

DATA SHEET

Ventolin™ Nebules

Salbutamol Nebules

Qualitative and quantitative composition

Ventolin nebulas 2.5mg are a plastic ampoule presentation containing a sterile, aqueous colourless solution of salbutamol sulphate in normal saline. The concentration of salbutamol is 0.1% (1mg salbutamol, as the sulphate, in 1mL). Each Nebule contains 2.5mL of solution equivalent to 2.5mg salbutamol.

Ventolin nebulas 5.0mg are a plastic ampoule presentation containing a sterile, aqueous colourless solution of salbutamol sulphate in normal saline. The concentration of salbutamol is 0.2% (2mg salbutamol, as the sulphate, in 1mL). Each Nebule contains 2.5mL of solution equivalent to 5.0mg salbutamol.

Clinical particulars

Therapeutic Indications

Salbutamol is a selective β_2 adrenoceptor agonist. At therapeutic doses it acts on the β_2 adrenoceptors of bronchial muscle, with little or no action on the heart. With its fast onset of action, it is particularly suitable for the management and prevention of attack in asthma.

Bronchodilators should not be the only or the main treatment in patients with severe or unstable asthma. Severe asthma requires regular medical assessment as death may occur. Patients with severe asthma have constant symptoms and frequent exacerbations, with limited physical capacity, and PEF values below 60% predicted at baseline with greater than 30% variability, usually not returning entirely to normal after a bronchodilator. These patients will require high dose inhaled (e.g >1mg/day beclomethasone dipropionate) or oral corticosteroid therapy. Sudden worsening of symptoms may require increased corticosteroid dosage which should be administered under urgent medical supervision.

Ventolin Nebules are indicated for use in the routine management of chronic bronchospasm - unresponsive to conventional therapy and in the treatment of acute severe asthma (status asthmaticus).

Posology and Method of Administration

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

Ventolin Nebules are intended to be used undiluted. However, if prolonged delivery time is desirable (more than 10 minutes) dilution using sterile normal saline as a diluent may be required.

Ventolin Nebules are to be used with a nebuliser, under the direction of a physician.

The solution must not be injected or swallowed.

Increasing use of β_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 agent will be released in the local environment. Ventolin nebulers should therefore be administered in a well ventilated room, particularly in hospitals when several patients may be using nebulisers at the same time.

Adults and Children:-

A suitable starting dose of salbutamol by wet inhalation is 2.5 milligrams. This may be increased to 5 milligrams. Treatment may be repeated four times daily. In adults higher dosing, up to 40 milligrams per day, can be given under strict medical supervision in hospital for the treatment of severe airways obstruction.

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

Contra-indications

Ventolin Nebules are contra-indicated in patients with a history of hypersensitivity to any of their components.

Although intravenous salbutamol and occasionally salbutamol tablets are used in the management of premature labour, uncomplicated by conditions such as placenta praevia, ante-partum haemorrhage or toxemia of pregnancy, inhaled salbutamol preparations are not appropriate for managing

premature labour. Salbutamol presentations should not be used for threatened abortion.

Special warnings and special precautions for use

Ventolin Nebules must only be used by inhalation, to be breathed in through the mouth, and must not be injected or swallowed.

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 β_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 receiving treatment at home with Ventolin Nebules 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 Nebules should be used with caution in patients known to have received large doses of other sympathomimetic agents.

Salbutamol 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 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.

Potentially serious hypokalaemia may result from β_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.

In common with other β -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 Undesirable Effects 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.

Interaction with other medicaments and other forms of interaction

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

Salbutamol is not contra-indicated in patients under treatment with monoamine oxidase inhibitors(MAOIs).

Pregnancy and lactation

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

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. Some of the mothers were taking multiple medications during their pregnancies.

Because 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.

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.

Undesirable effects

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common ($\geq 1/10$), common ($\geq 1/100$ and $< 1/10$), uncommon ($\geq 1/1000$ and $< 1/100$), rare ($\geq 1/10,000$ and $< 1/1000$) 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 beta₂ 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.

As with other inhalation therapy, paradoxical bronchospasm may occur with an immediate increase in wheezing after dosing. This should be treated immediately with an alternative presentation or a different fast-acting inhaled bronchodilator. Ventolin Nebules should be discontinued immediately, the patient assessed, and, if necessary, alternative therapy instituted.

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 salbutamol are transient beta agonist pharmacologically mediated events (see Special Warnings and Special Precautions for Use and Undesirable Effects).

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

Consideration should be given to discontinuation of treatment and appropriate symptomatic treatment such as a cardioselective β -blocking agent, in patients presenting with cardiac symptoms (e.g. tachycardia, palpitations). Beta-blocking agents should be used with caution in patients with a history of bronchospasm.

Pharmacological properties

Pharmacodynamic properties

Salbutamol is a selective β_2 adrenoceptor agonist. At therapeutic doses it acts on the β_2 adrenoceptors of bronchial muscle, with little or no action on the β_1 adrenoceptors of cardiac muscle.

Pharmacokinetic properties

Salbutamol administered intravenously has a half-life of 4 to 6 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. Salbutamol is bound to plasma proteins to the extent of 10%.

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.

On reaching the systemic circulation it 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.

Pre-Clinical safety data

In common with other potent selective β_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 2.5mg/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.

Pharmaceutical particulars

Shelf Life

36 months

Storage:-

Ventolin Nebules should be stored at a temperature below 30°C and protected from light.

Package Quantities

Ventolin Nebules 2.5mg and 5.0mg are each available in boxes containing 20 Nebules in strips of 5.

Dilution:-

Ventolin Nebules may be diluted with sterile normal saline. Any unused solution in the chamber of the nebuliser must be discarded.

Medicines classification

Prescription Only Medicine

Name and address

GlaxoSmithKline NZ Limited
Quay Tower
Cnr Albert & Customs Streets
Private Bag 106600
Downtown Auckland
NEW ZEALAND

Phone: (09) 367 2900
Facsimile: (09) 367 2506

Date of preparation

Issue date: 19 June 2007.

Version: 1.0

VENTOLIN™ is a trade mark of the GlaxoSmithKline group of companies