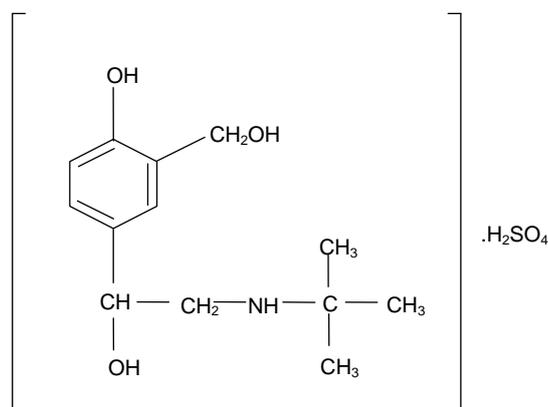


**PRODUCT INFORMATION**  
**SALBUTAMOL SANDOZ<sup>®</sup> 2.5MG/2.5ML, 5MG/2.5ML INHALATION**  
**AMPOULES**

**NAME OF THE MEDICINE**

*Generic name:* Salbutamol sulphate BP

*Chemical name:* di[(RS)-2-(1,1-dimethyl)ethylamino-1-[4-hydroxy-3-(hydroxymethyl)phenyl]ethanol] sulphate



*CAS Number:* 51022-70-9      *Empirical formula:* (C<sub>13</sub>H<sub>21</sub>NO<sub>3</sub>)<sub>2</sub>, H<sub>2</sub>SO<sub>4</sub>      *MW:* 576.7

**DESCRIPTION**

Salbutamol sulphate is a white or almost white, crystalline, 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 sulphate 1.2 mg is approximately equivalent to salbutamol 1 mg.

Each inhalation ampoule contains Salbutamol 2.5mg/2.5mL or 5mg/2.5mL.

Inactive ingredients: Sodium chloride, sulphuric acid (for pH adjustment), water for injection.

**PHARMACOLOGY**

Selective beta-2-adrenoceptor agonist

Pharmacodynamics

Salbutamol is a long acting, relatively selective beta-2-receptor stimulant. Administration by inhalation results in direct stimulation of beta-2-receptors in bronchial smooth muscle and hence bronchodilation. This is thought to be due to stimulation of adenylyl 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 beta-1 and beta-2 receptors occurs because beta-2 selectivity is not absolute. This results in the beta-1 effect of cardiac stimulation, though not so much as with isoprenaline, and beta-2 effects of peripheral vasodilation and hypotension, skeletal muscle tremor and uterine muscle relaxation. Stimulation of beta-2 receptors can result in changes in serum levels of glucose, insulin and potassium.

### Pharmacokinetics

#### *Absorption*

Following inhalation of salbutamol the onset of action is 5-15 minutes. Only 10-20% 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 2-3 hours, low concentrations are seen, due presumably to the portion of the dose that 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-sulphate ester. This metabolite has negligible beta stimulant activity. Salbutamol is not metabolised in the lung and the pattern of metabolism and excretion (as well as absorption) suggests that most aerosol is swallowed. The elimination half life is between 2.7 and 5 hours.

#### *Excretion*

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

## **INDICATIONS**

Relief of bronchospasm in patients with asthma or chronic obstructive pulmonary disease, and for acute prophylaxis against exercise-induced asthma or in other situations known to induce bronchospasm.

## **CONTRAINDICATIONS**

Hypersensitivity to any of the ingredients.

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 programme, and patient response should be monitored clinically and by lung function tests. Increasing uses of short-acting inhaled beta-2 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 cardioneurotic effects may occur with high dosages of some sympathomimetic amines. On this evidence the possibility of the occurrence of myocardial lesions cannot be excluded subsequent to 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.

Cardiovascular effects may be seen with sympathomimetic drugs, including salbutamol. There is some evidence from post-marketing data and published literature of rare occurrences of myocardial ischaemia associated with salbutamol. Patients with underlying severe heart disease (e.g. ischaemic heart disease, arrhythmia or severe heart failure) who are receiving salbutamol should be warned to seek medical advice if they experience chest pain or other symptoms of worsening heart disease. Attention should be paid to assessment of symptoms such as dyspnoea and chest pain, as they may be of either respiratory or cardiac origin.

In common with other beta-adrenoceptor agonists, salbutamol can induce reversible metabolic changes, for example increased blood sugar levels. 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.

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

Potentially serious hypokalaemia may result from beta-2-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. 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 Sandoz 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 beta-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 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.

#### Effects on Fertility

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

#### Use in pregnancy (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 being observed.

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 ante-partum 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 infant. Therefore it is not recommended for breastfeeding mothers unless the expected benefits outweigh any potential risk.

## **INTERACTIONS WITH OTHER MEDICINES**

*Beta 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.

*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.

*Antidepressant:* 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.

*Cardiac glycosides:* Hypokalaemia produced by beta-2-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 beta-2-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 beta-2-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.

Patients should receive adequate instructions in correct administration and be warned not to let the solution or mist enter the eye.

## ADVERSE EFFECTS

Adverse Events are described according to the CIOMS classification:

<i>Very common</i>	$\geq 10\%$
<i>Common</i>	$\geq 1\%$ and $< 10\%$
<i>Uncommon</i>	$\geq 0.1\%$ and $< 1\%$
<i>Rare</i>	$\geq 0.01\%$ and $< 0.1\%$
<i>Very rare</i>	$< 0.01\%$

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 10mg of salbutamol as 0.5% w/v solution is inhaled by adults over 3 minutes, 13 beats/minute when 20mg 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 usually sensitive to beta-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) and myocardial ischaemia have been reported (see Precautions). 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 reports of muscle cramps and restlessness.

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 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, resulting in an immediate increase in wheezing after dosing, should be kept in mind. If it occurs, the preparation should be discontinued immediately and alternative therapy instituted (see Precautions).

As with other beta-2-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 beta-2 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 Sandoz is to be used under the direction of a doctor.

The solution must not be injected or ingested.

Salbutamol Sandoz 2.5 mg/2.5 mL and 5 mg/2.5 mL ampoules may be delivered from any efficient nebulising device.

Salbutamol Sandoz may be used to achieve bronchodilatation 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 Sandoz is preferred.

Children 4-12 years: 2.5 mg

Adults: 5.0 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.

**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 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 to 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**

Contact the Poisons Information Centre on 13 11 26 for advice on management of overdose.

In general, beta-blocking drugs should be used with caution as they may cause bronchospasm in sensitive individuals.

#### Symptoms

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

#### Signs

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

#### Treatment

The specific antidote for overdose with salbutamol is a cardio-selective beta-blocking agent given by intravenous injection.

### **PRESENTATION AND STORAGE CONDITIONS**

Salbutamol Sandoz inhalation ampoules - Sterile aqueous solution (isotonic, preservative-free), salbutamol 2.5mg/2.5mL or 5mg/2.5mL. The ampoules are supplied in packs of 30 (6 x 5).

Store below 25°C. Protect from light.

Shelf life: 3 years, 3 months when removed from foil over-wrap.

**NAME AND ADDRESS OF THE SPONSOR**

Sandoz Pty Ltd  
ABN 60 075 449 553  
54 Waterloo Road  
Macquarie Park, NSW 2113  
Australia  
Tel: 1800 634 500

**POISON SCHEDULE OF THE MEDICINE**

Schedule 4 – Prescription Only Medicine

**DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG):** 28/09/2007

**DATE OF MOST RECENT AMENDMENT:** 30/08/2016