

# New Zealand Datasheet

## 1 PRODUCT NAME

Asthalin™

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Salbutamol respiratory solution

## 3 PHARMACEUTICAL FORM

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

Asthalin is a plastic ampoule presentation containing a sterile, aqueous colourless solution of salbutamol sulphate in normal saline. The concentration of salbutamol is 0.2% (2 mg salbutamol, as the sulphate, in 1 mL). Each ampoule contains 2.5 mL of solution equivalent to 5 mg salbutamol.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Salbutamol is a selective  $\beta_2$  adrenoceptor agonist. At therapeutic doses it acts on the  $\beta_2$  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.

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

### 4.2 Dose and method of administration

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

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

Asthalin is to be used with a nebuliser, 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 agent will be released in the local environment. Asthalin 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.

### **4.3 Contraindications**

Asthalin is contra-indicated in patients with a history of hypersensitivity to any of their components.

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**

Asthalin 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  $\beta_2$  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.

Patients receiving treatment at home with Asthalin 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.

Asthalin 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  $\beta_2$  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.

In common with other  $\beta$ -adrenoceptor agonists, salbutamol 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 Effects). 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.

#### 4.5 Interaction with other medicines and other forms of interaction

Salbutamol and non-selective  $\beta$ -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).

#### 4.6 Fertility, pregnancy and lactation

There is no information on the effects of salbutamol on human fertility. There were no adverse effects on fertility in animals (see Preclinical safety data).

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.

#### 4.7 Effects on ability to drive and use machines

Amlodipine is presumed to be safe or unlikely to impair a patient's ability to drive or use machinery.

#### 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 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.

#### 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 Special Warnings and Special Precautions for Use and Undesirable Effects).

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.

Contact the National Poisons Centre on 0800 764 766 for advice on the management of an overdose.

## **5 PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

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

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 6hour) bronchodilation with a fast onset (within 5 minutes) in reversible airways obstruction.

### **5.2 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.

### **5.3 Preclinical 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 2.5mg/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.

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.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Sodium chloride, Sulfuric acid, Water for injection.

## 6.2 Incompatibilities

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

## 6.3 Shelf life

Shelf life is 24 months (2 years) from manufacture.

## 6.4 Special precautions for storage

Asthalin should be stored at a temperature below 25°C and protected from light.

## 6.5 Nature and contents of container

Asthalin 2.5mg/ 2.5 ml and 5.0 mg/2.5 ml are available in boxes containing 20 ampoules.

## 6.6 Special precautions for disposal

None known.

## 8 SPONSOR

Rex Medical Ltd  
67L Elizabeth Knox Place  
Panmure  
AUCKLAND.  
Ph (09) 574 6060  
Fax (09) 574 6070

## 9 DATE OF FIRST APPROVAL

21 December 2006

## 10 DATE OF REVISION OF THE TEXT

26 April 2017

## SUMMARY TABLE OF CHANGES

Section changed	Summary of new information