AUSTRALIAN PRODUCT INFORMATION
APO-SALBUTAMOL (SALBUTAMOL SULFATE)
INHALATION AMPOULES

1 NAME OF THE MEDICINE
Salbutamol sulfate.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 2.5 mL ampoule contains salbutamol sulfate equivalent to either salbutamol 2.5 mg or 5 mg.

For the full list of excipients see section 6.1 List of excipients.

3 PHARMACEUTICAL FORM
Clear, colourless to pale yellow, sterile, isotonic solution for inhalation. It does not contain a preservative.

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC 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.

4.2 DOSE AND METHOD OF ADMINISTRATION

APO-Salbutamol Inhalation Solution is intended for administration by inhalation.

Dosage
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 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.

**Hepatic impairment**

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.

**Renal impairment**

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.

**4.3 CONTRAINDICATIONS**

- Patients with a history of hypersensitivity to salbutamol sulfate.
- Patients with a history of hypersensitivity to any of the excipients.

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

**4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**

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 large 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 section 4.5 Interactions with other medicines and other forms of interactions). 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, paradoxical bronchospasm may occur, resulting in an immediate increase in wheezing and 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 beta-agonist therapy, mainly in patients being treated for an acute asthma exacerbation (see section 4.8 Adverse effects (Undesirable 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 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 hepatic impairment
Impairment of liver function may necessitate a reduction in dosage (see section 4.2 Dose and method of administration).

Use in renal impairment
Impairment of renal function may necessitate a reduction in dosage (see section 4.2 Dose and method of administration).

Use in the elderly
No data available.

Paediatric use
No data available.

Effects on laboratory tests
No data available.
4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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.

4.6 FERTILITY, PREGNANCY AND LACTATION

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 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.

**4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES**

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

**4.8 ADVERSE EFFECTS (UNDESIRABLE 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 $\beta_2$-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 $\beta_2$-agonists, hyperactivity has been reported rarely in children. Overuse of salbutamol preparations may produce significant tachycardia, arrhythmias and hypotension.

**Reporting suspected adverse effects**

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at [www.tga.gov.au/reporting-problems](http://www.tga.gov.au/reporting-problems) and contact Apotex Medical Information Enquiries/Adverse Drug Reaction Reporting on 1800 195 055.

### 4.9 OVERDOSE

**Symptoms**

The most common signs and symptoms of overdose with salbutamol are transient beta agonist pharmacologically mediated events (see sections 4.4 Special warnings and precautions for use and 4.8 Adverse effects (Undesirable effects)). The signs of overdosage are significant tachycardia and/or significant muscle tremor.

**Treatment**

The specific antidote for overdosage with salbutamol is a cardioselective $\beta$-blocking agent given by intravenous injection in patients presenting with cardiac symptoms (e.g. tachycardia, palpitations). Consideration should be given to discontinuation of treatment.

**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.
For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action
Salbutamol is a β₂-adrenoreceptor agonist.

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. These are thought to inhibit the entry of calcium ions into the cells, thus 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.

Clinical trials
No data available.

5.2 PHARMACOKINETIC PROPERTIES

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.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
No data available.
Carcinogenicity
No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

- Sodium chloride
- water for injections

The pH of the solutions is adjusted with sulfuric acid to fall in the range 3.0 to 4.5.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR 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.

6.5 NATURE AND CONTENTS OF CONTAINER

**APO-Salbutamol Inhalation Solution 2.5 mg/2.5 mL:**

AUST R 142566.

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

**APO-Salbutamol Inhalation Solution 5 mg/2.5 mL:**

AUST R 142567.

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

APO is a registered trade mark of Apotex Inc.

Not all strengths may be available.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

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.
Chemical structure

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

Molecular Formula: \((\text{C}_{13}\text{H}_{21}\text{NO}_3)_2\cdot\text{H}_2\text{SO}_4\)

Molecular Weight: 576.7

CAS number: 51022-70-9

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

Apotex Pty Ltd
16 Giffnock Avenue
Macquarie Park NSW 2113
Australia
Tel: (02) 8877 8333
Web: www1.apotex.com/au

9 DATE OF FIRST APPROVAL

23 October 2007

10 DATE OF REVISION

9 October 2019

Summary table of changes

<table>
<thead>
<tr>
<th>Section Changed</th>
<th>Summary of new information</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>Reformatted product information; minor editorial changes.</td>
</tr>
<tr>
<td>4.3, 4.4 and 4.6</td>
<td>Safety related changes to align with Ventolin PI dated 21 September 2016.</td>
</tr>
</tbody>
</table>