PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]VENTOLIN Respirator Solution

salbutamol sulfate solution

Solution, 5 mg/mL salbutamol (as sulfate), for Oral Inhalation

Bronchodilator

(beta$_2$-adrenergic agonist)

GlaxoSmithKline Inc.
100 Milverton Drive, Suite 800
Mississauga, ON
L5R 4H1
Canada

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RECENT MAJOR LABEL CHANGES

Not applicable

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Adults and Children (5 years and older):
VENTOLIN Respirator Solution (salbutamol sulfate) is indicated for:

- the treatment of severe bronchospasm associated with exacerbations of chronic bronchitis and bronchial asthma.

1.1 Pediatrics

Pediatrics (< 5 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use in patients less than 5 years of age.

Pediatrics (5 years of age and older): Based on the available information to Health Canada, VENTOLIN Respirator Solution has been authorized for pediatric patients 5 to < 18 years of age.

1.2 Geriatrics

No dosage adjustment is required in geriatric patients. Caution should be observed for patients with concomitant cardiovascular disease that could be adversely affected by beta2-agonists.

2 CONTRAINDICATIONS

VENTOLIN Respirator Solution is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container and in patients with tachyarrythmias. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

VENTOLIN Respirator Solution is contraindicated as a tocolytic in patients at risk of premature labour or threatened abortion.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

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

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

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

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

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

4.2 Recommended Dose and Dosage Adjustment

Adults and Adolescents (≥ 13 years of age)*:* VENTOLIN Respirator Solution 0.5 to 1 mL (2.5 to 5 mg of salbutamol) should be diluted in 2 to 5 mL or more of sterile normal saline. Treatment may be repeated every 4 to 6 hours as needed to a maximum four times a day if necessary.

Pediatrics (5 - 12 years): The average dose for a single treatment is 0.25 to 0.5 mL of VENTOLIN 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 VENTOLIN Respirator Solution may be increased to 1 mL (5 mg of salbutamol). Treatment may be repeated every 4 to 6 hours as needed to a maximum 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 be advised to immediately consult their healthcare professionals or the nearest hospital.

4.3 Reconstitution

Instructions for the dilution of VENTOLIN Respirator Solution are given below in Table 1.

Table 1 Dilution Table for VENTOLIN Respirator Solution

Dose (mg) of Salbutamol (per treatment)	Volume (mL) of VENTOLIN 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.

4.4 Administration

To ensure administration of the proper dose of the drug, the patient should be instructed by a healthcare professional on the proper use of the nebulizer system or respirator system.

For inhalation use only. The solution must **not** be injected or swallowed.

VENTOLIN Respirator Solution is to be used only under the direction of a physician employing either a respirator or nebulizer. VENTOLIN Respirator Solution can be taken by either the nebulization or intermittent positive pressure ventilation method.

Nebulization
VENTOLIN Respirator Solution can be used by "wet" nebulization. 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 VENTOLIN Respirator Solution.

Ventilation
When VENTOLIN Respirator Solution 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.

Storage and Use
In hospitals, VENTOLIN 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.

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

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

4.5 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.

5 OVERDOSAGE

Symptoms and Signs

The most common signs and symptoms of overdose with salbutamol are transient beta agonist pharmacologically mediated events (see 7 Warnings and Precautions and 8.1 Adverse Reaction Overview). Overdosage may cause tachycardia, cardiac arrhythmia, hypokalemia, hypertension and, in extreme cases, sudden death. Serum potassium levels should be monitored.

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

Treatment

Consideration should be given to discontinuation of treatment and appropriate symptomatic therapy. To antagonise the effect of salbutamol, the judicious use of a cardioselective beta-adrenergic blocking agent (e.g. metoprolol, atenolol) may be considered, bearing in mind the danger of inducing an asthmatic attack. During continuous administration of VENTOLIN Respirator Solution, any signs of overdosage can usually be counteracted by withdrawal of the drug.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Oral Inhalation	Respirator Solution / 5 mg per mL / salbutamol (salbutamol sulfate)	Benzalkonium chloride, dilute sulphuric acid and water for injection.

VENTOLIN Respirator Solution is an isotonic solution adjusted to pH 3.4 to 4.4 and preserved with benzalkonium chloride 0.01% w/v. Available in 10 mL bottles.

7 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 healthcare professional 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.

VENTOLIN 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 VENTOLIN and ipratropium bromide. A combination of nebulized VENTOLIN 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 enter the eye.

Cardiovascular

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 heart rate, blood pressure, symptoms, and/or ECG changes.

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 8.1 Adverse Reaction Overview). 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.

Immune

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

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

Neurologic

Care should be taken with patients with convulsive disorders.

Respiratory

VENTOLIN Respirator Solution contains 0.1 mg/mL benzalkonium chloride, which may cause bronchospasm, particularly in patients with asthma.

As with other inhaled medications, paradoxical bronchospasm may occur characterized by an immediate increase in wheezing after dosing. This should be treated immediately with an alternative presentation or a different fast-acting inhaled bronchodilator to relieve acute asthmatic symptoms. VENTOLIN Respirator Solution should be discontinued immediately, the patient assessed and if necessary, alternative therapy instituted (see 8.1 Adverse Reaction Overview). 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.

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 a healthcare provider 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, such as salbutamol, 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 healthcare professional 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 4.1 Dosing Considerations).

- **Deterioration of Asthma**

Asthma may deteriorate over time. If the patient needs to use VENTOLIN Respirator Solution more often than usual, this may be a sign of worsening asthma. This requires re-evaluation of the patient and treatment plan and consideration of adjusting the asthma maintenance therapy. If inhaled salbutamol treatment alone is not adequate to control asthma, concomitant anti-inflammatory therapy should be part of the treatment regimen. It is essential that the physician instruct the patient in the need for further evaluation if the patient's asthma becomes worse (see 4.1 Dosing Considerations).

7.1 Special Populations

7.1.1 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 16 NON-CLINICAL 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 VENTOLIN Respirator Solution is required to avoid interference with uterine contractility.

7.1.2 Breast-feeding

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.

7.1.3 Pediatrics

Pediatrics (5 – 12 years of age): VENTOLIN 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 VENTOLIN Respirator Solution), and only as presented by the healthcare professional.

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

Pediatrics (< 5 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use in patients less than 5 years of age.

7.1.4 Geriatrics

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

8 ADVERSE REACTIONS

8.1 Adverse 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 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Metabolic Effects).

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 formulation 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.

9 DRUG INTERACTIONS

9.4 Drug-Drug Interactions

Table 3 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 not usually be prescribed together.
Non-potassium sparing 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.

Drug type	Ref	Effect	Clinical comment
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 enter the eye.

Legend: CS=Class Statement

9.5 Drug-Food Interactions

Interactions of salbutamol with food have not been established.

9.6 Drug-Herb Interactions

Interactions of salbutamol with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions of salbutamol with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 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.

10.2 Pharmacodynamics

Prolonged use of salbutamol 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.

10.3 Pharmacokinetics

After inhalation of recommended doses of salbutamol, plasma drug levels are very low. When 100 mcg of tritiated salbutamol aerosol was administered to two normal volunteers, plasma levels of drug-radioactivity were insignificant at 10, 20 and 30 minutes following inhalation. The plasma concentration of salbutamol may be even less as the amount of plasma drug-radioactivity does not differentiate salbutamol from its principal metabolite, a sulfate ester. In a separate study, plasma salbutamol levels ranged from less than 0.5 ng/mL to 1.6 ng/mL in ten asthmatic children one hour after inhalation of 200 mcg 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 forced expiratory volume in one second (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-sulfate, which has negligible pharmacologic activity. Salbutamol may also be metabolized by oxidative deamination and/or conjugation with glucuronide.

Salbutamol is longer acting than isoprenaline in most patients by any route of administration because it is not a substrate for the cellular uptake processes for catecholamines nor for catechol-O-methyl transferase. Salbutamol and its metabolites are excreted in the urine (>80%) and the feces (5% to 10%). Plasma levels are insignificant after administration of aerosolized salbutamol; the plasma half-life ranges from 3.8 to 7.1 hours.

11 STORAGE, STABILITY AND DISPOSAL

Keep out of the sight and reach of children.

Store between 15 to 25^{o}C. Protect from light. Discard if not used within one month of opening.

Reconstituted VENTOLIN Respirator Solution
In hospitals, VENTOLIN 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.

In the home, VENTOLIN Respirator Solution may be diluted with sterile normal saline immediately before use. Any unused solution in the nebulizer should be discarded.

12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

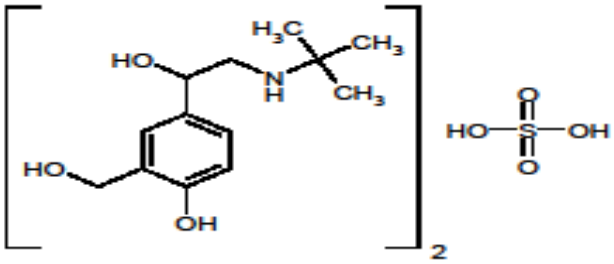
Drug Substance

Proper name: salbutamol sulfate

Chemical name: α^1-[(tert-butylamino)methyl]-4-hydroxy-m-xylene-α, α'-iol sulfate (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.

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.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Severe bronchospasm associated with exacerbations of chronic bronchitis and bronchial asthma
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 mcg), 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.

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 peak expiratory flow rate (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 Intermittent Positive-Pressure Ventilation (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 mL per treatment, diluted with normal saline, bringing the total volume to 2 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.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

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 mcg/kg intravenously.

Administration of salbutamol aerosol at a dose of 250 mcg/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 bypass, salbutamol, given at the dose of 25 mcg/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.

Acute Toxicity

Table 4 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 sulfate caused a significant dose-related increase in the incidence of benign leiomyomas of the mesovarium at doses corresponding to 111, 555, and 2,800 times the maximum human inhalation dose. In another study, the effect was blocked by the co-administration of propranolol. The relevance of these findings to humans is not known. An 18-month study in mice and a lifetime study in hamsters revealed no evidence of tumorigenicity.

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

A reproduction study in CD-1 mice given salbutamol at doses of 0.025, 0.25, and 2.5 mg/kg subcutaneously, corresponding to 1.4, 14, and 140 times the maximum human aerosol dose respectively, showed cleft palate formation in 5 of 111 (4.5%) fetuses at 0.25 mg/kg and in 10 of 108 (9.3%) fetuses at 2.5 mg/kg. No cleft palates were observed at a dose of 0.025 mg/kg salbutamol. Cleft palate occurred in 22 of 72 (30.5%) fetuses treated with 2.5 mg/kg isoprenaline (positive control).

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

Salbutamol had no adverse effect when given orally to Stride Dutch rabbits, at doses of 0.5, 2.32 and 10.75 mg/kg/day throughout pregnancy. At a dose of 50 mg/kg/day, which represents 2800 times the maximum human inhalation dose and 78 times the maximum human oral dose cranioschisis was observed in 7 of 19 (37%) fetuses.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]VENTOLIN Respirator Solution

salbutamol sulfate solution

Read this carefully before you start taking **VENTOLIN Respirator Solution** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **VENTOLIN Respirator Solution**.

What is VENTOLIN Respirator Solution used for?

VENTOLIN Respirator Solution is used in adults and children (5 years and older) to treat severe, worsening breathing problems (bronchospasm) associated with:

- chronic bronchitis (inflammation of the airways of the lungs with mucus production);
- bronchial asthma (inflammation of the airways of the lungs).

How does VENTOLIN Respirator Solution work?

VENTOLIN Respirator Solution belongs to a group of medicines known as “bronchodilators”. It works by relaxing the muscles of the small airways in the lungs. This helps open up the narrowed airways of the lungs making it easier to breath.

What are the ingredients in VENTOLIN Respirator Solution?

Medicinal ingredient: Salbutamol sulfate.

Non-medicinal ingredients: Benzalkonium chloride (0.01% w/v), dilute sulphuric acid, and water for injection.

VENTOLIN Respirator Solution comes in the following dosage forms:

Solution for oral inhalation using either a respirator or a nebulizer: 5 mg/mL of salbutamol (as salbutamol sulfate).

Do not use VENTOLIN Respirator Solution if:

- you are allergic to salbutamol sulfate or any of the other ingredients in VENTOLIN Respirator Solution.
- you have abnormal heart rhythms with a fast heartbeat (tachyarrhythmias).
- for the treatment of preterm labour or miscarriage.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take VENTOLIN Respirator Solution. Talk about any health conditions or problems you may have, including if you:

- have ever had to stop taking another medicine for this condition because you were allergic to it or because it caused problems.
- have thyroid problems.
- have heart or blood vessel problems.
- have high blood pressure.
- have diabetes.
- have a past history of seizures.
- have low levels of potassium in your blood (hypokalemia), especially if you are taking:
    - medicines known as xanthine derivatives (e.g., theophylline);
    - steroids, medicines used to treat asthma;
    - diuretics also known as “water pills”, medicines used to lower fluid levels and treat high blood pressure.
- have low oxygen levels in your body (hypoxia).
- are pregnant or plan to become pregnant. Taking VENTOLIN Respirator Solution during pregnancy may cause harm to your baby. Your healthcare professional will consider the benefit to you and the risk to your baby of taking VENTOLIN Respirator Solution while you're pregnant.
- are breastfeeding, plan to breastfeed, or are in labour. It is not known if VENTOLIN Respirator Solution passes into breast milk.

You should always carry your fast-acting aerosol or dry powder asthma medication with you to use immediately in case you experience an asthma attack.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with VENTOLIN Respirator Solution:

- anti-depressants, medicines used to treat depression (e.g., monoamine oxidase inhibitors, and tricyclic antidepressants).
- medicines used to treat allergies.
- beta-blockers, medicines used to lower blood pressure (e.g., propranolol).
- diuretics also known as “water pills”, medicines used to lower fluid levels and treat high blood pressure.
- other-bronchodilators, medicines used to open the airway (e.g., asthma medicines such as ipratropium bromide).
- epinephrine, a medicine that can be used to treat allergic reactions or sudden asthma attacks.
- digoxin, a medicine used to treat certain heart problems.

How to take VENTOLIN Respirator Solution:

- Take VENTOLIN Respirator Solution exactly as directed by your healthcare professional.
- It is important that you use your VENTOLIN Respirator Solution properly. This will ensure that you receive the prescribed dose of your medicine. Make sure you know how, when, and how

much solution you should use. Follow your healthcare professional's instructions carefully. If you are not sure, ask your healthcare professional.

- VENTOLIN Respirator Solution **should only be inhaled** from a nebulizer (or a respirator). It must not be injected or swallowed. Avoid any other routes of administration.
- At home, VENTOLIN Respirator Solution should be diluted immediately before use.
- The nebulizer or respirator should be properly functioning and regularly maintained. Before starting treatment, be certain that you are completely familiar with the use and proper care of your nebulizer or respirator.
- Do NOT let the VENTOLIN Respirator Solution or the mist produced by the nebulizer or respirator get in your eyes. This may cause unwanted side effects.
- 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.
- If VENTOLIN Respirator Solution is administered to you by a healthcare professional, they may monitor your blood and lung function.
- Other medicines (including asthma medicines) should only be used with VENTOLIN Respirator Solution when prescribed by your healthcare professional.

You should call your healthcare professional immediately if:

- the effects of one dose last less than 3 hours;
- you notice a sudden worsening of your shortness of breath shortly after taking your medicine;
- your symptoms get worse;
- your usual dose does not provide relief of wheezing or chest tightness;
- you need to use VENTOLIN Respirator Solution more often than before.

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

<u>Instructions for Use of VENTOLIN Respirator Solution</u>

1. When preparing the solution for inhalation, use a graduated syringe to draw up VENTOLIN Respirator Solution from the bottle at the dose directed by your physician. **Note**: Close the VENTOLIN Respirator Solution bottle as soon as the solution is drawn into the syringe. Keep the bottle closed at all times and do not open it unnecessarily.
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 VENTOLIN 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 nebulizing chamber. At this point, treatment is finished.
7. Any unused solution in the nebulizer should be discarded.

Children - VENTOLIN 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 healthcare professional.

Care of the VENTOLIN Respirator Solution and Nebulizer

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 VENTOLIN Respirator Solution bottle.

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

Usual dose:

Your healthcare professional will decide your dose of VENTOLIN Respirator Solution. This may depend on your condition, your age, and how you react to VENTOLIN Respirator Solution. Your dose may be repeated every 4 to 6 hours as directed.

The usual dose is as follows:

- **Adults and Adolescents (13 years of age and older):** 0.5 to 1 mL (2.5 to 5 mg of salbutamol) diluted in 2 to 5 mL or more of sterile normal saline. This may be repeated every 4 to 6 hours to a maximum 4 times a day if necessary.
- **Children (5 to 12 years of age):** 0.25 to 0.5 mL (1.25 to 2.5 mg of salbutamol) diluted in 2 to 5 mL or more of sterile normal saline. 1 mL (5 mg of salbutamol) may be used if the child's condition has not improved. This may be repeated every 4 to 6 hours to a maximum 4 times a day if necessary.

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

Overdose:

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

If you think you, or a person you are caring for, have taken too much VENTOLIN Respirator Solution, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss or forget to inhale a dose, skip the missed dose. Inhale the next dose at the time you would normally take it, or inhale a dose sooner than when it is scheduled if you become wheezy.

What are possible side effects from using VENTOLIN Respirator Solution?

These are not all the possible side effects you may have when taking VENTOLIN Respirator Solution. If you experience any side effects not listed here, tell your healthcare professional.

Side effects of VENTOLIN Respirator Solution may include:

- changes in behaviours such as restlessness, excitability (hyperactivity) in children;
- changes in sleep patterns in children;
- difficulty urinating;
- drowsiness;
- dry or irritated throat;
- feeling a little shaky;
- feeling anxious, irritable, or nervous;
- flushing;
- headache;
- muscle cramps;
- trouble sleeping (insomnia);
- unusual taste in your mouth;
- vertigo.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Heart problems: faster heartbeat than usual, irregular heartbeats or rhythms, palpitations, chest discomfort, shortness of breath, or weakness.		✓	
RARE			
Angina (not enough oxygen to the heart muscle): pain or pressure in the chest, or discomfort in the shoulder, arm, back, throat, jaw or teeth.			✓
Hallucinations in children: seeing or hearing things that are not there.		✓	
Hypertension (high blood pressure): shortness of breath, fatigue, dizziness, chest pain, or swelling in your ankles and legs.		✓	
Hypokalemia (low level of potassium in the blood): irregular heartbeats, muscle weakness, feeling unwell, cramping, constipation, feeling of skipped heart beats, fatigue.	✓		
VERY RARE			
Allergic reactions: swelling of the eyelids, face, lips, tongue or throat, difficulty breathing, difficulty speaking, difficulty swallowing, rash (hives), skin eruption or other effect on the skin or eyes, itchiness, fever, low blood pressure, or fainting.			✓
Bronchospasm (sudden narrowing of the airway): increased wheezing, tightness in the chest, or difficulty in breathing (can happen after taking your dose).			✓
Lactic acidosis (high level of acid in the blood): deep and rapid breathing, weight loss, fatigue, malaise, nausea, vomiting,			✓

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
abdominal pain, shortness of breath, feeling cold.			

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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

Storage:

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

Keep out of sight and reach of children.

If you want more information about VENTOLIN Respirator Solution:

- Talk to your healthcare professional.
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (www.gsk.ca), or by calling 1-800-387-7374.

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

This leaflet was prepared by GlaxoSmithKline Inc.

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