PRODUCT INFORMATION

VENTOLIN RESPIRATOR SOLUTION AND NEBULES

APPROVED NAME: Salbutamol Sulphate BP

PHYSICAL AND CHEMICAL CHARACTERISTICS:
Salbutamol sulphate 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 Sulphate.

STRUCTURE:

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\begin{array}{c}
\text{HOH}_2\text{C} \\
\text{HO} \\
\hline
\text{CHOH.CH}_2\text{NHC(CH}_3\text{)}_3 \\
\text{2SO}_4
\end{array}
\]

MOLECULAR FORMULA: \((\text{C}_{13}\text{H}_{21}\text{NO}_3)_2\text{H}_2\text{SO}_4\)

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 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-sulphate 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).

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.

CONTRAINDICATIONS:
Hypersensitivity to any of the ingredients.

WARNINGS AND 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 cardiocentric 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 Respirator Solution or to Ventolin Nebules cannot be recommended.

**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.

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.

**Interaction with other drugs**

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.

**ADVERSE REACTIONS:**

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 Respirator Solution or 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 Respirator Solution or 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.

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.

**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.

**VENTOLIN RESPIRATOR SOLUTION**

Ventolin Respirator Solution is to be used under the direction of a physician. The solution must not be injected or ingested.

0.5% w/v, may be delivered from any efficient nebulising device.

Ventolin Respirator Solution may be used to achieve bronchodilatation as part of an inhalational 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 Respirator Solution is preferred.

**Method 1 - Intermittent Administration:**

For patients requiring Ventolin Respirator Solution as part of an inhalational therapy regime.

**Dose**

Children
0.02 mL/kg/dose as required, up to 4 hourly. The maximum single dose is 5.00 mg (1.00 mL)

Adults
1.00 mL (5.00 mg) This dosage may be repeated as necessary every 4-6 hours.

Ventolin Respirator Solution may be administered as 0.5% undiluted solution as supplied or diluted according to individual requirements. Dilution of the specified dose is often necessary simply to allow efficient operation of the nebuliser.

Where dilution is necessary or preferred, dilutions of the order of 1 mL of Ventolin Respirator Solution 0.5% in 1 to 10 mL of normal saline are suitable.

The time taken to deliver a given volume of solution will depend upon the equipment used but most nebulisers will deliver 1 mL of solution over 3 minutes and 2 mL over 8-10 minutes.

Any solution remaining in the nebuliser after completion of therapy should be discarded.

Method 2 - Continuous Administration:

This is not the preferred method of administration because of the possibility of uncontrolled dosage (see above).

For patients requiring assisted ventilation. For continuous administration a dilute solution of salbutamol is required. The recommended dilution is 1 mL of Ventolin Respirator Solution 0.5% in 100 mL of normal saline giving a concentration of 50 micrograms/mL of salbutamol. The dilute solution is administered through a nebuliser coupled to an intermittent positive pressure ventilator usually employing oxygen enriched air. Inhalation of the dilute solution may be continued according to the direction of the attending physician until adequate bronchodilatation is achieved.

Some bronchodilatation occurs almost immediately, but maximum reduction in airways resistance may not occur until 15 minutes after commencing therapy.

Any diluted Ventolin Respirator Solution remaining after completion of therapy should be discarded.

Note: Ventolin Respirator Solution may be diluted with Normal Saline.

Important: Any Ventolin Respirator Solution remaining in the bottle once it has been opened should not be used later than 3 months after first opening the bottle.

Fresh dilutions should be prepared for each inhalation and any solution remaining in the nebuliser after therapy should be discarded immediately.

VENTOLIN NEBULES

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.

**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 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.

**OVERDOSE:**

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

The specific antidote for overdose with Ventolin is a cardio-selective beta-blocking agent given by intravenous injection. **IN GENERAL, BETA-BLOCKING DRUGS SHOULD BE USED WITH CAUTION AS THEY MAY CAUSE BRONCHOSPASM IN SENSITIVE INDIVIDUALS.**

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

**PRESENTATION:**

Ventolin Respirator Solution is an aqueous solution of salbutamol sulphate equivalent to 5mg salbutamol in 1 mL and is available in 30 mL screw-capped bottles.

Ventolin Nebules contain a sterile preservative-free, isotonic, aqueous solution of salbutamol sulphate 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 30, arranged as six individually foil wrapped strips of five Nebules.

**SHELF LIFE AND STORAGE CONDITIONS:**

Ventolin Respirator Solution has a shelf life of 2 years when stored below 30°C. Any solution remaining in the bottle once it has been opened should not be used later than 3 months after first opening the bottle. Solutions in nebulisers should be replaced daily.
Ventolin Nebules have a shelf life of 3 years when stored below 30°C. Store protected from light. Once removed from the foil overwrap Nebules have a shelf-life of three months when stored below 30°C.

**MANUFACTURER:**

Allen and Hanburys  
A division of  
Glaxo Wellcome Australia Ltd  
A.C.N. 004 148 065  
1061 Mountain Highway  
Boronia Victoria 3155

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