

# AUSTRALIAN PRODUCT INFORMATION

## VENTOLIN NEBULES (salbutamol sulfate) for inhalation

### 1 NAME OF THE MEDICINE

Salbutamol sulfate.

### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Nebuliser Solution.

2.5 mg: contain a concentration of salbutamol of 0.1% (1 mg salbutamol, as the sulfate, in 1 ml). Each NEBULE contains 2.5 mL of solution equivalent to 2.5 mg salbutamol.

5.0 mg: contain a concentration of salbutamol of 0.2% (2 mg salbutamol, as the sulfate, in 1 ml). Each NEBULE contains 2.5 mL of solution equivalent to 5.0 mg salbutamol.

#### List of excipients with known effect

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

### 3 PHARMACEUTICAL FORM

Inhalation

### 4 CLINICAL PARTICULARS

#### 4.1 THERAPEUTIC INDICATIONS

For the 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.

#### 4.2 DOSE AND METHOD OF 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.

VENTOLIN NEBULES 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.

VENTOLIN NEBULES 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 VENTOLIN NEBULES is preferred.

Adults and Children

|                        |        |
|------------------------|--------|
| Children 4 to 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.

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

### **Elderly**

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

### **In impaired liver 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 liver function may result in accumulation of unchanged salbutamol.

### **In 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.

## **4.3 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.

## **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**

The management of asthma should normally follow a stepwise programme, and patient response should be monitored clinically and by lung function tests. Increasing use 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.

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 Ventolin Injection.

Addition of other active substances to VENTOLIN NEBULES 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 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 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 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.

Care is recommended if it is proposed to administer salbutamol in concomitant therapy with other sympathomimetic amines as excess sympathetic stimulation may occur.

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.

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.

## **4.6 FERTILITY, PREGNANCY AND LACTATION**

### **Effects on fertility**

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

### **Use in pregnancy**

#### **(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, Ventolin presentations should not be used for threatened abortion during the first or second trimesters of pregnancy. Intravenous salbutamol is contra-indicated 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. Therefore it is not recommended for nursing 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)**

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 Ventolin 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 CNS stimulation.

Increases in heart rate may occur in patients with normal heart rate after administration of VENTOLIN NEBULES. 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 VENTOLIN NEBULES as the condition of the patient improves.

With higher doses than those recommended, or in patients who are unusually 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 extrasystoles) have been reported. Peripheral vasodilation and a compensatory small increase in heart rate may occur in some patients. Tachycardia may occur in some patients.

Other reactions which may occur are headaches, nausea, palpitations and sensations of warmth. 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. Ventolin 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, paradoxical bronchospasm may occur, resulting in an immediate increase in wheezing after dosing ( See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

As with other beta-2 agonists hyperactivity has been reported rarely in children.

### **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).

## **4.9 OVERDOSE**

The most common signs and symptoms of overdose with salbutamol are transient beta agonist pharmacologically mediated events ( See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and See Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). The signs of salbutamol overdosage are significant tachycardia and/or significant muscle tremor.

Hypokalaemia may occur following overdosage 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 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.

Consideration should be given to discontinuation of treatment and appropriate symptomatic treatment such as a cardio-selective beta-blocking agent given by intravenous injection in patients presenting with cardiac symptoms (e.g. tachycardia, palpitations). Beta-blocking drugs should be used with caution as they may cause bronchospasm in sensitive individuals.

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

## **5 PHARMACOLOGICAL PROPERTIES**

### **5.1 PHARMACODYNAMIC PROPERTIES**

#### **Mechanism of action**

Salbutamol is a relatively selective beta-2-adrenoreceptor stimulant. It is more specific than both isoprenaline and orciprenaline for adrenergic beta-2 receptors.

After oral and parenteral administration, stimulation of the beta receptors in the body, both beta-1 and beta-2, occurs because (a) beta-2 selectivity is not absolute, and (b) higher concentrations of salbutamol occur in the regions of these receptors with these modes of administration. 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.

#### **Clinical trials**

No data available.

### **5.2 PHARMACOKINETIC PROPERTIES**

Following inhalation, salbutamol acts topically in bronchial smooth muscle and initially the drug is undetectable in the blood. After 2 to 3 hours low concentrations are seen, due presumably to the portion of the dose which is swallowed and absorbed in the gut.

The elimination half-life of inhaled or oral salbutamol is between 2.7 and 5 hours. Salbutamol is not metabolized in the lung but is converted to the 4'-o-sulfate ester in the liver. Salbutamol is excreted in the urine as free drug and as the metabolite. After oral administration 58-78% of the dose is excreted in the urine in 24 hours, approximately 60% as metabolites. A small fraction is excreted in the faeces.

Impairment of liver or renal function may necessitate a reduction in dosage (See 4.2 DOSE AND METHOD OF ADMINISTRATION).

### **5.3 PRECLINICAL SAFETY DATA**

#### **Genotoxicity**

No data available.

#### **Carcinogenicity**

No data available.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 LIST OF EXCIPIENTS**

VENTOLIN NEBULES contains the excipients sodium chloride, sulfuric acid and purified water.

### **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**

VENTOLIN NEBULES should be stored below 30°C. Store protected from light. Once removed from the foil overwrap Nebules have a shelf-life of 3 months when stored below 30°C and should be protected from light.

### **6.5 NATURE AND CONTENTS OF CONTAINER**

VENTOLIN NEBULES are plastic ampoules containing a sterile preservative-free, isotonic, aqueous solution of salbutamol sulfate equivalent to either 2.5 mg salbutamol in 2.5 mL or 5 mg salbutamol in 2.5 mL. The NEBULES are supplied in packs of 5 and 20. The 20 pack size is arranged as four individually foil overwrapped pouches containing five Nebules linked together.

Not all strengths or pack sizes may be distributed in Australia.

## 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. It is soluble in 4 parts of water; slightly soluble in 95% alcohol, in chloroform and solvent ether.

### Chemical Name

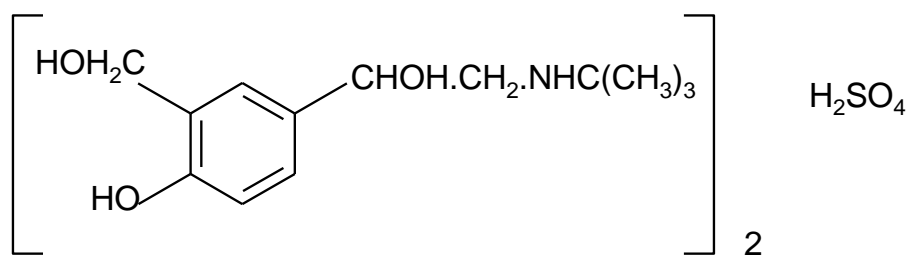
1-(4-hydroxy-3-hydroxymethylphenyl)-2-(t-butylamino)ethanol sulfate.

### Molecular Formula

(C<sub>13</sub>H<sub>21</sub>NO<sub>3</sub>)<sub>2</sub>H<sub>2</sub>SO<sub>4</sub>

The molecular weight for salbutamol sulfate is 576.7.

### Chemical structure



### CAS number

51022-70-9

## 7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

## 8 SPONSOR

GlaxoSmithKline Australia Pty Ltd  
Level 4, 436 Johnston Street,  
Abbotsford, Victoria, 3067

## 9 DATE OF FIRST APPROVAL

1 February 1999

## 10 DATE OF REVISION

25 October 2022

## SUMMARY TABLE OF CHANGES



| <b>Section Changed</b>                                | <b>Summary of new information</b>                                 |
|---|---|
| <b>Title, 2, 3, 4.2, 4.4, 4.8, 4.9, 6.1, 6.4, 6.5</b> | Removal of reference to VENTOLIN RESPIRATOR SOLUTION              |
| <b>End of document</b>                                | Update to trademark statement and addition of copyright statement |

Version 6.0

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