NAME OF THE MEDICINE
Salbutamol sulfate.

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

Structural Formula:

![StructuralFormula](image)

Molecular Formula: \((C_{13}H_{21}NO_3)2.H_2SO_4\)
Molecular Weight: 576.7
CAS Registry Number: 51022-70-9

DESCRIPTION
Salbutamol sulfate is a white or almost white, odourless powder. It is soluble in 4 parts of water; slightly soluble in 95% alcohol, in chloroform and solvent ether. Salbutamol sulfate 1.2 mg is approximately equivalent to 1 mg salbutamol.

Each ampoule contains 2.5 mg/2.5 mL or 5 mg/2.5 mL of salbutamol (as sulfate).

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. It does not contain a preservative.

PHARMACOLOGY
Pharmacological Actions
Salbutamol is a relatively selective \(\beta_2\)-adrenoreceptor stimulant. It is more specific than both isoprenaline and orciprenaline for adrenergic \(\beta_2\) receptors.

After administration of salbutamol, stimulation of the \(\beta\) receptors in the body, both \(\beta_1\) and \(\beta_2\)-receptors occurs because (a) \(\beta_2\) selectivity is not absolute, and (b) higher concentrations of salbutamol occur in the regions of these receptors. This results in the \(\beta_1\) effect of cardiac stimulation, though not so much as with isoprenaline, and \(\beta_2\) effects of peripheral vasodilatation and hypotension, skeletal muscle tremor and uterine muscle relaxation.

Metabolic effects such as hyperinsulinaemia and hyperglycaemia also may occur, although it is not known whether these effects are mediated by \(\beta_1\) or \(\beta_2\) receptors. The serum potassium levels have a tendency to fall.

Pharmacokinetics
Absorption
Following inhalation, salbutamol acts topically in bronchial smooth muscle.
Distribution
Initially, the drug is undetectable in the blood. After two to three hours, low concentrations are seen, due presumably to the portion of the dose which is swallowed and absorbed in the gut.

Metabolism
The elimination half-life is between 2.7 hours and 5 hours. Salbutamol is not metabolised in the lung but is converted to the 4'-o-sulfate ester in the liver.

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.

INDICATIONS
- For the 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
- Hypersensitivity to salbutamol sulfate.
- Hypersensitivity to any of the excipients.

Non-i.v. formulations of salbutamol must not be used to arrest uncomplicated premature labour or threatened abortion.

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. Under these conditions, the patient’s therapy plan should be reassessed. Sudden and progressive deterioration in asthma control is potentially life-threatening and consideration should be given to starting or increasing corticosteroid therapy. In patients considered at risk, daily peak flow monitoring may be instituted.

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 cardionecrotic effects may occur with high dosages of some sympathomimetic amines. 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 should be administered cautiously to patients with thyrotoxicosis.

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.

Impairment of liver or renal function may necessitate a reduction in dosage (see DOSAGE AND ADMINISTRATION).

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 digitalised patients, following the administration of salbutamol injection.

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

As with other inhalation therapy, paradoxical bronchospasm may occur, resulting in an immediate increase in wheezing after dosing. This should be treated immediately with an alternative presentation or a different fast-acting inhaled bronchodilator, if immediately available. The specific salbutamol presentation should be discontinued, and if necessary a different fast-acting bronchodilator instituted for ongoing use.

Lactic acidosis has been reported very rarely in association with high therapeutic doses of intravenous and nebulised short-acting β-agonist therapy, mainly in patients being treated for an acute asthma exacerbation (see ADVERSE EFFECTS). 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 β-agonist treatment. It is therefore recommended that patients are monitored for the development of elevated serum lactate and consequent metabolic acidosis in this setting.

Effects on Fertility
There is no information on the effects of salbutamol on human fertility.

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.

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.

Although intravenous salbutamol and occasionally salbutamol tablets are used in the management of uncomplicated premature 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.

Use in Lactation
It is not known whether salbutamol is excreted in breast milk nor whether it has a harmful effect on the newborn. Therefore, it is not recommended for breastfeeding mothers unless the expected benefits outweigh any potential risk.

INTERACTIONS WITH OTHER MEDICINES

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

Sympathomimetic Amines
Care is recommended if it is proposed to administer salbutamol in concomitant therapy with other sympathomimetic amines as excess sympathetic stimulation may occur.
Imipramine, Chlordiazepoxide, Chlorpromazine
Animal studies have shown that large doses of salbutamol may interact with imipramine, chlordiazepoxide and chlorpromazine but any practical significance of these results in man remains to be established.

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; with a few patients feeling tense. These effects are dose related and are caused by a direct action on skeletal muscle and not by direct central nervous system stimulation.

Increases in heart rate may occur 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 extrasystoles) 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.

Hypersensitivity reactions including angioedema, urticaria, bronchospasm, hypotension and collapse have been reported very rarely. There have been very rare reports of muscle cramps. Mouth and throat irritation may occur with inhaled salbutamol.

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, paradoxical bronchospasm may occur, resulting in an immediate increase in wheezing after dosing (see PRECAUTIONS). 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 nebulisers are to be used under the direction of a physician. The solution must not be injected or ingested.

2.5 mg/2.5 mL and 5 mg/2.5 mL may be delivered from any efficient nebulising device. Salbutamol nebulisers may be used to achieve bronchodilation as part of an inhalation therapy regime 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 4-6 hours. Any solution remaining in the nebuliser after completion of therapy should be discarded. 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 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 bronchodilation is not achieved.

**Impaired Hepatic Function**

As about 60% of orally administered salbutamol (this includes not only tablet and syrup preparations but also approximately 90% of an inhaled dose) is metabolised 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 urine unchanged. Impairment of renal function may therefore require a reduction in dosage to prevent exaggerated or prolonged effects.

OVERDOSAGE
Symptoms
The most common signs and symptoms of overdose with salbutamol are transient β agonist pharmacologically mediated events (see PRECAUTIONS and ADVERSE EVENTS). The signs of overdose are significant tachycardia and/or significant muscle tremor.

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

Lactic acidosis has been reported in association with high therapeutic doses as well as overdoses of short-acting β-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 treatment such as a cardio-selective β-blocking agent given by intravenous injection in patients presenting with cardiac symptoms (e.g. tachycardia, palpitations). β blocking drugs should be used with caution as they may cause bronchospasm in sensitive individuals.

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

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

PRESENTATION AND STORAGE CONDITIONS
APO-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

APO-Salbutamol Inhalation Solution 2.5 mg/2.5 mL:
Clear, colourless, sterile, isotonic solution for inhalation. It does not contain a preservative.
«AUST_R_25mg».

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

APO-Salbutamol Inhalation Solution 5 mg/2.5 mL:
Clear, colourless, sterile, isotonic solution for inhalation. It does not contain a preservative.
«AUST_R_25mg»7.

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

Storage
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
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**POISON SCHEDULE OF THE MEDICINE**

S4: Prescription Only Medicine.

**DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG):** 23 October 2007

**DATE OF MOST RECENT AMENDMENT:** 23 January 2015