

**PRODUCT MONOGRAPH**

**PrAPO-SALVENT RESPIRATOR SOLUTIONS  
(Salbutamol Sulfate Solutions BP)**

**PrAPO-SALVENT Respirator Solution 50 mg in 10 mL (5 mg/mL Salbutamol)**

**PrAPO-SALVENT Sterules 1.25 mg in 2.5 mL (0.5 mg/mL Salbutamol)**

**PrAPO-SALVENT Sterules 2.5 mg in 2.5 mL (1 mg/mL Salbutamol)**

**PrAPO-SALVENT Sterules 5.0 mg in 2.5 mL (2 mg/mL Salbutamol)**

**Bronchodilator,  $\beta_2$ -adrenergic Stimulant**

**APOTEX INC.  
150 Signet Drive  
Toronto, Ontario  
M9L 1T9**

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**Control # 236795**

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**PART I: HEALTH PROFESSIONAL INFORMATION**

**SUMMARY PRODUCT INFORMATION**

<b>Route of Administration</b>	<b>Dosage Form / Strength</b>	<b>All Nonmedicinal Ingredients</b>
Oral Inhalation	Respirator Solution 50 mg in 10 mL (5 mg/mL Salbutamol)	dilute sulfuric acid, benzalkonium chloride and water.
	Sterules 1.25 mg in 2.5 mL (0.5 mg/mL Salbutamol)	dilute sulfuric acid, sodium chloride and water.
	Sterules 2.5 mg in 2.5 mL (1 mg/mL Salbutamol)	
	Sterules 5.0 mg in 2.5 mL (2 mg/mL Salbutamol)	

**INDICATIONS AND CLINICAL USE**

**Adults and Children (5 years and older):**

APO-SALVENT Respirator Solutions (Salbutamol Sulfate Solution BP) 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, APO-SALVENT Respirator Solutions (Salbutamol Sulfate Solution BP) 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.

APO-SALVENT Respirator Solutions. 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 respirator solutions and ipratropium bromide. A combination of nebulized salbutamol respirator solutions 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.

### **Deterioration of Asthma**

Asthma may deteriorate over time. If the patient needs to use salbutamol 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 **DOSAGE AND ADMINISTRATION**).

### **Cardiovascular**

In individual patients, any beta<sub>2</sub>-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 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**

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. APO-SALVENT Respirator Solutions 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 to 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 APO-SALVENT 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 to 12 years):**

### **APO-SALVENT Respirator Solutions**

APO-SALVENT Respirator Solutions should be used under the supervision of an adult who understands the proper use of the respirator and/or nebulizer (as well as APO-SALVENT Respirator Solution and APO-SALVENT STERULES), 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<sub>2</sub>-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<sub>2</sub>-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<sub>2</sub>-agonists, special caution should be observed when using APO-SALVENT Respirator Solutions 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 ( $\geq 1/10$ ), common ( $\geq 1/100$  and  $< 1/10$ ), uncommon ( $\geq 1/1000$  and  $< 1/100$ ), rare ( $\geq 1/10,000$  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<sub>2</sub>-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 respiratory 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<sub>2</sub>-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**

<b>Drug type</b>	<b>Ref</b>	<b>Effect</b>	<b>Clinical comment</b>
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.
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

Drug type	Ref	Effect	Clinical comment
			cautiously. Patients should receive adequate instruction in correct administration and be warned not to let the solution or mist enter the eye.

Legend: CS=Class Statement

## DOSAGE AND ADMINISTRATION

### Dosing Considerations

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

Increasing demand for APO-SALVENT (salbutamol sulphate) Respirator Solution or Sterules 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 doctors or the nearest hospital.

APO-SALVENT Respirator Solutions (Salbutamol Sulfate Solution BP) may be preferred in the treatment of severe bronchospasm associated with exacerbations of chronic bronchitis and bronchial asthma.

### Recommended Dose and Dosage Adjustment

#### **Apo-Salvent Respirator Solution**

**Adults and Adolescent  $\geq 13$  years of age:** In adults, APO-SALVENT 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.

**Children (5 to 12 years):** The average dose for a single treatment is 0.25 to 0.5 mL of APO-SALVENT 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 APO-SALVENT Respirator

Solution (Salbutamol Sulfate Solution BP) 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 doctor or the nearest hospital.

### **Apo-Salvent Sterules**

**Adults and Adolescents  $\geq 13$  years of age:** Patients requiring single doses of 2.5 mg or 5 mg may be administered the contents of a single APO-SALVENT Respirator Solution unit dose (APO-SALVENT Sterules 2.5 or 5 mg of salbutamol). Treatment may be repeated every 4 to 6 hours as needed to a maximum 4 times a day if necessary.

**Children (5 to 12 years):** Children requiring single doses of 1.25 or 2.5 mg may be administered the contents of a single APO-SALVENT Respirator Solution unit dose (APO-SALVENT Sterules 2.5 mg of salbutamol). For more refractory cases children may use a 5 mg unit dose (see dosage above). Treatment may be repeated every 4 to 6 hours as needed to a maximum 4 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.

APO-SALVENT Respirator Solutions (Salbutamol Sulfate Solution BP) are to be used only under the direction of a physician employing either a respirator or nebulizer. APO-SALVENT Respirator Solutions 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 APO-SALVENT Respirator Solution, or to utilize the Unit Dose (APO-SALVENT Sterules) presentation.

When APO-SALVENT Respirator Solution is administered through intermittent positive pressure ventilation, the inspiratory pressure is usually 10 to 20 cm H<sub>2</sub>O 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*, APO-SALVENT 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 not exceeding 25°C 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. APO-SALVENT Sterules and APO-SALVENT 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.

APO-SALVENT Sterules are to be used with a nebulizer, under the direction of a physician. APO-SALVENT Sterules are intended to be used undiluted. However, if prolonged delivery time is desirable (more than 10 minutes) dilution using sterile normal saline as a diluent may be required.

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

## **OVERDOSAGE**

### **Symptoms and signs**

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

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 salbutamol Respirator Solution, any signs of overdose can usually be counteracted by withdrawal of the drug.

For management of a suspected drug overdose, contact your regional Poison Control Centre.
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## **ACTION AND CLINICAL PHARMACOLOGY**

### **Mechanism of Action**

Salbutamol produces bronchodilation through stimulation of beta<sub>2</sub>-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<sub>2</sub>-receptors are the predominant adrenergic receptors in bronchial smooth muscle and beta<sub>1</sub>-receptors are the predominant receptors in the heart, there are also beta<sub>2</sub>-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<sub>2</sub>-agonists may have cardiac effects. At therapeutic doses, salbutamol has little action on the beta<sub>1</sub>- 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<sub>1</sub> 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

*APO-SALVENT Respirator Solution:* Store between 15°C to 25°C. Protect from light.

*APO-SALVENT Sterules:* Store between 15°C to 25°C. Protect from light. Discard any unused sterules in opened foil pouches after 3 months.

### Reconstituted APO-SALVENT Respirator Solution

*In hospitals,* APO-SALVENT Respirator Solution, diluted (1:5 or 1:10) with sterile normal saline, should be used within 24 hours from the time of dilution when stored at room temperature not exceeding 25°C or within 48 hours when stored under refrigeration. Instructions for the dilution of APO-SALVENT Respirator Solution are given below in the Dilution Table.

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

<b>Table 2 DILUTION TABLE FOR APO-SALVENT RESPIRATOR SOLUTION</b>
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Dose (mg) of Salbutamol (per treatment)	Volume (mL) of APO-SALVENT 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**

APO-SALVENT Respirator Solution (Salbutamol Sulfate Solution BP) (sterile) contains salbutamol sulfate equivalent to 5 mg of salbutamol base per mL. In addition to salbutamol sulfate, APO-SALVENT Respirator Solution also contains the non-medicinal ingredients: dilute sulfuric acid, benzalkonium chloride and water.

APO-SALVENT Sterules (Salbutamol Sulfate Solution BP) (unit dose) (sterile) contain salbutamol sulfate equivalent to 1.25 or 2.5 or 5 mg of salbutamol base in 2.5 mL. It is an isotonic solution adjusted to pH 3.0 to 4.5. In addition to salbutamol sulfate, APO-SALVENT Sterules also contain the non-medicinal ingredients: dilute sulfuric acid, sodium chloride and water.

APO-SALVENT Respirator Solution (salbutamol sulfate solution BP) is available in bottles of 10 mL.

APO-SALVENT Sterules (Salbutamol Sulfate Solution BP) (unit dose) are available in:  
 Cartons of 20 (0.5 mg/mL)  
 Cartons of 10 and 20 (1 and 2 mg/mL).

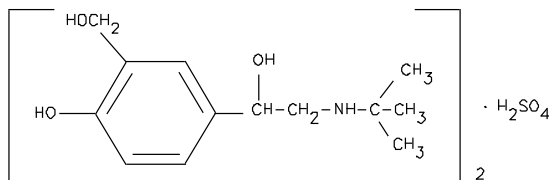
## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

#### Drug Substance

*Proper Name:* salbutamol sulfate BP  
*Chemical Name:* 2-t-butylamino-1-(4-hydroxy-3-hydroxymethylphenyl) ethanol sulfate

*Structural Formula:*



*Molecular Formula and Molecular Mass:*  $(C_{13}H_{21}NO_3)_2 \cdot H_2SO_4$  576.7 g/mol

#### Physicochemical Properties

*Description:*

Salbutamol sulfate is a white, crystalline solid that is soluble in water.

### 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<sub>1</sub>. 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<sub>1</sub> 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<sub>1</sub> 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<sub>1</sub> 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 to 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 to 3) and inhalation of aerosol and powder (weeks 4 to 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<sub>1</sub> 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 outpatient 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.

## **DETAILED PHARMACOLOGY**

### **Clinical Pharmacology**

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.

### **Animal Pharmacology**

*In vitro* studies and *in vivo* pharmacologic studies have demonstrated that salbutamol has a preferential effect on beta<sub>2</sub>-adrenergic receptors compared with isoprenaline. While it is

recognized that beta<sub>2</sub>-adrenergic receptors are the predominant receptors in bronchial smooth muscle, recent data indicate that there is a population of beta<sub>2</sub>-receptors in the human heart existing in a concentration between 10% and 50%. The precise function of these, however, is not yet established.

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

The muscle-relaxing effect of salbutamol was found to be more prolonged than when the effect was induced by isoprenaline. As suggested from the results of experiments in isolated animal tissues, salbutamol has been shown to produce a substantial bronchodilator effect in the intact animal. In the 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<sub>1</sub>-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 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 <sub>50</sub>	Intravenous LD <sub>50</sub>
Mouse (10)	>2000 mg/kg	72 mg/kg
Rat (10)	>2000 mg/kg	60 mg/kg

Rat (n)	Intraperitoneal LD <sub>50</sub>
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.

## REFERENCES

- 1) 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.
- 2) 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: 393-397.
- 3) Product Monograph. Ventolin<sup>®</sup> Respirator Solutions/Ventolin<sup>®</sup> Nebules P.F. Bronchodilator, Beta<sub>2</sub>-adrenergic Stimulant. GlaxoSmithKline Inc., Mississauga, Ontario, Control# 207158, Date of Revision: November 17, 2017.

**PART III: CONSUMER INFORMATION****Pr APO-SALVENT Respirator Solution  
(Salbutamol Sulfate Solutions BP)****50 mg / 10 mL  
(5 mg/mL Salbutamol)**

This leaflet is part III of a three-part "Product Monograph" for APO-SALVENT Respirator Solution 50 mg in 10 mL (5 mg/mL Salbutamol) and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about APO-SALVENT Respirator Solution 50 mg/10 mL (5 mg/mL Salbutamol). 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:**

APO-SALVENT 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 APO-SALVENT 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 APO-SALVENT 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:**

Salbutamol sulphate.

**What the nonmedicinal ingredients are:**

dilute sulfuric acid, benzalkonium chloride and water.

**What dosage forms it comes in:**

Solution for oral inhalation; 50 mg in 10 mL (5 mg/mL Salbutamol).

**WARNINGS AND PRECAUTIONS**

BEFORE you use APO-SALVENT 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 APO-SALVENT 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 APO-SALVENT Respirator Solution while you're pregnant.
- You are breastfeeding. It is not known if APO-SALVENT 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 APO-SALVENT 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 behavior 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 APO-SALVENT 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**

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

Do not let the APO-SALVENT Respirator Solution or the mist produced by the nebulizer, get in your eyes.

At home, APO-SALVENT 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 APO-SALVENT Respirator Solution only as directed by your doctor. During administration your doctor may want to monitor your blood.

The action of APO-SALVENT Respirator Solution may last for up to 6 hours and should last at least 4 hours. **You should call your doctor immediately if:**

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

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

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

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

**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 every 4 to 6 hours to a maximum 4 times a day if necessary.

**Children (5 to 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 every 4 to 6 hours to a maximum 4 times a day if necessary.

**How to Use APO-SALVENT Respirator Solution:**

It is important that you use your APO-SALVENT 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 APO-SALVENT Respirator Solution from the bottle at the dose directed by your physician. **Note:** close the APO-SALVENT 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. Discard unused, diluted APO-SALVENT 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 APO-SALVENT 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** –APO-SALVENT 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 APO-SALVENT 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

- 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 APO-SALVENT Respirator Solution bottle.

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

**Overdose:**

If you think you have taken too much APO-SALVENT Respirator Solution, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

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

- 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 DO THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom/Effect		Talk to your doctor or pharmacist		Stop taking drug and seek immediate emergency medical attention
		Only if severe	In all cases	
Common	<b>Faster heart beat than usual</b>		√	
Uncommon	<b>Irregular heart beat</b> (palpitations)		√	
Rare	<b>Low levels of potassium</b> in your blood (hypokalemia)	√		
	<b>Hallucinations in Children:</b> see or hear things that are not there		√	
Very Rare	<b>Bronchospasm:</b> Increased wheezing or tightness in the chest or difficulty in breathing.			√

SERIOUS SIDE EFFECTS, HOW OFTEN DO THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom/Effect	Talk to your doctor or pharmacist		Stop taking drug and seek immediate emergency medical attention
	Only if severe	In all cases	
<b>Allergic reactions:</b> (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).			√
<b>Deep and rapid breathing, vomiting, abdominal pain, weight loss, fatigue, malaise</b> (sign of lactic acidosis too much lactic acid in the blood)			√
<b>Irregular Heart Beat</b> (atrial fibrillation. Supraventricular tachycardia, extrasystoles)		√	

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

**HOW TO STORE IT**

**Keep out of sight and reach of children.**

Keep the APO-SALVENT Respirator Solution in a dry

place and store it between 15°C to 25°C. Protect from light.

#### Reporting Side Effects

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

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

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

#### MORE INFORMATION

##### If you want more information about APO-SALVENT Respirator Solution:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website (<https://health-products.canada.ca/dpd-bdpp/index-eng.jsp>). Find the Consumer Information on the manufacturer's website <http://www.apotex.ca/products>, or by calling 1-800-667-4708.

This leaflet was prepared by **Apotex Inc., Toronto, Ontario, M9L 1T9.**

Last revised: February 03, 2020

**PART III: CONSUMER INFORMATION**

**<sup>Pr</sup>APO-SALVENT STERULES  
(Salbutamol Sulfate Solutions BP)**

**1.25 mg/2.5 mL  
(0.5 mg/mL Salbutamol)**

**2.5 mg/2.5 mL  
(1 mg/mL Salbutamol)**

**5.0 mg/2.5 mL  
(2 mg/mL Salbutamol)**

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

APO-SALVENT Sterules are used in Adults and Children 5 years or older. They treat 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 APO-SALVENT Sterules in children below the age of 5 years are not known.

**What it does:**

It can relieve chest tightness and wheezing if you have asthma or another chest illness.

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 APO-SALVENT Sterules if:

- you are allergic to it or any of the components of its formulation (see **What the nonmedicinal ingredients are**).
- your heart beats faster than normal.
- for the treatment of preterm labour or miscarriage.

**What the medicinal ingredient is:**

Salbutamol sulphate.

**What the nonmedicinal ingredients are:**

dilute sulfuric acid, sodium chloride and water.

**What dosage forms it comes in:**

Sterules 1.25 mg in 2.5 mL (0.5 mg/mL Salbutamol), 2.5 mg in 2.5 mL (1 mg/mL Salbutamol) and 5.0 mg in 2.5 mL (2 mg/mL Salbutamol)

**WARNINGS AND PRECAUTIONS**

BEFORE you use APO-SALVENT Sterules 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 raised 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 APO-SALVENT Sterules during pregnancy may cause harm to your baby. Your doctor will consider the benefit to you and the risk to your baby of taking APO-SALVENT Sterules while you're pregnant.
- You are breastfeeding. It is not known if APO-SALVENT Sterules 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 APO-SALVENT Sterules. 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 behavior 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 APO-SALVENT Sterules:

- 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**

APO-SALVENT Sterules **should only be inhaled** from a nebulizer. It must not be injected or swallowed.

Do not let the APO-SALVENT Sterules or the mist

produced by the nebulizer, get in your eyes.

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 APO-SALVENT Sterules only as directed by your doctor. During administration your doctor may want to monitor your blood.

The action of APO-SALVENT Sterules may last for up to 6 hours and should last at least 4 hours.

**You should call your doctor immediately if:**

- **the effect of one dose last less than 3 hours**
- **you notice a sudden worsening of your shortness of breath**
- **your symptoms get worse;**
- your usual dose does not provide relief of wheezing or chest tightness;
- **you need to use APO-SALVENT Sterules more than before**

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

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

When using APO-SALVENT Sterules, other medicines (including asthma medicines) should only be used when prescribed by your doctor.

**Usual dose:**

**Adults and Adolescents 13 years and older:** 1 ampoule (either 2.5 to 5 mg), repeated every 4 to 6 hours to a maximum 4 times a day if necessary.

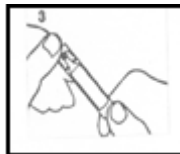
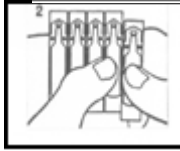
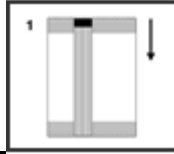
**Children (5 to 12 years):** 1 ampoule (2.5 mg), repeated every 4 to 6 hours to a maximum 4 times a day if necessary.

Patients who have not improved on this does, may need 1 ampoule (5 mg), repeated 4 times a day if necessary.

**How to Use APO-SALVENT Sterules:**

1. Prepare the nebulizer for filling according to the manufacturer’s instructions.

2. To open the foil pouch, lift the foil at the centre and peel downwards (**Diagram 1**). Do not peel the foil wrap of the pouch completely. Remove the sterules.
3. To detach an APO-SALVENT Sterule, push one sterule downwards and away while holding the remaining sterules securely (**Diagram 2**). Return the remaining sterules to the foil pouch and place the pouch back in the carton.
4. Holding the top of the sterule securely, twist the body to open (**Diagram 3**).
5. Place the open end of the sterule well into the nebulizer cup and squeeze slowly (**Diagram 4**). Ensure the contents are emptied into the nebulizer cup.
6. Gently shake the nebulizer and connect it with the mouthpiece or face mask. Connect the apparatus to the air pump or oxygen and start the treatment.
7. Breathe calmly and evenly as much as possible until no more mist is formed in the nebulizer chamber. At this point, treatment is finished.
8. After use discard any solution remaining in the nebulizer cup. Clean the nebulizer according to the manufacturer's instructions.



- a. supply tube.
- b. Turn on the pump and blow air through for 1 minute. If there is evidence of clogging, clean the openings and tube connectors with the detergent, then rinse with water.
- c. Reassemble.

**Overdose:**

If you think you have taken too much APO-SALVENT Sterules, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

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**

**Children** –APO-SALVENT Sterules should be used under the supervision of an adult who understands the proper use of the nebulizer and only as prescribed by the doctor.

**Care of the APO-SALVENT Sterules and Nebulizer.**

**To clean the nebulizer**

After each use, clean the nebulizer as follows:

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

Side effects may include:

Effects on heart

- Hypertension

Effects on nervous system

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

Effects on muscles and joints

- Muscle cramps

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 DO THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom/Effect		Talk to your doctor or pharmacist		Stop taking drug and seek immediate emergency medical attention
		Only if severe	In all cases	
<b>Common</b>	Faster heart beat than usual		√	
<b>Uncommon</b>	Irregular heart beat (palpitations)		√	
<b>Rare</b>	Low level of potassium in your blood (hypokalemia)	√		
	<b>Hallucinations in Children:</b> see or hear things that are not there		√	
Very Rare	<b>Bronchospasm:</b> Increased wheezing or tightness in the chest or difficulty in breathing			√
	<b>Allergic reactions:</b> (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)			√
<b>Irregular Heart Beat</b> (atrial fibrillation) supraventricular tachycardia, extrasystoles)	√		

*This is not a complete list of side effects. If you have any unexpected effects after receiving APO-SALVENT Sterules contact your doctor or pharmacist.*

#### HOW TO STORE IT

**Keep out of sight and reach of children.**

Keep the APO-SALVENT Sterules 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.

Discard any unused sterules in opened foil pouches after 3 months.

#### Reporting Side Effects

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

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

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

**MORE INFORMATION**

**If you want more information about APO-SALVENT STERULES:**

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website (<https://health-products.canada.ca/dpd-bdpp/index-eng.jsp>). Find the Consumer Information on the manufacturer's website <http://www.apotex.ca/products>, or by calling 1-800-667-4708.

This leaflet was prepared by **Apotex Inc., Toronto, Ontario, M9L 1T9.**

Last revised: March 16, 2020