AUSTRALIAN PRODUCT INFORMATION

VENTOLIN (salbutamol sulfate) SYRUP oral liquid and VENTOLIN Injection

1 NAME OF THE MEDICINE

Salbutamol Sulfate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

VENTOLIN SYRUP:

Bottles containing 2.0 mg salbutamol as the sulfate in each 5 mL in an orange flavoured sugar free and dye free formulation.

VENTOLIN Injection:

Ampoules of salbutamol sulfate equivalent to 500 mcg salbutamol in 1 mL sterile isotonic solution. The ampoules are clear, neutral glass and the solution is colourless or faintly straw coloured.

Excipients with known effect

VENTOLIN SYRUP contains benzoates.

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

3 PHARMACEUTICAL FORM

VENTOLIN SYRUP: Oral liquid

VENTOLIN Injection: Injection, solution

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

VENTOLIN SYRUP is indicated for the prevention and relief of bronchospasm in bronchial asthma of all types and for the alleviation of reversible airways obstruction associated with conditions such as chronic bronchitis or emphysema.

VENTOLIN Injection is indicated for the prevention and relief of bronchospasm in bronchial asthma of all types.

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 SYRUP

Adults:

5-10 mL three or four times a day. The optimum single dose for many patients is 10 mL but, especially with elderly patients or with patients who are unusually sensitive to beta-adrenergic stimulant drugs, it is advisable to initiate treatment with 5 mL three or four times a day. If adequate bronchodilatation is not obtained the dose may be gradually increased to as much as 20 mL, usually without significant cardiovascular side effects.

Children:

0.15 mg/kg/dose which may be repeated as required, up to 6 hourly. The maximum single dose is 4 mg (10 mL).

Note: VENTOLIN SYRUP does not contain sugars. It may be diluted with Purified Water BP. The resulting mixture should be protected from light and used within 28 days. A 50% v/v dilution of VENTOLIN SYRUP has been shown to be adequately preserved against microbial contamination. However, to avoid the possibility of introducing excessive microbial contamination, the Purified Water used for dilution should be recently prepared or alternatively it should be boiled and cooled immediately before use. Dilution of VENTOLIN SYRUP with SYRUP BP or sorbitol solution is not recommended as this may result in precipitation of the cellulose thickening agent. Admixture of VENTOLIN SYRUP with other liquid preparations is not recommended.

VENTOLIN Injection

VENTOLIN Injection is to be used under the direction of a physician.

VENTOLIN Injection should not be administered in the same syringe or infusion as any other medication.

VENTOLIN Injection may be administered subcutaneously, intramuscularly or intravenously.

Subcutaneous Route

Adults:

1 mL repeated every three to four hours as required.

Intramuscular Route

Adults:

1 mL repeated every three to four hours as required.

Children 2-12 years:

10-20 microgram/kg/dose repeated up to 4-6 hourly. The maximum single dose is 400 microgram.

Intravenous Route

Adults:

0.4-0.6 mL (200-300 mcg) injected over one minute. Repeat after fifteen minutes if required.

Children 2-12 years:

0.1-0.4 mL (50-200 mcg) injected over one minute. Repeat after fifteen minutes if required.

Infusion

Adults:

A starting dose of 5 microgram/min is recommended with appropriate adjustments in dosage according to patient response. The dose can be increased to 10 microgram/min and 20 microgram/min. Infusion rate should not exceed 20 microgram/min except in patients with severe bronchospasm. A loading dose of 200 microgram may be given over one minute to speed onset of action before commencing infusion of 5 microgram/min.

Children 2-12 years:

A loading dose given over 1 minute of 5 to 7.5 microgram/kg followed by an infusion at the rate of 5 to 7.5 microgram/kg/hour.

Note: VENTOLIN Injection may be diluted with Water for Injection BP, Sodium Chloride Injection BP or Sodium Chloride and Dextrose Injection BP. The intramuscular route is recommended as the route of choice. When patients are to be treated with an infusion, it is recommended that an initial intravenous injection should be given as a loading dose. VENTOLIN Injection should be used in conjunction with the usual drug therapy for patients with severe bronchospasm. VENTOLIN Injection can be used following use of bronchodilators by inhalation. All unused admixtures of salbutamol parenteral preparations with infusion fluids should be discarded twenty-four hours after preparation.

4.3 CONTRAINDICATIONS

Hypersensitivity to any of the ingredients.

Non-intravenous 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 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 not increase the dose or its frequency of administration, but should seek medical advice. As there may be adverse effects associated with excessive dosing, the dosage or frequency of administration should only be increased on medical advice.

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.

Animal studies suggest that cardionecrotic 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.

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.

Special Warnings and Precautions for VENTOLIN Injection

The use of VENTOLIN parenteral preparations in the treatment of severe bronchospasm or status asthmaticus does not obviate the requirement for glucocorticoid steroid therapy as appropriate. When practicable, administration of oxygen concurrently with parenteral VENTOLIN is recommended, particularly when it is given by intravenous infusion to hypoxic patients.

In common with other beta-adrenoceptor agonists, VENTOLIN can induce reversible metabolic changes such as reversible hypokalaemia and increased blood glucose 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.

Diabetic patients and those concurrently receiving corticosteroids should be monitored frequently during intravenous infusion of VENTOLIN so that remedial steps (eg an increase in insulin dosage) can be taken to counter any metabolic change occurring. For these patients VENTOLIN Solution for Intravenous Infusion should be diluted with Sodium Chloride Injection BP, rather than Sodium Chloride and Dextrose Injection BP.

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. The population at risk primarily includes patients with an acute exacerbation of the underlying respiratory disease undergoing high dose treatment regimens, particularly with intravenous and nebulised salbutamol. 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

As about 60% of orally administered salbutamol (this includes not only the SYRUP preparation but also approximately 90% of an inhaled dose) is metabolized to an inactive form, impairment of liver function may result in accumulation of unchanged salbutamol.

Use in renal impairment

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.

Use in the 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.

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.

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 benefit outweighs 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 is used in the management of uncomplicated premature labour, it should not be used for threatened abortion during the first or second trimesters of pregnancy (see Section 4.3 CONTRAINDICATIONS). 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 very commonly reported, the hands being the most obviously affected; a few patients experience a feeling of muscle tension however this is a very rare occurrence. 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 a common occurrence after administration of VENTOLIN Injection. These increases are dose dependent and are of the order of 20 beats/minute with subcutaneous doses of 20 mcg/kg, intramuscular doses of 12 mcg/kg and intravenous infusion rates of 10 mcg/min in adults. In patients with pre-existing sinus tachycardia, especially those in status asthmaticus, the heart rate tends to fall after VENTOLIN Injection 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.

Slight pain or stinging after injection may occur.

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 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.

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 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.

Nausea, vomiting and hyperglycaemia have been reported, predominantly in children and when salbutamol overdose has been taken via the oral route.

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 clinical data available

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Peak plasma levels occur at 2 to 4 hours after oral administration of salbutamol.

Distribution

The elimination half-life of oral or inhaled salbutamol is between 2.7 and 5 hours.

Metabolism

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.

Excretion

Impairment of liver or renal function may necessitate a reduction in dosage (see Section 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 SYRUP contains the following excipients: sodium citrate, citric acid monohydrate, hypromellose, sodium benzoate, saccharin sodium, sodium chloride, water – purified and orange flavouring.

VENTOLIN Injection contains the following excipients: sodium chloride, sulfuric acid and water for injections.

6.2 INCOMPATIBILITIES

VENTOLIN SYRUP:

Dilution of salbutamol syrup with syrup BP or sorbitol solution is not recommended as this may result in precipitation of the cellulose thickening agent.

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 SYRUP should be stored below 30°C and protected from light.

VENTOLIN Injection should be stored below 25°C and protected from light.

6.5 NATURE AND CONTENTS OF CONTAINER

VENTOLIN SYRUP contains 2.0 mg salbutamol (as sulfate) in each 5 mL in an orange flavoured sugar free and dye free formulation available in glass bottles of 150 mL.

VENTOLIN Injection Ampoules of salbutamol sulfate equivalent to 500 mcg salbutamol in 1 mL sterile isotonic solution. The ampoules are clear, neutral glass and the solution is

colourless or faintly straw coloured. VENTOLIN Injection is available in packs of 5 x 1 mL ampoules.

Not all strengths, dose forms, pack sizes, container types may be distributed in Australia.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

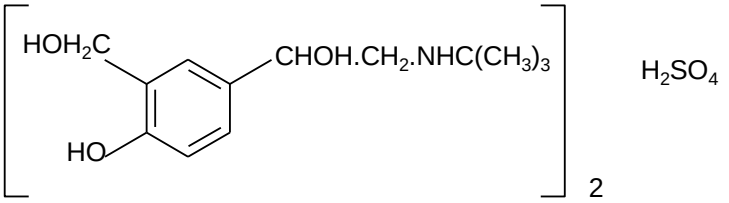
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Name

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

Chemical structure



Molecular Formula: $(C_{13}H_{21}NO_3)_2H_2SO_4$

Salbutamol sulfate is a white or almost white odourless powder. It is soluble in 4 parts of water; slightly soluble in 95% alcohol, chloroform and solvent ether.

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

3 December 2002

10 DATE OF REVISION

29 September 2022

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	PI Reformat
2	Addition of benzoates statement
3	Addition of pharmaceutical form as per ARTG entry
6.2	Added incompatibilities statement for VENTOLIN SYRUP
End of document	Update to trademark statement and addition of copyright statement

Version 6.0

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