

VENTOLIN NEBULES

Salbutamol



1. QUALITATIVE AND QUANTITATIVE COMPOSITION

VENTOLIN Nebules 2.5 mg: contain a concentration of salbutamol of 0.1% (1 mg salbutamol, as the sulfate, in 1 mL). Each nebule contains 2.5 mL of solution equivalent to 2.5 mg salbutamol.

2. PHARMACEUTICAL FORM

Nebuliser solution.

3. CLINICAL PARTICULARS

3.1 Indications

VENTOLIN is a selective beta₂-adrenoceptor agonist. At therapeutic doses it acts on the beta₂-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 Peak Expiratory Flow (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 >1 mg/day beclomethasone dipropionate) or oral corticosteroid therapy. Sudden worsening of symptoms may require increased corticosteroid dosage which should be administered under urgent medical supervision.

Routine management of chronic bronchospasm-unresponsive to conventional therapy.

Treatment of acute severe asthma (status asthmaticus).

3.2 Dosage and Administration

VENTOLIN 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 beta₂-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* Nebules 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.

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

3.3 Contraindications

VENTOLIN Nebules are contraindicated in patients with a history of hypersensitivity to any of their components.

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

3.4 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 beta₂-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 Nebules 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* 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 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 beta₂-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* Nebules should be discontinued, and if necessary a different fast-acting bronchodilator instituted for ongoing use.

In common with other beta-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.

3.5 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 (MAOIs).

3.6 Pregnancy and Lactation

Fertility

There is no information on the effects of *VENTOLIN* 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 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.

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.

3.7 Effects on Ability to Drive and Use Machines

None reported.

3.8 Adverse Reactions

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

Gastrointestinal disorders

Uncommon: Mouth and throat irritation

Musculoskeletal and connective tissue disorders

Uncommon: Muscle cramps

3.9 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.

4. PHARMACOLOGICAL PROPERTIES

4.1 Pharmacodynamics

Salbutamol is a selective beta₂-adrenoceptor agonist. At therapeutic doses it acts on the beta₂-adrenoceptors of bronchial muscle providing short-acting (4 to 6 hour) bronchodilation with a fast onset (within 5 minutes) in reversible airways obstruction.

4.2 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 it becomes accessible to hepatic metabolism and is excreted, primarily in the urine, as unchanged drug and as the phenolic sulfate. The swallowed portion of an inhaled dose is absorbed from the gastrointestinal tract and undergoes considerable first-pass

metabolism to the phenolic sulfate. 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-sulfate (phenolic sulfate) 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.

4.3 Pre-clinical Safety Data

In common with other potent selective beta₂-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. In rats, treatment at the levels of 0.5, 2.32, 10.75 and 50 mg/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 50 mg/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.

5. PHARMACEUTICAL PARTICULARS

5.1 List of Excipients

Sodium chloride.
Sulfuric acid.
Purified water.

5.2 Incompatibilities

None reported.

5.3 Shelf Life

The expiry date is indicated on the packaging.

5.4 Special Precautions for Storage

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

5.5 Nature and Contents of Container

VENTOLIN Nebules are plastic ampoules containing a solution of salbutamol sulfate in normal saline. Each nebule contains 2.5 mL of solution.

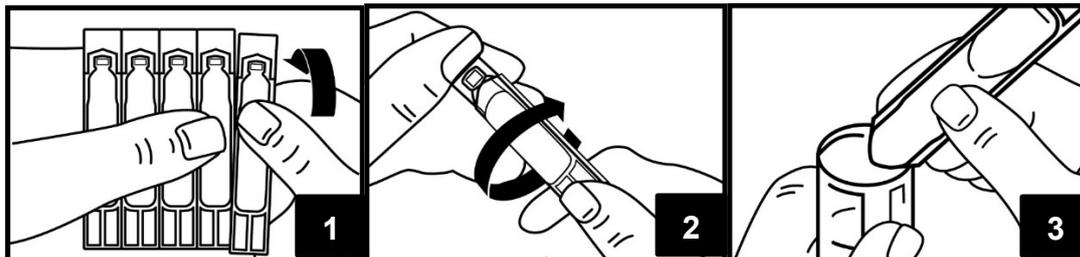
5.6 Instructions for Use/Handling

Dilution:

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

5.7 Directions for Use/Handling

ONCE A NEBULE HAS BEEN DETACHED FROM THE PLASTIC BAR, IT IS OPENED AND SHOULD BE USED IMMEDIATELY.



1. Prepare your nebuliser for filling.
2. Separate one *VENTOLIN* Nebule and detach by twisting it firmly.
3. The nebuliser is now open. Take care not to spill the content.
4. Squeeze the contents of the nebuliser into the reservoir of the nebuliser. Do not dilute the contents unless instructed to do so by your doctor.
5. Assemble the nebuliser and use it as directed.
6. After use, discard any remaining solution and clear the nebuliser the usual way.

If dilution is necessary this should be carried out only as prescribed by your doctor. The usual method of dilution is to empty the *VENTOLIN* Nebule into the nebuliser reservoir, as above and then to add the prescribed amount of sterile normal saline. The reservoir should then be gently shaken to mix the contents.

Package Quantities and Registration Number

VENTOLIN Nebules 2.5 mg are each available in boxes containing 20 nebulisers in pack 4x5.

VENTOLIN Nebules 0.1%

Reg No. DKIXXXXXXXXXXXXX

HARUS DENGAN RESEP DOKTER

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