

NEW ZEALAND DATA SHEET

RESPIGEN™



1. Product Name

Respigen™ 100 micrograms per actuation inhalation aerosol

2. Qualitative and Quantitative Composition

Each pressurised metered-dose aerosol inhaler contains 100 micrograms of salbutamol (as sulfate)

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

Respigen consists of a white microfine suspension of salbutamol in a non-CFC liquid propellant mixture packed under its own vapour pressure in an aluminium can sealed with a metering valve.

Respigen is a metered-dose aerosol inhaler which delivers 100 micrograms of salbutamol per actuation, into the mouthpiece of a specially designed actuator.

4. Clinical Particulars

4.1 *Therapeutic indications*

Salbutamol is a selective β_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 salbutamol, treatment with inhaled corticosteroids is recommended to achieve and maintain control. Failure to respond promptly or fully to such rescue medication signals a need for urgent medical advice and treatment.

4.2 *Dose and method of administration*

Dose

Relief of acute bronchospasm:

Adults: 100 or 200 micrograms.

Children: 100 micrograms, the dose may be increased to 200 micrograms if required.

Prevention of allergen or exercise-induced bronchospasm:

Adults: 200 micrograms before challenge

Children: 100 micrograms before challenge, the dose may be increased to 200 micrograms if required.

Chronic therapy:

Adults: Up to 200 micrograms four times daily

Children: Up to 200 micrograms four times daily

On demand use of Respigen should not exceed four times daily. Reliance on such supplementary use or a sudden increase in dose indicates deteriorating asthma (see section 4.4).

Method of administration

Respigen is administered by the oral inhaled route only.

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

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.

In patients who find co-ordination of a pressurised metered-dose inhaler difficult a spacer device may be used with the Respigen inhaler.

Babies and young children may benefit from use of a spacer device with the Respigen Inhaler.

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

4.3 Contraindications

Respigen is contra-indicated in patients with a history of hypersensitivity to any of its components (see section 6.1).

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

4.4 Special warnings and precautions for use

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.

In the event of a previously effective dose of inhaled salbutamol 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.

Patients' inhaler technique should be checked to make sure that aerosol actuation is synchronised with inspiration of breath for optimum delivery of the drug to the lungs.

Cardiovascular effects may be seen with sympathomimetic drugs, including salbutamol. There is some evidence from post-marketing data and published literature of rare occurrences of myocardial ischaemia associated with beta agonists. Patients with underlying severe heart disease (e.g. ischaemic heart disease, arrhythmia or severe heart failure) who are receiving salbutamol should be warned to seek medical advice if they experience chest pain or other symptoms of worsening heart disease. Attention should be paid to assessment of symptoms such as dyspnoea and chest pain, as they may be of either respiratory or cardiac origin.

Salbutamol should be administered cautiously to patients with thyrotoxicosis.

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.

As with other inhalation therapy, paradoxical bronchospasm may occur, resulting in an immediate increase in wheezing after dosing. Tachycardia may occur in some patients. This should be treated immediately with an alternative presentation or a different fast-acting inhaled bronchodilator, if immediately available. Respigen should be discontinued, and if necessary a different fast-acting bronchodilator instituted for ongoing use.

Respigen contains ethyl alcohol (ethanol) 7% w/w. This equates to 4.13 mg of ethanol per actuation.

4.5 Interaction with other medicines and other forms of interaction

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

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.

Breast-feeding

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.

Fertility

There is no information on the effects of salbutamol on human fertility. There were no adverse effects on fertility in animals (see section 5.3).

4.7 Effects on ability to drive and use machines

None reported.

4.8 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 β_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.

Unknown: Myocardial ischaemia[#].

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.

[#]Myocardial ischaemia has been reported spontaneously in post-marketing data therefore frequency regarded as unknown.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

The most common signs and symptoms of overdose with salbutamol are transient beta agonist pharmacologically mediated events (see section 4.4 and 4.8).

Hypokalaemia may occur following overdose with salbutamol. 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

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 *Pharmacodynamic properties*

Pharmacotherapeutic group: Adrenergics, inhalants. Selective beta-2-adrenoreceptor agonists.
ATC code: R03AC02.

Salbutamol is a selective β_2 adrenoceptor agonist. At therapeutic doses it acts on the β_2 adrenoceptors of bronchial muscle, providing short acting (4 to 6 hour) bronchodilation with a fast onset (within 5 minutes) in reversible airways obstruction.

5.2 *Pharmacokinetic properties*

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%.

Biotransformation

On reaching the systemic circulation it becomes accessible to hepatic metabolism and is excreted, primarily in the urine, as unchanged salbutamol 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 salbutamol and conjugate are excreted primarily in the urine.

Elimination

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- 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.

5.3 *Preclinical 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 2.5 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.

HFA 134a has been shown to be non-toxic at very high vapour concentrations, far in excess of those likely to be experienced by patients, in a wide range of animal species exposed daily for periods of two years.

6. Pharmaceutical Particulars

6.1 *List of excipients*

1,1,1,2-tetrafluoroethane (also known as HFA 134a or norflurane), oleic acid, ethanol.

6.2 *Incompatibilities*

Not applicable.

6.3 *Shelf life*

2 years.

6.4 *Special precautions for storage*

Respigen should be stored below 25°C. Protect from frost and direct sunlight.

The canister contains a pressurised liquid. Do not expose to temperatures higher than 50°C.

As with most inhaled medications in aerosol canisters, the therapeutic effect of this medication may decrease when the canister is cold. Do not freeze or refrigerate.

The canister should not be broken, punctured or burnt, even when apparently empty.

6.5 *Nature and contents of container*

Respigen comprises a suspension of salbutamol sulfate in the non-CFC propellant HFA 134a. Respigen delivers 100 micrograms of salbutamol (as sulfate) per actuation.

Each canister contains a minimum of 200 actuations.

6.6 *Special precautions for disposal and other handling*

1. Remove the cap from the mouthpiece by holding it between thumb and forefinger and squeezing gently whilst pulling them apart. Check that there are no objects in the mouthpiece and that it is clean.

Testing your Respigen inhaler

If the inhaler is new, or has not been used for more than one week, shake it well and fire two puffs into the air to check that it works.

2. Hold the inhaler upright with your thumb on the base and your first finger on the top of the can, and shake well.
3. Breathe out slowly through your mouth as far as is comfortable and then immediately place the mouthpiece fully into your mouth and close your lips lightly around it, but do not bite it.
4. Breathe in slowly and deeply and as you start to do so press the metal canister down firmly with your first finger to spray the aerosol and release the medicine. Continue to breathe in steadily and deeply.
5. Hold your breath and remove the mouthpiece from your mouth. Continue to hold your breath for about 10 seconds, or as long as comfortable, then breathe out slowly.

6. Wait for about one minute before taking another puff, if needed. Then repeat steps 2 to 5.
7. Replace the cap on the mouthpiece by snapping it into place to protect it from dirt and dust.

It is VERY important that you do not rush steps 3 and 4.

It is very important that you breathe in slowly before pressing the metal canister. It is a good idea to practice this in front of a mirror. If you see mist coming from your mouth or the inhaler then you should repeat the instructions from step 2. However do not have more than 4 goes at this whilst practising.

If you have difficulty in operating the inhaler with one hand, it is possible to use both hands. At step 2 put both forefingers on top of the canister and place both thumbs on the base. Then proceed as instructed.

Your doctor may give you different instructions to these on how to use your inhaler. If so please follow them. If you have any difficulties in using this inhaler please tell your doctor, nurse or pharmacist.

Cleaning

You should clean your inhaler once a week. To clean it:

1. Remove the metal canister by gripping it firmly and pulling it out of the plastic case. Then remove the dust cap from the case.
2. Clean the mouthpiece and dust cap in warm water. You can also add a mild detergent or baby bottle cleaning solution to the water, your pharmacist can advise you about this. If you use a cleaning solution rinse the plastic case and dust cover in running water. DO NOT put the metal canister into water.
3. Dry the case and dust cover in a warm place, but avoid direct heat.
4. Replace the dust cap and metal canister by reversing step 1.

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

Mylan New Zealand Ltd
PO Box 11-183
Ellerslie
AUCKLAND
Telephone 09-579-2792

9. Date of First Approval

9 February 2006

10. Date of Revision of the Text

25 March 2019

Summary table of changes

Section	Summary of new information
4.4	Alcohol content moved from section 3 to 4.4 and amount per actuation added
5.2	Headings added to section