

VENTOLIN™ ACCUHALER™

Salbutamol

QUALITATIVE AND QUANTITATIVE COMPOSITION

VENTOLIN Accuhaler is a moulded plastic device containing a foil strip with 60 regularly distributed blisters. Each blister contains a powder blend of 200 micrograms of salbutamol (as sulphate) and lactose.

The device incorporates a dose counter which displays the number of doses remaining in the device.

PHARMACEUTICAL FORM

Inhalation powder

CLINICAL PARTICULARS

Indications

VENTOLIN Accuhaler can be used in the management of reversible airways obstruction. It is particularly suitable for the relief of asthma symptoms. It should be used to relieve symptoms when they occur and to prevent them in those circumstances recognised by the patient to precipitate an asthmatic attack (e.g. before exercise or unavoidable allergen exposure).

VENTOLIN Accuhaler is particularly valuable as relief medication in mild, moderate or severe asthma, provided that reliance on it does not delay the introduction and use of regular inhaled corticosteroid therapy.

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. 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.

Dosage and Administration

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

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.

VENTOLIN Accuhaler is administered by the inhaled route only, to be breathed in through the mouth.

Patients' inhaler technique should be checked to ensure that the device is used at maximum efficiency

- **Elderly**

There is no need to adjust the dose in the elderly.

Adults (Including The Elderly)

For the relief of acute bronchospasm, 200 micrograms as a single dose. The maximum daily dose is 200 micrograms four times a day.

To prevent allergen- or exercise-induced asthma, 200 micrograms should be taken 10-15 minutes before challenge or exertion.

Children

The recommended dose for relief of acute bronchospasm or before allergen exposure or exercise is 200 micrograms before challenge or exertion. The maximum daily dose is 200 micrograms four times daily.

On demand use of *VENTOLIN* Accuhaler should not exceed four times daily. Reliance on such frequent supplementary use or a sudden increase in dose indicates poorly controlled or deteriorating asthma (see *Warnings & Precautions*).

CONTRAINDICATIONS

VENTOLIN dry powder inhaler formulations are contraindicated in patients with severe milk-protein allergy or who have a history of hypersensitivity to salbutamol or any of its formulation components (see *Excipients*). 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 the patient response should be monitored clinically and by lung function tests. Increasing use of short-acting bronchodilators, in particular beta₂ agonists to relieve 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 should be administered cautiously to patients suffering from thyrotoxicosis.

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

In the event of a previously effective dose of inhaled *VENTOLIN* failing to give relief for at least three hours, the patient should be advised to seek medical advice in order that any necessary additional steps may be taken.

INTERACTIONS

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

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

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 Ventolin. 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 to 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 the 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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1000$ to $< 1/100$), rare ($\geq 1/10,000$ 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.

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.

PHARMACOLOGICAL PROPERTIES

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) bronchodilatation 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, four times the maximum human oral dose. 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.

PHARMACEUTICAL PARTICULARS

Excipients

Lactose (which contains milk protein).

Incompatibilities

None reported.

Special Precautions for Storage

Store below 30°C.

Store in a dry place.

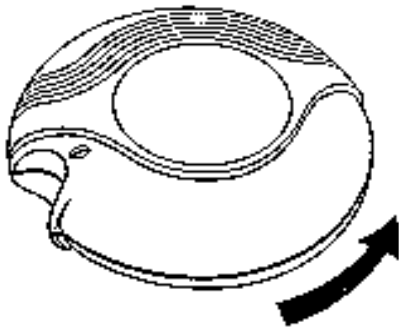
Protect from frost and light.

The Accuhaler should be discarded 6 months after removal from the foil overwrap pack.

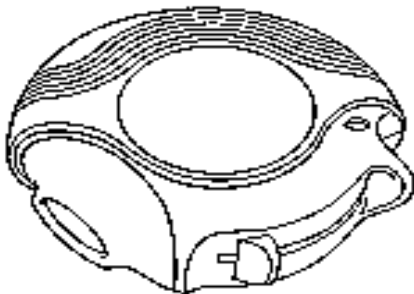
Instructions for Use/Handling

The Accuhaler is sealed in a foil overwrap. The overwrap provides moisture protection and should only be opened when you are ready to use it for the first time. Once removed/opened the foil overwrap should be discarded.

When you take your Accuhaler out of its box and remove the foil overwrap, it will be in the closed position.



This Accuhaler contains 60 individually protected doses of your medicine, in powder form. The dose counter tells you how many doses are left.



Each dose is accurately measured and hygienically protected. It requires no maintenance and no refilling.

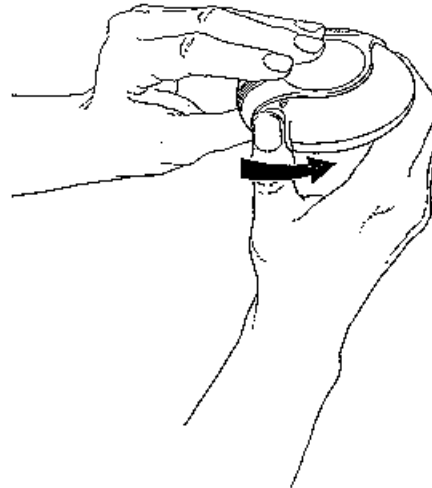
The dose indicator on top of your Accuhaler tells you how many doses are left. Numbers 5 to 0 will appear in **RED**, to warn you when there are only a few doses left.

The Accuhaler is easy to use. When you need to use a dose, just follow the four simple steps as illustrated:

- 1. OPEN**
- 2. SLIDE**
- 3. INHALE**
- 4. CLOSE**

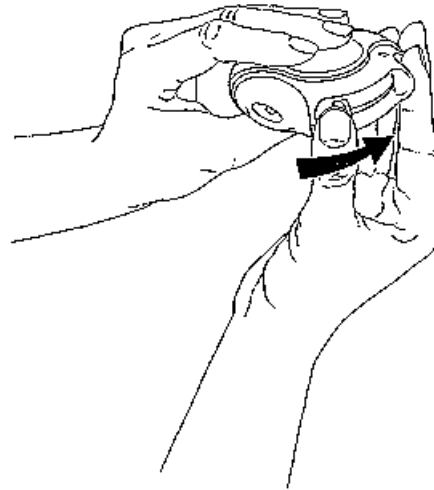
1. OPEN – How to use the Accuhaler

To open your Accuhaler, hold the outer case in one hand and put the thumb of your other hand on the thumbgrip. Push your thumb away from you as far as it will go.



2. SLIDE

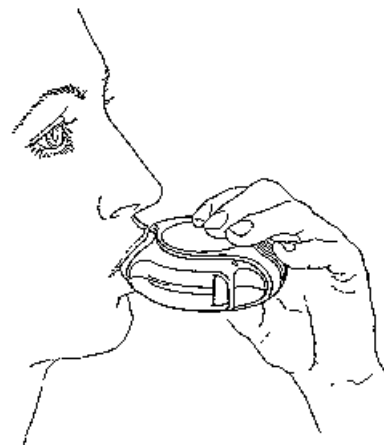
Hold your Accuhaler with the mouthpiece towards you. You can hold it in either your right or left hand. Slide the lever away from you, as far as it will go - until it clicks. Your Accuhaler is now ready to use. Every time the lever is pushed back, a dose is made available for inhaling. This is shown by the dose counter. Do not play with the lever as this releases doses which will be wasted.



3. INHALE

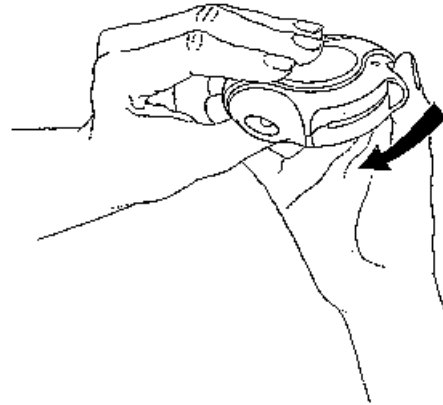
BEFORE YOU START TO INHALE THE DOSE, READ THROUGH THIS SECTION CAREFULLY.

- * Hold the Accuhaler away from your mouth. Breathe out as far as is comfortable. Remember - never breathe into your Accuhaler.
- * Put the mouthpiece to your lips. Breathe in steadily and deeply through the Accuhaler with your mouth, not through your nose.
- * Remove the Accuhaler from your mouth.
- * Hold your breath for about 10 seconds, or as long as is comfortable.
- * Breathe out slowly.



4. CLOSE

To close your Accuhaler, put your thumb in the thumbgrip, and slide the thumbgrip back towards you, as far as it will go. When you close the Accuhaler, it clicks shut. The lever automatically returns to its original position and is reset. Your Accuhaler is now ready for you to use again. If you have been instructed to take two inhalations you must repeat steps 1 to 4.



REMEMBER

Keep your Accuhaler dry.
Keep it closed when not in use.
Never breathe into your Accuhaler.
Only slide the lever when you are ready to take a dose.
Ventolin Accuhaler must only be breathed in through the mouth.
Do not exceed the stated dose. Keep out of reach of children.

CLEANING

Wipe the mouthpiece of the Accuhaler with a dry tissue to clean it.

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