

PRODUCT INFORMATION

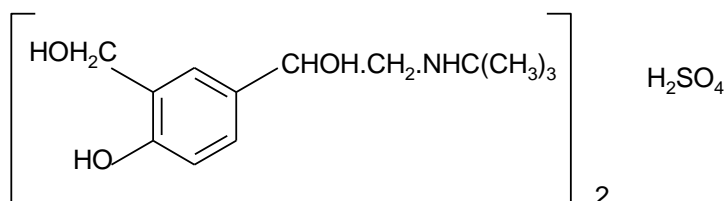
VENTOLIN CFC-FREE INHALER

NAME OF THE MEDICINE: Salbutamol Sulfate B.P.

Chemical name:

di[(RS)-2-(1,1-dimethylethyl)amino-1-(4-hydroxy-3-hydroxymethylphenyl)ethanol]sulfate.

Structure:



Molecular Formula: $\text{C}_{26}\text{H}_{44}\text{N}_2\text{O}_{10}\text{S}$

CAS No: 51022 - 70 - 9

DESCRIPTION:

Salbutamol sulfate is a white or almost white crystalline powder, freely soluble in water, practically insoluble or very slightly soluble in ethanol (96 per cent) and in methylene chloride.

Ventolin CFC-Free Inhaler also contains the inactive ingredient norflurane.

PHARMACOLOGY:

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.

Pharmacokinetics

Following inhalation, salbutamol acts topically on 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 **DOSAGE AND ADMINISTRATION**).

CLINICAL TRIALS:

Salbutamol, delivered from a pressurised metered-dose inhaler using propellants 11 and 12 (Ventolin Inhaler P11/12), has been used for over 20 years in clinical practice and has been demonstrated to be safe and effective in the treatment of reversible obstructive airways disease. The following section describes clinical studies conducted to assess the therapeutic equivalence of salbutamol reformulated using a non-chlorofluorocarbon propellant (Ventolin Inhaler/GR106642X), with the established product.

A clinical program was devised that included paediatric and adult patients, smokers and patients aged over 65 years. A total of 1064 patients were randomised and received study medication in six clinical studies. Of these, 586 received Ventolin Inhaler/GR106642X (approx. 81 patient-years) and 572 received Ventolin Inhaler P11/12 (approx. 79 patient-years). All studies compared Ventolin Inhaler/GR106642X against Ventolin Inhaler P11/12.

Three single dose crossover studies, two bronchial provocation studies with histamine and a dose-ranging bronchodilatation study, in adults demonstrated the efficacy of salbutamol formulated with GR106642X. Another bronchial provocation study demonstrated efficacy in paediatric patients.

Two randomised, double-blind, parallel group multiple dosing studies were also conducted in adults. In a four-week '100µg prn' dosing study (n=423), patients with mild to moderate reversible airways obstruction demonstrated equivalent usage of inhaled salbutamol (daily median usage of 4 actuations/day) in both treatment groups. In a twelve-week 200µg qds dosing study (n=547), patients with moderate reversible airways obstruction recorded no change in heart rate (as a measure of tolerability) following the treatment period, and no detrimental effect was seen as a result of 'switching' from Ventolin Inhaler P11/12 to Ventolin Inhaler/GR106642X.

These studies in both adult and paediatric patients showed that Ventolin Inhaler/GR106642X at the same dose is clinically equivalent to, and is as well tolerated as, Ventolin Inhaler P11/12. There was no evidence to suggest any possible interactions between salbutamol and GR106642X. There were no reports of hypokalaemia or paradoxical bronchospasm in the clinical programme. No new or unexpected adverse events were highlighted when compared to Ventolin Inhaler P11/12.

INDICATIONS:

Ventolin Inhaler is indicated for the relief of bronchospasm in patients with asthma or chronic obstructive pulmonary disease, and for acute prophylaxis against exercise-induced asthma and other stimuli 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 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.

Ventolin Inhaler contains a hydrofluoroalkane (norflurane) propellant. In animal studies, norflurane has been shown to have no significant pharmacological effects, except at very high exposure concentrations when narcosis and a relatively weak sensitisation to the arrhythmogenic effects of catecholamines were found. The potency of the cardiac sensitisation was less than that of trichloromethane (CFC-11).

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.

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.

Spacer Devices

Most patients will benefit from the consistent use of a spacer device with their metered dose inhaler (MDI or 'puffer'), particularly those with poor inhaler technique. Use of a spacer will also decrease the amount of drug deposited in the mouth and back of the throat, and therefore reduce the incidence of local side effects such as 'thrush' and a hoarse voice.

In those people using a spacer, a change in formulation of the drug used, or a change in the make of spacer may be associated with alterations in the amount of drug delivered to the lungs. The clinical significance of these alterations is uncertain. However, in these situations, the person should be monitored for any loss of asthma control.

If using a spacer, the patient should be instructed to actuate the inhaler into the spacer and then slowly breathe in as far as possible. Hold your breath for as long as comfortable, before breathing out slowly. This should be repeated for each actuation of the drug into the spacer. Any delays between actuation and inhalation should be kept to a minimum.

Static on the walls of the spacer may cause variability in drug delivery. Patients should be instructed to wash the spacer in warm water and detergent and allow it to air dry without rinsing or drying with a cloth. This should be performed before initial use of the spacer and at least monthly thereafter.

Effects on Fertility

There is no information on the effects of salbutamol on human fertility. Reproductive studies in rats revealed no evidence of impaired 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, but evidence of retardation of fetal development was recorded in an inhalational teratology study in rabbits at an estimated dose of 149 µg/kg/day.

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

As salbutamol is probably secreted in breast milk, its use in nursing mothers is not recommended unless the expected benefit to the mother is greater than any possible risk to the infant.

Genotoxicity and Carcinogenicity

Salbutamol sulfate caused a significant dose-related increase in the incidence of benign leiomyomas of the mesovarium in a 2-year study in the rat at oral doses of 2, 10 and 50 mg/kg. In another study this effect was blocked by the coadministration of propranolol. These findings are a drug class effect and are thought not to be relevant to the clinical use of the drug. An 18-month study in mice and a lifetime study in hamsters revealed no evidence of tumorigenicity. Studies with salbutamol revealed no evidence of mutagenesis.

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. Salbutamol and non-selective beta-blocking drugs, such as propranolol, should not usually be prescribed together.

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.

ADVERSE EFFECTS:

A fine tremor of skeletal muscle has been reported in some patients when salbutamol is administered orally or by inhalation, 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.

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. Tachycardia may occur in some patients.

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.

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.

As with other inhalation therapy, paradoxical bronchospasm may occur, resulting in an immediate increase in wheezing after dosing (See **PRECAUTIONS**).

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

DOSAGE AND ADMINISTRATION:

Ventolin Inhaler is administered by the inhaled route only, to be breathed in through the mouth.

Ventolin Inhalers need to be primed before use for the first time or if the Inhaler has not been used for 5 days or more. Priming can be achieved by activating the Inhaler twice to waste before use.

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.

As there may be adverse effects associated with excessive dosing, the dosage or frequency of administration should only be increased on medical advice.

Adults and children

One or two inhalations, repeated four-hourly if required. The bronchodilator effect of each administration of Ventolin Inhaler lasts for at least four hours and more frequent use should be unnecessary. The patient can readily recognise any reduction in the length of action and should be instructed to consult a doctor if the effect of a previously adequate dose lasts for less than three hours.

Note 1: Failure to obtain relief from the Inhaler may be a medical emergency. Other appropriate treatment must be instituted without delay.

Note 2: It is important that the patient be instructed in the proper use of the pressurised aerosol.

Geriatric

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 metabolized 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.

Use and handling

Using your inhaler

1. Remove the mouthpiece cover by gently squeezing the sides of the cover.
2. Check inside and outside of the inhaler including the mouthpiece for the presence of loose objects.
3. Shake the inhaler well to ensure that any loose objects are removed and that the contents of the inhaler are evenly mixed.
4. Hold the inhaler upright between fingers and thumb with your thumb on the base, below the mouthpiece.
5. Breathe out as far as is comfortable and then place the mouthpiece in your mouth between your teeth and close your lips around it but do not bite it.
6. Just after starting to breathe in through your mouth press down on the top of the inhaler to release salbutamol while still breathing in steadily and deeply.
7. While holding your breath, take the inhaler from your mouth and take your finger off the top of the inhaler. Continue holding your breath for as long as is comfortable.
8. If you are to take further puffs keep the inhaler upright and wait about half a minute before repeating stages 3 to 7.
9. Replace the mouthpiece cover by firmly pushing and snapping the cap into position.

OVERDOSAGE:

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

The most common signs and symptoms of overdose with salbutamol are transient beta agonist pharmacologically mediated events (see **PRECAUTIONS** and **ADVERSE EFFECTS**). The signs of salbutamol 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 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.

In treating overdose with Ventolin Inhaler, it is to be remembered that forty 100 microgram puffs of the inhaler contain as much salbutamol as one 4 milligram Ventolin tablet.

PRESENTATION AND STORAGE CONDITIONS:

Ventolin Inhaler is a pressurised metered dose inhaler which delivers 100 micrograms of salbutamol (as sulfate) per actuation, suspended in the non-chlorofluorocarbon propellant 1,1,1,2-tetrafluoroethane (GR106642X or HFA-134a or norflurane). Each canister contains at least 200 actuations.

Replace the mouthpiece cover firmly and snap it into position.

Ventolin Inhaler should be stored below 30°C. Protect from frost and direct sunlight. As with most inhaled medications in pressurised canisters, the therapeutic effect of this medication may decrease when the canister is cold. The canister should not be punctured, broken or burnt even when apparently empty.

Ventolin Inhaler should be cleaned once a week. To do so, remove the metal canister from the plastic casing of the inhaler and remove the mouth piece cover. Rinse the actuator thoroughly under warm running water, then dry the actuator thoroughly inside and out. Replace the metal canister and the mouth piece cover. DO NOT put the metal canister in water.

NAME AND ADDRESS OF THE SPONSOR:

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

POISON SCHEDULE OF THE MEDICINE: Schedule 3 – Pharmacist Only Medicine

**DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS
(THE ARTG): 30 June 1998**

DATE OF MOST RECENT AMENDMENT: 16 June 2017

Version 5.0

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