increasing scale. The rate of increase of hemoglobin and packed cell volume was depressed, particularly at higher doses. Leukocyte count decreased after sixteen weeks of treatment at each dose level. Platelet count was increased after eight weeks at the highest dose. No significant biochemical effects were observed. The only significant histological change was the appearance of corpora amylacea in the stomach which was attributed to altered mucus secretion. Inhalation of 1000 mcg of salbutamol 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 and 78 times the maximum human oral dose cranioschisis was observed in 7 of 19 (37%) fetuses.

REFERENCES

1. Ahrens RC, Smith GD. Albuterol: an adrenergic agent for use in the treatment of asthma pharmacology, pharmacokinetics and clinical use. Pharmacotherapy 1984; 4(3):105-121.

2. Anderson PB, Goude A, Peake MD. Comparison of salbutamol given by intermittent positive-pressure breathing and pressure-packed aerosol in chronic asthma. Thorax 1982; 37(8):612-616.

3. Anderson SD, Seale JP, Rozea P, Bandler L, Theobald G, Lindsay DA. Inhaled and oral salbutamol in exercise-induced asthma. Am Rev Respir Dis 1976; 114(3):493-500.

4. Anon. Salbutamol: a review. Drugs 1971; 1:274-302.

5. Assem ES, Schild HO. Inhibition by sympathomimetic amines of histamine release by antigen in passively sensitized human lung. Nature 1969; 224(223):1028-1029.

6. Asthma bronchodilators and asthma mortality. Lancet 1969; 2(7615):305-307.

7. Barnes PJ, Pride NB. Dose-response curves to inhaled beta-adrenoceptor agonists in normal and asthmatic subjects. Br J Clin Pharmacol 1983; 15(6):677-682.

8. Bass BH, Disney ME, Morrison-Smith J. Effect of salbutamol on respiratory function in children with asthma. Lancet 1969; 2(7617):438.

9. Becker AB, Nelson NA, Simons FE. Inhaled salbutamol (albuterol) vs injected epinephrine in the treatment of acute asthma in children. J Pediatr 1983; 102(3):465-469.

10. Berg IM, Berg T, Rindqvist I. Salbutamol in the treatment of asthmatic children. A comparison of oral and inhalation therapy alone and in combination. European Journal of Respiratory Diseases 1981; 63:305-309.

11. Boe J, Wicksell M. Domiciliary nebulized salbutamol solution in the treatment of severe asthma bronchial. Current Therapeutic Research 1982; 32(4):555-565.

12. Brittain RT, Farmer JB, Jack D, Martin LE, Simpson WT. Alpha-[(t-Butylamine)methyl]-4-hydroxy-m-xylene-alpha 1,alpha 3-diol (AH.3365): a selective beta-adrenergic stimulant. Nature 1968; 219(156):862-863.

13. Brittain RT. A comparison of the pharmacology of salbutamol with that of isoprenaline, orciprenaline and trimetoquinol. Postgrad Med J 1971; 47:Suppl-6.

14. Cayton RM, Webber B, Paterson JW, Clark TJ. A comparison of salbutamol given by pressure-packed aerosol or nebulization via IPPB in acute asthma. Br J Dis Chest 1978; 72(3):222-224.

15. Choo-Kang YF, Simpson WT, Grant IW. Controlled comparison of the bronchodilator effects of three beta-adrenergic stimulant drugs administered by inhalation to patients with asthma. Br Med J 1969; 2(652):287-289.

16. Choo-Kang YF, Grant IW. Comparison of two methods of administering bronchodilator aerosol to asthmatic patients. Br Med J 1975; 2(5963):119-120.

17. Christensson P, Arborelius M, Jr., Lilja B. Salbutamol inhalation in chronic asthma bronchiale: dose aerosol vs jet nebulizer. Chest 1981; 79(4):416-419.

18. Collier JG, Dornhorst AC. Evidence for two different types of beta-receptors in man. Nature 1969; 223(212):1283-1284.

19. Corris PA, Neville E, Nariman S, Gibson GJ. Dose-response study of inhaled salbutamol powder in chronic airflow obstruction. Thorax 1983; 38(4):292-296.

20. Croner S, Hedenskog S, Kjellman NI, Odelram H. Salbutamol by powder or spray inhalation in childhood asthma. Allergy 1980; 35(7):589-592.

21. Cullum VA, Farmer JB, Jack D, Levy GP. Salbutamol: a new, selective beta-adrenoceptive receptor stimulant. Br J Pharmacol 1969; 35(1):141-151.

22. Dawson KP, Unter CE, Deo S, Fergusson DM. Inhalation powder and oral salbutamol combination. Arch Dis Child 1986; 61(11):1111-1113.

23. Duncan D, Paterson IC, Harris D, Crompton GK. Comparison of the bronchodilator effects of salbutamol inhaled as a dry powder and by conventional pressurized aerosol. British Journal of Clinical Pharmacology 1977; 4:669-671.

24. Evans ME, Walker SR, Brittain RT, Paterson JW. The metabolism of salbutamol in man. Xenobiotica 1973; 3(2):113-120.

25. Farmer JB, Levy PG. New sympathomimetic amines: actions on catecholamine receptors. Br J Pharmacol 1968; 34(3):698P.

26. Farmer JB, Levy GP. Comparative beta-adrenoceptive stimulant properties of salbutamol (AH 3365), orciprenaline and soterenol (MJ 1992). Br J Pharmacol 1969; 35(2):358-359.

27. Farmer JB, Levy GP, Marshall RJ. A comparison of the beta-adrenoceptor stimulant properties of salbutamol, orciprenaline and soterenol with those of isoprenaline. J Pharm Pharmacol 1970; 22(12):945-947.

28. Farmer JB, Kennedy I, Levy GP, Marshall RJ. A comparison of the beta-adrenoceptor stimulant properties of isoprenaline, with those of orciprenaline, salbutamol, soterenol and trimetoquinol on isolated atria and trachea of the guinea pig. J Pharm Pharmacol 1970; 22(1):61-63.

29. Fergusson RJ, Carmichael J, Rafferty P, Willey RF, Crompton GK, Grant IW. Nebulized salbutamol in life-threatening asthma: is IPPB necessary? Br J Dis Chest 1983; 77(3):255-261.

30. Fletcher CM, Herzheimer H. Salbutamol: Proceedings of an international symposium. Postgrad Med J 1971; 47(suppl):3-133.

31. Francis PW, Krastins IR, Levison H. Oral and inhaled salbutamol in the prevention of exercise-induced bronchospasm. Pediatrics 1980; 66(1):103-108.

32. Gayrard P, Orehek J, Charpin J. Comparative study of new beta-adrenergic stimulant in asthma: salbutamol. Postgrad Med J 1971; 47(Suppl):46.

33. Goldman JM, Hadley ME. The effect of butoxamine, N-isopropylmethoxamine and salbutamol (AH-3365) on melanophore beta-adrenergic receptors. J Pharm Pharmacol 1969; 21(12):854-855.

34. Grant IWB. Bronchodilator aerosols. Proceedings of the chest and heart association conference on new ideas in asthma and its management. 1969; 48-53.

35. Grimwood K, Johnson-Barrett JJ, Taylor B. Salbutamol: tablets, inhalational powder, or nebulizer? Br Med J (Clin Res Ed) 1981; 282(6258):105-106.

36. Grimwood K, Fergusson DM, Dawson KP. Combination of salbutamol inhalational powder and tablets in asthma. Arch Dis Child 1983; 58(4):283-285.

37. Hallworth GW. An improved design of powder inhaler. Br J Clin Pharmacol 1977; 4:673-675.

38. Hargreave FE, Dolovich J, Newhouse MT. The assessment and treatment of asthma: a conference report. J Allergy Clin Immunol 1990; 85(6):1098-1111.

39. Hartley D, Jack D, Lunts LH, Ritchie AC. New class of selective stimulants of beta-adrenergic receptors. Nature 1968; 219(156):861-862.

40. Hartley JP, Nogrady SG, Seaton A. Long-term comparison of salbutamol powder with salbutamol aerosol in asthmatic out-patients. Br J Dis Chest 1979; 73(3):271-276.

41. Hartley JPR, Nogrady SG, Gibby OM, Seaton A. Bronchodilator effects of dry salbutamol powder administered by rotahaler. British Journal of Clinical Pharmacology 1977; 4:673-675.

42. Heaf PJ, Mattila MJ. Assessment of bronchodilator drugs on asthmatic out-patients by daily measurements of the peak expiratory flow rate. Arzneimittelforschung 1969; 19(12):1927-1929.

43. Hetzel MR, Clark TJ. Comparison of salbutamol Rotahaler with conventional pressurized

aerosol. Clin Allergy 1977; 7(6):563-568.

44. Kamburoff PL, Rime FJ. Oral and inhaled salbutamol as a bronchodilator. Br J Dis Chest 1970; 64(1):46-54.

45. Kelman GR, Palmer KN, Cross MR. Cardiovascular effects of AH.3365 (salbutamol). Nature 1969; 221(187):1251.

46. Kennedy MC. Beta-adrenergic stimulants in asthma. Br Med J 1969; 3(663):174.

47. Kennedy MC, Simpson WT. Human pharmacological and clinical studies on salbutamol: a specific beta-adrenergic bronchodilator. Br J Dis Chest 1969; 63(3):165-174.

48. Konig P. Treatment of severe attacks of asthma in children with nebulized B2 adrenergic agents. Ann Allergy 1978; 40(3):185-188.

49. Latimer KM, Roberts R, Dolovich J, Hargreave FE. Salbutamol: comparison of bronchodilating effect of inhaled powder and aerosol in asthmatic subjects. Can Med Assoc J 1982; 127(9):857-859.

50. Lee H, Evans HE. Lack of cardiac effect from repeated doses of albuterol aerosol. A margin of safety. Clin Pediatr (Phila) 1986; 25(7):349-352.

51. Lenney W, Milner AD, Hiller EJ. Use of salbutamol powder in childhood asthma. Arch Dis Child 1978; 53(12):958-961.

52. Lenney W, Milner AD, Hiller EJ. At what age do bronchodialator drugs work? Arch Dis Child 1978; 53(7):532-535.

53. Lewis AAG, ed. Salbutamol: Proceedings of an international symposium. Post Grad Med J 1971; 47(Suppl):3-133.

54. Lewis RA, Fleming JS. Fractional deposition from a jet nebulizer: how it differs from a metered-dose inhaler. Br J Dis Chest 1985; 79(4):361-367.

55. Muittari A, Ahonen A. Comparison of the bronchodilator effect of inhaled salbutamol powder and pressurized salbutamol aerosol. Current Therapeutic Research 1979; 25(6):804-808.

56. Nayler WG. Some observations on the pharmacological effects of salbutamol, with particular reference to the cardiovascular system. Postgrad Med J 1971; 47(Suppl):21.

57. Neville A, Palmer JB, Gaddie J, May CS, Palmer KN, Murchison LE. Metabolic effects of salbutamol: comparison of aerosol and intravenous administration. Br Med J 1977; 1(6058):413-414.

58. Newman SP. Aerosol deposition considerations in inhalation therapy. Chest 1985; 88(2

Suppl):152S-160S.

59. Orgel HA, Meltzer EO, Welch MJ, Kemp JP. Inhaled albuterol powder for the treatment of asthma - a dose-response study. J Allergy Clin Immunol 1985; 75(4):468-471.

60. Palmer KN, Diament ML. Effect of salbutamol on blood-gas tensions in asthma. Lancet 1969; 2(7619):541.

61. Palmer KN, Legge JS. Disodium chromoglycate in exercise-induced asthma. Lancet 1969; 2(7613):219.

62. Palmer KN, Diament ML. Dynamic and static lung volumes, blood-gas tensions, and transfer factor in chronic obstructive bronchitis. Lancet 1969; 1(7605):1073-1075.

63. Palmer KN. Progress in asthma. Postgrad Med J 1969; 45(523):336-341.

64. Palmer KN, Diament ML. Dynamic and static lung volumes and blood-gas tensions in bronchial asthma. Lancet 1969; 1(7595):591-593.

65. Palmer KN, Diament ML. Effect of salbutamol on spirometry and blood-gas tensions in bronchial asthma. Br Med J 1969; 1(635):31-32.

66. Paterson JW. Salbutamol (Ventolin). Prescribers 1970; 10:19.

67. Postgrad Med J. March 1971; (Supplement 47).

68. Pover GM, Browning AK, Mullinger BM, Butler AG, Dash CH. A new dry powder inhaler. Practitioner 1982; 226(1365):565-567.

69. Pullan CR, Martin AJ. Protective effect of inhaled salbutamol powder in children assessed by histamine challenge. Br Med J 1980; 280(6211):364-365.

70. Radford M. Effect of salbutamol in infants with wheezy bronchitis. Arch Dis Child 1975; 50(7):535-538.

71. Riding WD, Chatterjee SS, Dinda P. Clinical trial of a new B-adrenergic stimulant in asthma. Br J Clin Pract 1969; 23(5):217-219.

72. Riding WD, Dinda P, Chatterjee SS. The bronchodilator and cardiac effects of five pressure-packed aerosols in asthma. Br J Dis Chest 1970; 64(1):37-45.

73. Ruffin RE, Obminski G, Newhouse MT. Aerosol salbutamol administration by IPPB: lowest effective dose. Thorax 1978; 33(6):689-693.

74. Rutter N, Milner AD, Hiller EJ. Effect of bronchodilators on respiratory resistance in infants and young children with bronchiolitis and wheezy bronchitis. Arch Dis Child 1975; 50(9):719-722.

75. Salbutamol (Ventolin) for asthma. Drug 1969; 7(10):38-39.

76. Shanahan EA, Wahlqvist ML, Wilmshurst EG. Effects of beta 2-adrenoceptor stimulation on cardiac metabolism in the conscious dog. Br J Pharmacol 1979; 66(2):229-233.

77. Shenfield GM, Evans ME, Walker SR, Paterson JW. The fate of nebulized salbutamol (albuterol) administered by intermittent positive pressure respiration to asthmatic patients. Am Rev Respir Dis 1973; 108(3):501-505.

78. Shenfield GM, Evans ME, Peterson JW. The effect of different nebulizers with and without intermittent positive pressure breathing on the absorption and metabolism of salbutamol. British Journal Clinical Pharmacology 1974; 1:295-300.

79. Shepherd GL, Hetzel MR, Clark TJ. Regular versus symptomatic aerosol bronchodilator treatment of asthma. Br J Dis Chest 1981; 75(2):215-217.

80. Sodha RJ, Schneider H. Transplacental transfer of beta-adrenergic drugs studied by an in vitro perfusion method of an isolated human placental lobule. Am J Obstet Gynecol 1983; 147(3):303-310.

81. Sovijarvi ARA, Lahdensuo A, Muittari A. Bronchodilating effect of salbutamol inhalation powder and salbutamol aerosol after metacholine-induced bronchoconstriction. Current Therapeutic Research 1982; 32(4):566-573.

82. Spector SL, Garza GM. Dose-response effects of albuterol aerosol compared with isoproterenol and placebo aerosols: response to albuterol, isoproterenol, and placebo aerosols. J Allergy Clin Immunol 1977; 59(4):280-286.

83. Swenson ER, Aitken ML. Hypokalemia occurs with inhaled albuterol. American Review of Respiratory Disease 1985; 131(4 Pt.2):A99.

84. Tal A, Bavilski C, Yohai D, Bearman JE, Gorodischer R, Moses SW. Dexamethasone and salbutamol in the treatment of acute wheezing in infants. Pediatrics 1983; 71(1):13-18.

85. Tarala RA, Madsen BW, Paterson JW. Comparative efficacy of salbutamol by pressurized aerosol and wet nebulizer in acute asthma. Br J Clin Pharmacol 1980; 10(4):393-397.

86. Tarlo SM, Broder I, Corey P, Davies G. A one-year study of salbutamol inhaled powder administered by a breath-activated device in asthmatics. Current Therapeutic Research 1984; 35(4):566-574.

87. Tattersfield AD, McNicol MW. Salbutamol and isoproterenol: A double-blind trial to compare bronchodilator and cardiovascular activity. New Eng J 1970; 1:65.

88. Today's Drugs - Bronchodilators. Br Med J 1970; 1(693):415-416.

89. Walker SR, Evans ME, Richards AJ, Paterson JW. The clinical pharmacology of oral and inhaled salbutamol. Clin Pharmacol Ther 1972; 13(6):861-867.

90. Walters EH, Cockroft A, Griffiths T, Rocchiccioli K, Davies BH. Optimal dose of salbutamol respiratory solution: comparison of three doses with plasma levels. Thorax 1981; 36(8):625-628.

91. Warrell DA, Robertson DG, Howes JN, Conolly ME, Paterson JW, Beilin LJ, et al. Comparison of cardiorespiratory effects of isoprenaline and salbutamol in patients with bronchial asthma. Br Med J 1970; 1(688):65-70.

92. Webber BA, Shenfield GM, Paterson JW. A comparison of three different techniques for giving nebulized albuterol to asthmatic patients. Am Rev Respir Dis 1974; 109(2):293-295.

93. Webber BA, Collins JV, Branthwaite MA. Severe acute asthma: a comparison of three methods of inhaling salbutamol. Br J Dis Chest 1982; 76(1):69-74.

94. Wood DO, Chandler D, Dugdale AE. Two methods of administering nebulized salbutamol: a controlled study. Aust Paediatr J 1978; 14(3):150-153.

95. PrVENTOLIN® Product Monograph GlaxoSmithKline Inc., Date of Revision October 2, 2014.

PART III: CONSUMER INFORMATION

[Pr]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:
ratio-SALBUTAMOL Respirator Solution is used in Adults and Children 5 years or older. It treats severe, worsening breathing problems (bronchospasm) associated with:

- Chronic bronchitis
- Bronchial asthma

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

The safety and effectiveness of ratio-SALBUTAMOL Respirator Solution in children below the age of 5 years are not known.

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.
- If your heart beats faster than normal.
- For the treatment of preterm labour or miscarriage.

What the medicinal ingredient is:
ratio-SALBUTAMOL Respirator Solution contains the active ingredient, salbutamol sulphate.

What the nonmedicinal ingredients are:
Benzalkonium chloride, dilute sulphuric acid and water.

What dosage forms it comes in:
ratio-SALBUTAMOL Respirator Solution contains 5 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 have low levels of potassium in your blood (hypokalemia), especially if you are taking:
    - Drugs known as xanthine derivatives (such as theophylline)
    - Steroids to treat asthma
    - Water pills (diuretics)
- You are pregnant or intend to become pregnant. Taking ratio-SALBUTAMOL Respirator Solution during pregnancy may cause harm to your baby. Your doctor will consider the benefit to you and the risk to your baby of taking ratio-SALBUTAMOL Respirator Solution while you're pregnant.
- You are breastfeeding. It is not known if ratio-SALBUTAMOL Respirator Solution passes into breast milk.

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, or the effect lasts for less than three hours, tell your doctor as soon as possible. If you notice a sudden worsening of your shortness of breath and wheeze shortly after taking your medicine, tell your doctor as soon as possible. It may be that your chest condition is worsening and you may need to add another type of medicine to your treatment.

You should always carry other asthma medication with you to use immediately in case you experience an asthma attack.

Effects on Children:
Children may experience:
- Changes in sleep patterns
- Changes in behaviour such as restlessness, excitability (hyperactivity)
- Seeing or hearing things that are not there

INTERACTIONS WITH THIS MEDICATION

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

The following may interact with ratio-SALBUTAMOL Respirator Solution:
- Anti-depressants
- Allergy medication
- Blood pressure-lowering drugs, including propranolol
- Diuretics ("water pills")
- Bronchodilators used to open the airway (such as other asthma medication)
- Epinephrine
- Digoxin, a heart medication

PROPER USE OF THIS MEDICATION

ratio-SALBUTAMOL Respirator Solution **should only be inhaled** from a nebulizer. It must not be injected or swallowed.

Do not let the ratio-SALBUTAMOL Respirator Solution or the mist produced by the nebulizer get in your eyes.

At home, ratio-SALBUTAMOL Respirator Solution should be diluted immediately before use.

Use your nebulizer in a well ventilated room. Some of the mist will be released into the air and may be breathed in by others.

Use ratio-SALBUTAMOL Respirator Solution only as directed by your doctor. During administration, your doctor may want to monitor your blood.

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 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, since this is usually a sign of worsening asthma.** Do not increase the dose or how often you take your medicine without informing your doctor**, as this may make you feel worse**. 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.

Usual dose:
Adults and Adolescents 13 years and older: 0.5 to 1 mL (2.5 to 5 mg of salbutamol).
Dilute in 2 to 5 mL or more of sterile normal saline.
Treatment may be repeated 4 times a day if necessary.

Children (5-12 years): 0.25 to 0.5 mL (1.25 to 2.5 mg of salbutamol).
Dilute in 2 to 5 mL or more of sterile normal saline.
Patients who have not improved on this dose may need 1 mL (5 mg salbutamol). Treatment may be repeated 4 times a day if necessary.

How to Use ratio-SALBUTAMOL Respirator Solution:
It is important that you use your ratio-SALBUTAMOL Respirator Solution properly. This will ensure that you receive the maximum benefit from your medicine. Make sure you know how, when and how much solution you should use. Follow your doctor's instructions carefully. If you are not sure, ask your doctor.

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.
   1 mL of ratio-SALBUTAMOL Respirator Solution is usually diluted with 2 to 5 mL of sterile normal saline.
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 nebulizer should be discarded.

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

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.

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

Overdose:

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

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

Missed dose:
If you forget to inhale a dose do not worry, 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

Side effects may include:

Effects on heart
- Faster heart beat than usual
- Palpitations
- Hypertension

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

Effects on muscles and joints
- Muscle cramps

Other effects
- Nausea and vomiting
- Chest pain or discomfort
- Flushing

- Difficulty urinating
- Unusual taste in your mouth
- Dry or irritated throat

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

Symptom/effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Very Rare	**Bronchospasm:** Increased wheezing or tightness in the chest or difficulty in breathing.			✓
	Allergic Reactions: (Hypersensitivity) Swelling of the eyelids, face, lips, tongue or throat, accompanied by difficulty in breathing, speaking or 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).			✓
Rare	Low level of potassium in your blood (hypokalemia).	✓		
	Hallucinations in Children: See or hear things that are not there.		✓	

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.

HOW TO STORE IT

Keep out of sight and reach of 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.

Reporting Side Effects

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php).

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

MORE INFORMATION

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

This document plus the full Product Monograph, prepared for health professionals can be found by contacting Teva Canada Limited at:

1-800-268-4127 ext. 1255005 (English);
1-877-777-9117 (French); or
druginfo@tevacanada.com

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