

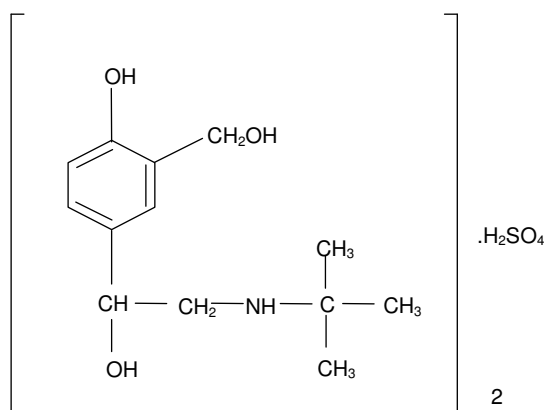
# Arrow – Salbutamol

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## Description

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Salbutamol (as salbutamol sulfate). The chemical name for salbutamol sulfate 1-(4-hydroxy-3-hydroxymethylphenyl)-2-(t-butylamino)-ethanol sulfate. Its structural formula is:



(C<sub>13</sub>H<sub>21</sub>NO<sub>3</sub>)<sub>2</sub>.H<sub>2</sub>SO<sub>4</sub> Molecular weight: 576.7

CAS No.: 51022-70-9

Salbutamol sulfate is a white or almost white odourless powder. It is soluble in 4 parts of water, slightly soluble in 95% alcohol, in chloroform and solvent ether. Approximately 1.2mg of salbutamol sulfate is equivalent to 1 mg of salbutamol.

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## Presentation

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The inhalation is presented in ampoules containing a sterile, clear aqueous isotonic, preservative-free nebuliser solution for single use. Each ampoule of Arrow - Salbutamol ampoules 2.5 mg/2.5 mL contains salbutamol sulfate equivalent to 2.5 mg of salbutamol. Each ampoule of Arrow - Salbutamol 5 mg/2.5 mL contains salbutamol sulfate equivalent to 5mg of salbutamol. Each ampoule also contains the inactive ingredients sodium chloride and sulfuric acid in 2.5 mL.

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## Clinical Particulars

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### Actions

Salbutamol is a short-acting, relatively selective beta<sub>2</sub>-adrenoceptor agonist. Administration by inhalation results in direct stimulation of beta<sub>2</sub>-adrenoceptors in bronchial smooth muscle and hence bronchodilation. This is thought to be due to stimulation of adenylyl cyclase by salbutamol, resulting in increased levels of cyclic AMP within cells. These are thought to inhibit the entry of calcium ions into the cells, thus inhibiting smooth muscle contraction. High levels of cyclic AMP in mast cells may also inhibit the release of histamine and slow reacting substance-A (SRS-A).

After administration of salbutamol, stimulation of both beta<sub>1</sub>- and beta<sub>2</sub>-adrenoceptors occurs because beta<sub>2</sub> selectivity is not absolute. This results in the beta<sub>1</sub> effect of cardiac stimulation, though not so much as with isoprenaline, and beta<sub>2</sub> effects of peripheral vasodilation and hypotension, skeletal muscle tremor and uterine muscle

relaxation. Stimulation of beta<sub>2</sub>-adrenoceptors can result in changes in serum levels of glucose, insulin and potassium.

### **Pharmacokinetics**

**Absorption:** Following inhalation of salbutamol the onset of action is 5-15 minutes. Only 10-20% of the dose reaches the lungs, the remainder stays in the mouth, stomach or on the apparatus. Salbutamol reaching the lungs acts rapidly and directly on bronchial smooth muscle. Initially, the drug is undetectable in blood but after 2-3 hours, low concentrations are seen, due presumably to the portion of the dose that is swallowed and absorbed by the gut.

**Distribution:** Salbutamol is not bound to plasma proteins.

**Metabolism:** The major metabolite of salbutamol, recovered from urine, has been identified as the 4'-o-sulfate ester. This metabolite has negligible beta stimulant activity. Salbutamol is not metabolised in the lung and the pattern of metabolism and excretion (as well as absorption) suggests that most aerosol is swallowed. The half life is between 2.7-5 hours.

**Excretion:** Following inhalation of salbutamol 77%-97% of the dose is recovered in the urine after 48 hours, 45-60% as the 4'-o-sulfate ester and the rest as unchanged salbutamol. A small fraction is excreted in the faeces.

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## **Indications**

Arrow - Salbutamol is indicated for the relief of bronchospasm in patients with asthma or chronic obstructive pulmonary disease, and for acute prophylaxis against exercise-induced asthma or in other situations known to induce bronchospasm.

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## **Dosage and Administration**

Increasing use of beta<sub>2</sub> 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.

Arrow - Salbutamol must be used under the direction of a doctor.

The solution may be delivered from any efficient nebulising device.

The solution must not be injected or ingested.

There is a large safety margin between therapeutic effects and unpleasant side effects. Nevertheless, because of the possibility of uncontrolled dosage associated with continuous administration, intermittent administration of appropriate amounts of Arrow - Salbutamol is preferred.

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.

Children 4 to 12 years: 2.5 mg

Adults: 5.0 mg

This dosage may be repeated as necessary every 4-6 hours. Any solution remaining in the nebuliser after completion of therapy should be discarded.

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

Use in the Elderly: Initial doses of salbutamol in the elderly should be lower than the recommended adult dosage. The dose may then be gradually increased if sufficient bronchodilatation is not achieved.

Impaired liver function: Approximately 60% of orally administered salbutamol (this includes approximately 90% of an inhaled dose) is metabolised to an inactive form. Consequently impairment of hepatic function may result in accumulation of unchanged salbutamol.

Impaired renal function: About 60 to 70% of salbutamol administered by inhalation is excreted in urine unchanged. The dose may therefore need to be reduced in patients with impaired renal function, in order to prevent exaggerated or prolonged effects.

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## **Contraindications**

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Hypersensitivity to any of the ingredients.

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## **Warnings and Precautions**

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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<sub>2</sub>- 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 should be warned that if either the usual relief is diminished or the usual duration of action reduced, they should seek medical advice at the earliest opportunity after increasing the dose.

Animal studies suggest that cardioneurotic effects may occur with high dosages of some sympathomimetic amines. On this evidence the possibility of the occurrence of myocardial lesions cannot be excluded subsequent to long term treatment with these drugs.

Care should be taken with patients who are known to have received large doses of salbutamol or other sympathomimetic drugs, or who are suffering from hypertension, hyperthyroidism, myocardial insufficiency, or diabetes mellitus.

Salbutamol should be administered cautiously to patients with thyrotoxicosis.

Excessive use may induce a non-responsive state leading to a worsening of hypoxaemia.

Potentially serious hypokalaemia may result from beta<sub>2</sub> 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 (see **Interactions**).

Hypokalaemia may increase the risk of serious cardiac arrhythmias, especially in digitalised patients. Serum potassium levels should be monitored in these situations.

As with other inhalation therapy, the potential for paradoxical bronchospasm should be kept in mind. If it occurs, the preparation should be discontinued immediately and alternative therapy instituted.

In common with other beta<sub>2</sub>-adrenoreceptor agonists, Arrow – Salbutamol can reduce 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.

### ***Use in Pregnancy (Category A)***

Salbutamol is known to cross the placental barrier in humans.

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.

Oral administration of salbutamol to rats and rabbits during pregnancy showed no teratogenic effects in offspring.

Although intravenous salbutamol and occasionally salbutamol tablets are used in the management of uncomplicated labour, salbutamol presentations should not be used for threatened abortion during the first or second trimesters of pregnancy. Intravenous salbutamol is contraindicated in cases of antepartum haemorrhage because of the risk of further haemorrhage from an atonic uterus and there is the risk of the same problem arising inadvertently in asthmatics using salbutamol. Profuse uterine bleeding following spontaneous abortion has been reported after the use of salbutamol. Special care is required in pregnant diabetic women.

### ***Use in Lactation***

It is not known whether salbutamol is excreted in breast milk nor whether it has a harmful effect on the newborn. Therefore it is not recommended for nursing mothers unless the expected benefits outweigh any potential risk.

### ***Pre-clinical safety data***

In common with other potent selective β<sub>2</sub> 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.

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## Adverse Effects

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The incidence and severity of salbutamol side effects depends on the dosage and route of administration.

**Musculoskeletal:** A fine tremor of skeletal muscle has been reported in some patients when salbutamol is administered by inhalation; the hands being the most obviously affected with a few patients feeling tense. These effects are dose related and are caused by a direct action on skeletal muscle and not by direct CNS stimulation.

There have been very rare reports of muscle cramps.

**Cardiovascular:** Patients with normal heart rate may experience an increase in heart rate after inhalation of salbutamol. These increases are dose dependent and are of the order of 9 beats/minute when 10 mg of salbutamol as 0.5% w/v solution is inhaled by adults over three minutes, 13 beats/minute when 20 mg of salbutamol as 0.1% w/v solution is inhaled by adults over three minutes. In patients with pre-existing sinus tachycardia, especially those in status asthmaticus, the heart rate tends to fall after the administration of nebulised salbutamol as the condition of the patient improves.

With higher doses than those recommended, or in patients who are unusually sensitive to beta-adrenergic stimulants, dilatation of some peripheral arterioles may occur leading to a small reduction in arterial pressure. A compensatory increase in cardiac output may then occur.

Cardiac arrhythmias (including atrial fibrillation, supraventricular tachycardia and extrasystoles) have been reported. Tachycardia or peripheral vasodilation with a compensatory small increase in heart rate may occur in some patients.

Other cardiovascular reactions which may occur are palpitations and sensations of warmth.

**Central Nervous System:** Headache. As with other beta<sub>2</sub>- agonists, hyperactivity has been reported rarely in children.

**Gastrointestinal:** Nausea. Mouth and throat irritation may occur with inhaled salbutamol.

**Immunological:** Hypersensitivity reactions including angioedema, urticaria, bronchospasm, hypotension and collapse have been reported very rarely.

**Metabolic:** Potentially serious hypokalaemia may result from beta<sub>2</sub>- agonist therapy (see **Warnings and Precautions**, and **Interactions**).

**Other:** As with other inhalation therapy, the potential for paradoxical bronchospasm should be kept in mind. If it occurs, the preparation should be discontinued immediately and alternative therapy initiated.

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## Interactions

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**Beta-Adrenergic blockers:** Beta-Adrenergic blocking drugs increase airway resistance in asthmatic patients and inhibit the bronchodilator action of salbutamol and other sympathomimetic bronchodilators.

**Sympathomimetics:** Salbutamol should not be administered by oral inhalation concurrently with other short acting, orally inhaled sympathomimetic agents. In addition, if other sympathomimetic agents are to be administered by any route in patients receiving orally inhaled salbutamol, the additional agents should be used with caution to avoid deleterious cardiovascular effects.

Care is recommended if it is proposed to administer salbutamol in concomitant therapy with other sympathomimetic amines and beta-adrenergic stimulants as excess sympathetic stimulation may occur. Salbutamol should not be given to patients who have already received large doses of sympathomimetics.

**Potassium depleting drugs:** Beta-Adrenergic agonists, such as salbutamol, can cause hypokalaemia. This can be increased by other potassium depleting drugs such as the corticosteroids, diuretics and theophylline (see **Warnings and Precautions**).

**Ipratropium:** 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.

**Imipramine, chlordiazepoxide, chlorpromazine:** Animal studies have shown that large doses of salbutamol may interact with imipramine, chlordiazepoxide and chlorpromazine but any practical significance of these results in humans remains to be established.

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## Overdosage

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**Symptoms:** Overdosage of inhaled salbutamol may produce significant tachycardia and/or significant muscle tremor.

**Treatment:** The specific antidote for overdosage with salbutamol is a cardio-selective beta-blocking agent given by intravenous injection. IN GENERAL, BETA-BLOCKING DRUGS SHOULD BE USED WITH CAUTION AS THEY MAY CAUSE BRONCHOSPASM IN SENSITIVE INDIVIDUALS.

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

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## Pharmaceutical Precautions

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Arrow - Salbutamol has a shelf-life of 2 years when stored below 25°C, protected from light. Once removed from the foil overwrap, ampoules have a shelf-life of three months when stored below 25°C.

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### **Medicines Classification**

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Prescription Medicine

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### **Package Quantities**

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The ampoules are supplied in packs of 30, arranged as three individually foil wrapped strips of ten ampoules.

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### **Further Information**

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### **Name and Address of Sponsor**

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Arrow Pharmaceuticals (NZ) Limited  
Mount Eden Central Business Park  
33a Normanby Road, Mt Eden  
Auckland, New Zealand

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### **Date of preparation**

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10 November 2006