Ventolin

Versión GDSv25-IPIv09

Ventolin

RESPIRATOR SOLUTION

Salbutamol

QUALITATIVE AND QUANTITATIVE COMPOSITION
VENTOLIN Respirator Solution contains 5mg salbutamol, as sulphate, per ml of solution and is supplied in 10 ml and 20 ml bottles.

PHARMACEUTICAL FORM
Nebuliser solution.

CLINICAL PARTICULARS

Indications

Salbutamol is a selective beta$_2$ adrenoceptor agonist indicated for the treatment or prevention of bronchospasm. It provides short acting (four hours) bronchodilation in reversible airways obstruction due to asthma, chronic bronchitis and emphysema. For patients with asthma salbutamol may be used to relieve symptoms when they occur and to prevent them prior to a known trigger.

Bronchodilators should not be the only or main treatment in patients with persistent asthma. In patients with persistent asthma unresponsive to *VENTOLIN*, treatment with inhaled corticosteroids is recommended to achieve and maintain control. Failing to respond to treatment with *VENTOLIN* may signal a need for urgent medical advice or treatment.

VENTOLIN Respirator Solution is indicated for the routine management of chronic bronchospasm (unresponsive to conventional therapy) and treatment of acute severe asthma (status asthmaticus).

Dosage and Administration

VENTOLIN has a duration of action of 4 to 6 hours in most patients.

VENTOLIN Respirator Solution is to be used with a respirator or nebuliser, only under the direction of a physician.

The solution must not be injected, or swallowed.

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.

Delivery of the aerosol may be by facemask, 'T' piece or via an endotracheal tube. Intermittent positive pressure ventilation may be used but is rarely necessary. When there is a risk of anoxia through hypoventilation, oxygen should be added to the inspired air.

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

As many nebulisers operate on a continuous flow basis, it is likely that nebulised drug will be released in the local environment. *VENTOLIN* Respirator Solution should therefore be administered in a well-ventilated room, particularly in hospitals when several patients may be using nebulisers in the same space at the same time.

1. By intermittent administration

Intermittent treatment may be repeated 4 times daily.

- **Adults**

VENTOLIN Respirator Solution 0.5 to 1.0ml (2.5 to 5.0 milligrams of salbutamol) should be diluted to a final volume of 2.0 or 2.5ml using sterile normal saline as a diluent. The resulting solution is inhaled from a suitably driven nebuliser until aerosol generation ceases. Using a correctly matched nebuliser and driving source this should take about 10 minutes.

VENTOLIN Respirator Solution may be used undiluted for intermittent administration. For this, 2.0ml of *VENTOLIN* Respirator Solution (10.0 milligrams salbutamol) is placed in the nebuliser and the patient allowed to inhale the nebulised solution until bronchodilatation is achieved.

This usually takes 3 to 5 minutes.

Some adult patients may require higher doses of salbutamol, up to 10 milligrams, in which case nebulisation of the undiluted solution may continue until aerosol generation ceases.

- **Children**

The same mode of administration for intermittent administration is also applicable to children. The usual dosage for children under the age of 12 years is 0.5ml (2.5 milligrams salbutamol) diluted to 2.0 or 2.5ml using sterile normal saline as diluent. Some children may however require higher doses of salbutamol up to 5.0 milligrams.

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

2. By continuous administration

VENTOLIN Respirator Solution is diluted using sterile normal saline to contain 50-100 □g of salbutamol per ml, (1 to 2ml solution made up to 100ml with diluent). The diluted solution is administered as an aerosol by a suitably driven nebuliser. The usual rate of administration is 1 to 2 milligrams per hour.

Contraindications

VENTOLIN Respirator Solution is contraindicated in patients with a history of hypersensitivity to any of its components.

Non-i.v. formulations of *VENTOLIN* must not be used to arrest uncomplicated premature labour or threatened abortion.

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.

VENTOLIN Respirator solution must only be used by inhalation, to be breathed in through the mouth, and must not be injected or swallowed.

Patients receiving treatment at home with *VENTOLIN* Respirator Solution must 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.

VENTOLIN Respirator Solution should be used with caution in patients known to have received large doses of other sympathomimetic drugs.

VENTOLIN should be administered cautiously to patients with thyrotoxicosis.

A small number of cases of acute angle closure glaucoma have been reported in patients treated with a combination of nebulised *VENTOLIN* and ipratropium bromide. A combination of nebulised *VENTOLIN* 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.

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 by hypoxia. It is recommended that serum potassium levels are monitored in such situations.

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. *VENTOLIN* Respirator Solution should be discontinued, and if necessary a different fast-acting bronchodilator instituted for ongoing use.

In common with other □-adrenoceptor agonists, *VENTOLIN* 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 ketacidosis has been reported. Concurrent administration of corticosteroids can exaggerate this effect.

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 Reaction section*). 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.

Interactions

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

VENTOLIN is not contraindicated in patients under treatment with monoamine oxidase inhibitors.

Pregnancy and Lactation

FERTILITY

There is no information on the effects of salbutamol on human fertility. There were no adverse effects on fertility in animals (*see Pre-clinical Safety Data*).

PREGNANCY

Administration of drugs during pregnancy should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus.

During world-wide 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. Some of the mothers were taking multiple medications during their pregnancies. As no consistent pattern of defects can be discerned, and baseline rate for congenital anomalies is 2-3%, a relationship with salbutamol use cannot be established.

LACTATION

As salbutamol is probably secreted in breast milk, its use in nursing mothers is not recommended unless the expected benefits outweigh any potential risk. It is not known whether salbutamol in breast milk has a harmful effect on the neonate.

Effects on Ability to Drive and Use Machines

None reported.

Adverse Reactions

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000) and very rare (<1/10,000) including isolated reports. Very common and common events were generally determined from clinical trial data. Rare and very rare events were generally determined from spontaneous data.

IMMUNE SYSTEM DISORDERS

Very rare: Hypersensitivity reactions including angioedema, urticaria, bronchospasm, hypotension and collapse

Metabolism and nutrition disorders

Rare: Hypokalaemia

Potentially serious hypokalaemia may result from beta$_2$ agonist therapy.

Very rare: Lactic acidosis

Lactic acidosis has been reported very rarely in patients receiving intravenous and nebulised salbutamol therapy for the treatment of acute asthma exacerbation.

Nervous system disorders

Common: Tremor, headache

Very rare: Hyperactivity

Cardiac disorders

Common: Tachycardia

Uncommon: Palpitations

Very rare: Cardiac arrhythmias including atrial fibrillation, supraventricular tachycardia and extrasystoles

Vascular disorders

Rare: Peripheral vasodilatation

Respiratory, thoracic and mediastinal disorders

Very rare: Paradoxical bronchospasm

Gastrointestinal disorders

Uncommon: Mouth and throat irritation

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS

Uncommon: Muscle cramps

Overdose

The most common signs and symptoms of overdose with *VENTOLIN* are transient beta agonist pharmacologically mediated events (see Warnings and Precautions and Adverse Reactions).

Hypokalaemia may occur following overdosage with *VENTOLIN*. 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.

During continuous administration of VENTOLIN Respirator Solution, any signs of overdosage can usually be counteracted by withdrawal of the drug.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

Salbutamol is a selective beta$_2$-adrenoceptor agonist. At therapeutic doses it acts on the beta$_2$-adrenoceptors of bronchial muscle providing short acting (4 to 6 hour) bronchodilation with a fast onset (within 5 minutes) in reversible airways obstruction.

Pharmacokinetics

Absorption

After administration by the inhaled route, between 10 and 20% of the dose reaches the lower airways. The remainder is retained in the delivery system or is deposited in the oropharynx from where it is swallowed. The fraction deposited in the airways is absorbed into the pulmonary tissues and circulation but is not metabolised by the lung.

Distribution

Salbutamol is bound to plasma proteins to the extent of 10%.

Metabolism

On reaching the systemic circulation, salbutamol becomes accessible to hepatic metabolism and is excreted, primarily in the urine, as unchanged drug and as the phenolic sulphate.

The swallowed portion of an inhaled dose is absorbed from the gastrointestinal tract and undergoes considerable first-pass metabolism to the phenolic sulphate. Both unchanged drug and conjugate are excreted primarily in the urine.

Elimination

Salbutamol administered intravenously has a half-life of four to six hours and is cleared partly renally and partly by metabolism to the inactive 4'-O-sulphate (phenolic sulphate) which is also excreted primarily in the urine. The faeces are a minor route of excretion. The majority of a dose of salbutamol given intravenously, orally or by inhalation is excreted within 72 hours.

Pre-clinical Safety Data

In common with other potent selective beta$_2$ receptor agonists, salbutamol has been shown to be teratogenic in mice when given subcutaneously. In a reproductive study, 9.3% of foetuses were found to have cleft palate, at 2.5 mg/kg, 4 times the maximum human oral dose. In rats, treatment at the levels of 0.5, 2.32, 10.75 and 50mg/kg/day orally throughout pregnancy resulted in no significant foetal abnormalities. The only toxic effect was an increase in neonatal mortality at the highest dose level as the result of lack of maternal care. A reproductive study in rabbits revealed cranial malformations in 37% of foetuses at 50mg/kg/day, 78 times the maximum human oral dose.

In an oral fertility and general reproductive performance study in rats at doses of 2 and 50 mg/kg/day, with the exception of a reduction in number of weanlings surviving to day 21 post partum at 50 mg/kg/day, there were no adverse effects on fertility, embryofetal development, litter size, birth weight or growth rate.

PHARMACEUTICAL PARTICULARS

List of Excipients

Purified water.
Benzalkonium chloride.
Dilute sulphuric acid.

Incompatibilities

None reported.

Shelf Life

The expiry date is indicated on the packaging.

Special Precautions for Storage

VENTOLIN Respirator Solution should be stored at a temperature below 25 °C and protected from light.

Once the bottle has been opened the contents should be discarded after one month.

Nature and Contents of Container

Salbutamol, as sulphate, is supplied as a 5mg/ml solution in bottles of 10 ml and 20 ml.

Instructions for Use/Handling

Dilution:

VENTOLIN Respirator Solution may be diluted with sterile normal saline.

Any unused solution in the chamber of the nebuliser must be discarded.

Not all presentations are available in every country.

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