**GenRx SALBUTAMOL INHALATION AMPOULE**

**NAME OF THE MEDICINE**
Salbutamol sulfate.

Chemical Name: \([RS]-2\-(1,1\text{-dimethyl})\text{ethylamino}-1\-[4\text{-hydroxy}-3\-(\text{hydroxymethyl})\text{phenyl}]\text{ethanol}\] sulfate.

Structural Formula:

\[
\text{HO} \quad \text{HO} \quad \text{N} \quad \text{OH} \\
\text{CH}_3 \quad \text{CH}_3 \quad \text{CH}_3 \quad \text{H}_2\text{SO}_4
\]

Molecular Formula: \((C_{13}H_{21}NO_3)_2\cdot H_2SO_4\)
Molecular Weight: 576.7
CAS Registry Number: 51022-70-9

**DESCRIPTION**
Salbutamol sulfate is a white or almost white, odourless powder with a slightly bitter taste. It is freely soluble in water; slightly soluble in alcohol, chloroform and ether, very slightly soluble in methylene chloride. Salbutamol sulfate 1.2 mg is approximately equivalent to 1 mg salbutamol.

**PHARMACOLOGY**
Salbutamol is a \(\beta_2\)-adrenoreceptor agonist.

**Pharmacokinetics**
Absorption
Following inhalation of salbutamol the onset of action is 5 to 15 minutes. Only 10 to 20% of the dose reaches the lungs, the remainder stays in the mouth, stomach or on the apparatus. Salbutamol reaching the lungs acts rapidly and directly on bronchial smooth muscle. Initially, the drug is undetectable in blood but after two to three hours, low concentrations are seen, due presumably to the portion of the dose which is swallowed and absorbed by the gut.

Distribution
Salbutamol is not bound to plasma proteins.
**Metabolism**
The major metabolite of salbutamol, recovered from urine, has been identified as the 4'-o-sulfate ester. This metabolite has negligible β-stimulant activity. Salbutamol is not metabolised in the lung and the pattern of metabolism and excretion (as well as absorption) suggest that most aerosol is swallowed. The elimination half-life is between 2.7 hours and 5 hours.

**Excretion**
Following inhalation of salbutamol 77 to 97% of the dose is recovered in the urine after 48 hours, 45 to 60% as the 4'-o-sulfate ester and the rest as unchanged salbutamol. A small fraction is excreted in the faeces.

**Pharmacodynamics**
Salbutamol is a long acting, relatively selective β₂-receptor stimulant. Administration by inhalation results in direct stimulation of β₂-receptors in bronchial smooth muscle and hence bronchodilatation. This is thought to be due to stimulation of adenyl cyclase by salbutamol, resulting in increased levels of cyclic AMP within cells. There are thought to inhibit the entry of calcium ions into the cells, this inhibiting smooth muscle contraction. High levels of cyclic AMP in mast cells may also inhibit the release of histamine and slow reacting substance A (SRS-A).

After administration of salbutamol stimulation of both β₁ and β₂-receptors occurs because β₂ selectivity is not absolute. This results in the β₁ effect of cardiac stimulation, though not so much as with isoprenaline, and β₂ effects of peripheral vasodilatation and hypotension, skeletal muscle tremor and uterine muscle relaxation. Stimulation of β₂-receptors can result in changes in serum levels of glucose, insulin and potassium.

**INDICATIONS**
- Relief of bronchospasm in patients with asthma or chronic obstructive pulmonary disease.
- Acute prophylaxis against exercise-induced asthma or in other situations known to induce bronchospasm.

**CONTRAINDICATIONS**
- Patients with a history of hypersensitivity to salbutamol sulfate.
- Patients with a history of hypersensitivity to any of the components listed under PRESENTATIONS AND STORAGE CONDITIONS.

**PRECAUTIONS**
The management of asthma should normally follow a stepwise program, and patient response should be monitored clinically and by lung function tests. Increasing use of short acting inhaled β₂-agonists to control symptoms indicates deterioration of asthma control. In this situation, the patient’s therapy plan should be re-assessed. Sudden and progressive deterioration in asthma control is potentially life-threatening and consideration should be given to starting or increasing corticosteroid therapy. Daily peak flow monitoring may be instituted in patients considered at risk.

Patients should be warned that if either the usual relief is diminished or the usual duration of action reduced, they should seek medical advice at the earliest opportunity after increasing the dose.

Animal studies suggest that high dosages of some sympathomimetic amines may cause cardionecrotic effects. Based on this evidence, the possibility of the occurrence of myocardial lesions cannot be excluded following long-term treatment with these drugs.
Care should be taken with patients who are known to have received large doses of salbutamol or other sympathomimetic drugs, or who are suffering from hypertension, hyperthyroidism, myocardial insufficiency or diabetes mellitus.

Salbutamol, like other β-adrenergic agonists, can induce reversible metabolic changes, for example increased blood sugar levels. Diabetic patients may be unable to compensate for this and the development of ketoacidosis has been reported. Concurrent administration of corticosteroids can exaggerate this effect.

Salbutamol should be administered cautiously to patients with thyrotoxicosis.

Excessive use may induce a non-responsive state leading to a worsening of hypoxaemia.

Potentially serious hypokalaemia may result from β₂-agonist therapy, mainly from parenteral and nebulised administration. Particular caution is advised in acute severe asthma as this effect may be potentiated by concomitant treatment with xanthine derivatives, steroids, diuretics and hypoxia. (see PRECAUTIONS, Interaction with Other Medicines).

It is recommended that serum potassium levels are monitored in such situations.

The possibility of cardiac arrhythmias arising as a consequence of salbutamol induced hypokalaemia should be borne in mind, especially in digitalized patients, following the administration of salbutamol injection.

Addition of other active substances to salbutamol solution cannot be recommended.

As with other 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.

Lactic acidosis has been reported very rarely in association with high therapeutic doses of intravenous and nebulised short-acting beta-agonist therapy, mainly in patients being treated for an acute asthma exacerbation (see ADVERSE EFFECTS section). Increase in lactate levels may lead to dyspnoea 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.

Use in Pregnancy (Category A)

Salbutamol is known to cross the placental barrier in humans. Safety for use in pregnancy has not been demonstrated, therefore the drug should not be used in pregnant women, or those likely to become pregnant, unless the expected benefits outweigh any potential risk.

Oral administration of salbutamol to rats and rabbits during pregnancy showed no teratogenic effects in offspring.

Although intravenous salbutamol and occasionally salbutamol tablets are used in the management of uncomplicated labour, salbutamol presentations should not be used for threatened abortion during the first or second trimesters of pregnancy. Intravenous salbutamol is contraindicated in cases of antepartum haemorrhage because of the risk of further haemorrhage from an atonic uterus and there is the risk of the same problem arising inadvertently in asthmatics using salbutamol. Profuse uterine bleeding following spontaneous abortion has been reported after the use of salbutamol. Special care is required in pregnant diabetic women.

Definition of Category A:

Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed.
Use in Lactation
It is not known whether salbutamol is excreted in breast milk or whether it has a harmful effect on the newborn infant. Therefore, it is not recommended for breast-feeding mothers unless the expected benefits outweigh any potential risk.

Interactions with Other Medicines

**Beta-Adrenergic Blocking Drugs**
Beta-adrenergic blocking drugs inhibit the bronchodilator action of salbutamol and other sympathomimetic bronchodilators. Such drugs should not be used in asthmatic patients as they may increase airway resistance.

**Other Beta-Adrenergic Stimulants or Sympathomimetic Amines**
Beta-adrenergic stimulants or sympathomimetic amines such as ephedrine should not be given concomitantly. Salbutamol should not be given to patients who have already received large doses of sympathomimetics.

**Imipramine, Chlordiazepoxide, Chlorpromazine**
Salbutamol has been shown to produce possible interactions in animals with the following drugs: imipramine, chlordiazepoxide and chlorpromazine. The clinical significance of this is undetermined.

**Anticholinergics – Ipratropium**
A small number of cases of acute angle closure glaucoma have been reported in patients treated with a combination of nebulised salbutamol and ipratropium bromide. A combination of nebulised salbutamol with nebulised 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.

**Cardiac Glycosides**
Hypokalaemia produced by β2-agonists may result in an increased susceptibility to digitalis induced arrhythmias although salbutamol intravenously and by mouth can also decrease serum concentrations of digoxin.

**Corticosteroids**
Corticosteroids and β2-agonists may both produce falls in plasma potassium concentrations; these may be exacerbated by concomitant administration. The possibility of enhanced hypoglycaemic effects from such a combination should also be borne in mind.

**Diuretics**
Hypokalaemia is known to be a possible side effect during treatment with β2-agonists such as salbutamol, and this may be enhanced during concomitant diuretic therapy. In addition the arrhythmogenic potential of this interaction may be important in patients with ischaemic heart disease.

**ADVERSE EFFECTS**
Adverse events are described according to the CIOMS classification:

- Very common ≥ 10 %
- Common ≥ 1% and < 10%
- Uncommon ≥ 0.1% and < 1%
- Rare ≥ 0.01% and < 0.1%
- Very rare < 0.01%

Very common: a fine tremor of skeletal muscle has been reported in some patients when salbutamol is administered orally or by inhalation and in about 20% of patients receiving salbutamol injection, the hands being the most obviously affected; a few patients feel tense. These effects are dose related and are caused by a direct action on skeletal muscle and not by direct CNS stimulation.
Increases in heart rate are common in patients with normal heart rate after administration of salbutamol respirator solution. These increases are dose dependent and are of the order of 9 beats/minute when 10 mg of salbutamol as 0.5% w/v solution is inhaled by adults over 3 minutes, 13 beats/minute when 20 mg of salbutamol as 0.1% w/v solution is inhaled by adults over 3 minutes. In patients with pre-existing sinus tachycardia, especially those in status asthmaticus, the heart rate tends to fall after the administration of salbutamol respirator solution as the condition of the patient improves.

With higher doses than those recommended, or in patients who are unusually sensitive to β-adrenergic stimulants, dilatation of some peripheral arterioles may occur leading to a small reduction in arterial pressure; a compensatory increase in cardiac output may then occur.

Cardiac arrhythmias (including atrial fibrillation, supraventricular tachycardia and extra systoles) have been reported. Peripheral vasodilatation and a compensatory small increase in heart rate may occur in some patients. Tachycardia may occur in some patients.

Other common side effects which may occur are headaches, nausea, palpitations and sensations of warmth. Mouth and throat irritation may occur with inhaled salbutamol.

There have been rare reports of muscle cramps and restlessness. Hypersensitivity reactions including angioedema, urticaria, bronchospasm, hypotension and collapse have been reported very rarely.

Note:
The incidence and severity of particular side effects depends on the dosage and route of administration. Salbutamol does not cause difficulty in micturition because, unlike sympathomimetic drugs such as ephedrine, therapeutic doses have no alpha-adrenergic receptor stimulant activity.

Potentially serious hypokalaemia may result from β2-agonist therapy.

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

As with other 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.

As with other β2-agonists, hyperactivity has been reported rarely in children. Overuse of salbutamol preparations may produce significant tachycardia, arrhythmias and hypotension.

**DOSAGE AND ADMINISTRATION**

Increasing use of β2-agonists may be a sign of worsening asthma. Under these conditions a reassessment of the patient’s therapy plan may be required and concomitant glucocorticosteroid therapy should be considered.

Salbutamol solution is to be used under the direction of a doctor.

The solution may be delivered from any efficient nebulising device.

The solution must not be injected or ingested.

Salbutamol solution may be used to achieve bronchodilation as part of an inhalation therapy regimen or for patients requiring assisted ventilation.

There is a large safety margin between therapeutic effects and unpleasant side effects. Nevertheless, because of the possibility of uncontrolled dosage associated with continuous administration, intermittent administration of appropriate amounts of salbutamol is preferred.
Adults and Children

Children (4-12 years): 2.5 mg
Adults: 5 mg

This dosage may be repeated as necessary every four to six hours.

Important:
Fresh dilutions should be prepared for each inhalation and any solution remaining in the nebuliser after treatment should be discarded immediately. To avoid contamination, nebulising devices should be thoroughly cleaned after use according to manufacturer’s instructions.

Clinical efficacy of nebulised salbutamol in infants under 18 months is uncertain. As transient hypoxaemia may occur, supplemental oxygen therapy should be considered.

Use in the Elderly
Initial doses of salbutamol in the elderly should be lower than the recommended adult dose. The dose may then be gradually increased if sufficient bronchodilatation is not achieved.

Impaired Hepatic Function
As about 60% of orally administered salbutamol (this includes not only tablet or syrup preparations but also approximately 90% of an inhaled dose) is metabolized to an inactive form; impairment of hepatic function may result in accumulation of unchanged salbutamol.

Impaired Renal Function
About 60-70% of salbutamol administered by inhalation or intravenous injection is excreted in the urine unchanged. Impairment or renal function may therefore require a reduction in dosage to prevent exaggerated or prolonged effects.

OVERDOSAGE

Symptoms
The signs of overdosage are significant tachycardia and/or significant muscle tremor.

Treatment
The specific antidote for overdosage with salbutamol is a cardioselective β-blocking agent given by intravenous injection.

IN GENERAL, BETA-BLOCKING DRUGS SHOULD BE USED WITH CAUTION AS THEY MAY CAUSE BRONCHOSPASM IN SENSITIVE INDIVIDUALS.

Hypokalaemia may occur following overdosage with salbutamol. Serum potassium levels should be monitored.

Contact the Poisons Information Centre on 13 11 26 (Australia) for advice on the management of overdosage.
PRESENTATIONS AND STORAGE CONDITIONS

30 ampoules, packed in strips of 5 ampoules per foil pouch.

**GenRx Salbutamol Inhalation Solution 2.5 mg/2.5 mL:**
Clear, colourless, sterile, isotonic solution for inhalation. It does not contain a preservative.
AUST R 142568

**GenRx Salbutamol Inhalation Solution 5 mg/2.5 mL:**
Clear, colourless, sterile, isotonic solution for inhalation. It does not contain a preservative.
AUST R 142569.

**GenRx Salbutamol Inhalation Solution** is intended for administration by inhalation. Each 2.5 mL ampoule contains salbutamol sulfate equivalent to either salbutamol 2.5 mg or 5 mg.

In addition, the solution contains the following inactive ingredients: sodium chloride and water for injections. The pH of the solutions is adjusted with sulfuric acid to fall in the range 3.0 to 4.5.

Store below 25°C. Protect from light.

Single dose units should be kept in carton until immediately before use. Use within 3 months of opening foil pouch.

NAME AND ADDRESS OF THE SPONSOR

Apotex Pty Ltd
66 Waterloo Road
North Ryde NSW 2113
Australia

GenRx is a registered trade mark of Apotex Pty Ltd.

POISONS SCHEDULE OF THE MEDICINE

S4: Prescription Only Medicine.

**Date of TGA approval:** 4 October 2007

**Date of most recent amendment:** 15 January 2010