PRODUCT INFORMATION
SALBUTAMOL INHALATION SOLUTION
(salbutamol sulfate)

NAME OF THE MEDICINE
Salbutamol sulfate is di[(RS)-2-(1,1-dimethyl)ethylamino-1-[4-hydroxy-3-(hydroxymethyl)phenyl]ethanol] sulfate. It is a white or almost white, crystalline, odourless powder with a slightly bitter taste. It is freely soluble in water, slightly soluble in alcohol and in ether, very slightly soluble in methylene chloride. Salbutamol sulfate 1.2 mg is approximately equivalent to 1 mg of salbutamol.

The structural formula is represented below.

![Structural formula of salbutamol sulfate]

Molecular Formula: \((C_{13}H_{21}NO_3)_2\cdot H_2SO_4\)
Molecular Weight: 576.7
CAS Number: 51022-70-9

DESCRIPTION
Salbutamol Inhalation Solution in bottles is a clear nebuliser solution containing salbutamol 0.5%w/v (5 mg/mL) as Salbutamol Sulfate and benzalkonium chloride as preservative and Water for Injections.

Salbutamol Inhalation Solution Sterinebs is a clear, isotonic, preservative-free nebuliser solution for single use. Sterinebs contain either salbutamol 2.5 mg or 5 mg as Salbutamol Sulfate and sodium chloride and Water for Injections to 2.5 mL.
PHARMACOLOGY

Class of Drug
Selective beta-2 adrenoceptor agonist.

Mode of Action
Salbutamol is a long acting, relatively selective beta-2-receptor stimulant. Administration by inhalation results in direct stimulation of beta-2-receptors in bronchial smooth muscle and hence bronchodilation. This is thought to be due to stimulation of adenyl 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-1 and beta-2 receptors occurs because beta-2 selectivity is not absolute. This results in the beta-1 effect of cardiac stimulation, though not so much as with isoprenaline, and beta-2 effects of peripheral vasodilation and hypotension, skeletal muscle tremor and uterine muscle relaxation. Stimulation of beta-2 receptors 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 which 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.
INDICATIONS

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.

CONTRAINDICATIONS

Hypersensitivity to any of the ingredients.

PRECAUTIONS

The management of asthma should normally follow a stepwise programme, and patient response should be monitored clinically and by lung function tests. Increasing uses 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 should be warned that if 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 cardionecrotic 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 thyrotoxocosis.

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 ketoacidosis has been reported. Concurrent administration of corticosteroids can exaggerate this effect.*

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

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 hypoxia. It is recommended that serum potassium levels are monitored in such situations.

The possibility of cardiac arrhythmias arising as a consequence of salbutamol induced hypokalaemia should be borne in mind, especially in digitalised patients, following the administration of salbutamol injection.
Addition of other active substances to Salbutamol Inhalation Solution cannot be recommended.

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 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.*

**Use in Pregnancy: Category A**

Salbutamol is known to cross the placental barrier in humans. Safety for use in pregnancy has not been demonstrated, therefore the drug should not be used in pregnant women, or those likely to become pregnant, unless the expected benefit outweighs any potential risk. Oral administration of salbutamol in 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 premature* 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.

**INTERACTIONS WITH OTHER MEDICINES**

Beta-adrenergic blocking drugs inhibit the bronchodilator action of salbutamol and other sympathomimetic bronchodilators. However, such drugs should not be used in asthmatic patients as they may increase airway resistance.

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1 Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed.
Other beta-adrenergic stimulants or sympathomimetic amines such as ephedrine should not be given concomitantly. Salbutamol should not be given to patients who have already received large doses of sympathomimetics.

Salbutamol has been shown to produce possible interactions in animals with the following drugs: imipramine, chlordiazepoxide, and chlorpromazine. The clinical significance of this is undetermined.

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.

ADVERSE EFFECTS

The following side effects have been reported for salbutamol regardless of route of administration.

More Common Reactions

Cardiovascular
Tachycardia, hypotension, superficial vasodilation, flushing, cardiac arrhythmias*, palpitations*.

Musculo-skeletal
Fine muscle tremor, most noticeable in hands. Leg cramps.

Nervous System
Headache, dizziness, feelings of tension or nervousness and other emotional upsets.

Less Common Reactions

Biochemical Abnormalities
Increases in plasma concentrations of glucose, insulin, non esterified fatty acids; decrease in plasma concentrations of potassium.

Gastrointestinal
Nausea, vomiting.

Respiratory
Reduction of pa oxygen has been observed in a small number of patients following administration of bronchodilators, including salbutamol.
Serious or Life Threatening Reactions

Overuse of salbutamol preparations may produce significant tachycardia, arrhythmia and hypotension.

DOSAGE AND ADMINISTRATION

Increasing use of beta-2 agonists may be a sign of worsening asthma. Under these conditions a reassessment of the patient’s therapy may be required and concomitant corticosteroid therapy should be considered.

Salbutamol may be delivered from any efficient nebulising device.

Salbutamol may be used to achieve bronchodilation as part of an inhalation therapy regime or for patients requiring assisted ventilation.

There is a significant safety margin between therapeutic effects and unpleasant side effects. Nevertheless, because of the possibility of uncontrolled dosage associated with continuous administration of Salbutamol Inhalation Solution, intermittent administration is preferred.

Salbutamol should be used under the direction of a physician. The solution must not be injected or ingested.

Intermittent Administration

For patients requiring salbutamol as part of an inhalational therapy regime.

Salbutamol Inhalation Solution in Sterinebs

Children (4–12 years): 2.5 mg. This dose may be repeated as necessary every 4-6 hours.

Adults: 5 mg. This dose may be repeated as necessary every 4-6 hours.

Salbutamol Inhalation Solution in Bottles

Children: 0.02 mL/kg/dose as required up to 4 hourly. Maximum single dose is 5 mg (1 mL).

Adults: 1 mL (5 mg). This dose may be repeated as necessary every 4-6 hours.

Salbutamol Inhalation Solution in bottles may be administered as the undiluted solution as supplied or diluted according to individual requirements. Dilution of the specified dose is often necessary to allow efficient operation of the nebulising device. Where dilution is preferred, dilutions in the order of 1 mL of Salbutamol Inhalation Solution in 1 mL to 10 mL of normal saline are suitable.

The time taken to deliver a given volume of solution will depend upon the equipment used but most nebulisers deliver 1 mL of solution over 3 minutes and 2 mL over 8-10 minutes.
**Continuous Administration**

For patients requiring assisted ventilation. This is not the preferred method of administration because of the possibility of uncontrolled dosage as stated above.

Continuous administration requires a diluted solution of Salbutamol Inhalation Solution. The recommended dilution is 1 mL of Salbutamol Inhalation Solution (bottles) made up to 100 mL with normal saline, giving a concentration of 50 micrograms/mL salbutamol. The diluted solution is administered through a nebuliser coupled to an intermittent positive pressure ventilator usually employing oxygen enriched air or a continuous source of air depending on the patients condition. Inhalation of the diluted solution may be continued according to the direction of the attending physician until adequate bronchodilation is achieved.

Some bronchodilation occurs almost immediately, but maximum effect may not occur until 15 minutes after commencing therapy.

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

**Geriatric**

Initial doses of salbutamol in the elderly should be lower than the recommended adult dose. The dose may be gradually increased if sufficient bronchodilation is not achieved.

**In Impaired Liver Function**

As about 60% of orally administered salbutamol (this includes not only tablet and syrup presentations but also approximately 90% of an inhaled dose) is metabolised to an inactive form, impairment of liver function may result in accumulation of unchanged salbutamol.

**In Impaired Renal Function**

About 60-70% of salbutamol administered by inhalation is excreted in urine unchanged. Impairment of renal function may therefore require a reduction in dosage to prevent exaggerated or prolonged effects.

**IMPORTANT**

Fresh dilutions should be prepared for each inhalation and any solution remaining in the nebuliser after treatment should be discarded immediately.

Any Salbutamol Inhalation Solution remaining in the bottle once it has been opened should be discarded 3 months after opening.

**Nebulisers**

To avoid contamination, nebulising devices should be thoroughly cleaned after use according to manufacturer’s instructions.
OVERDOSAGE

The signs of overdosage are significant tachycardia and/or significant muscle tremor. The specific antidote for overdosage is a cardioselective 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.

PRESENTATION AND STORAGE CONDITIONS

*Salbutamol Inhalation Solution in Sterinebs* is an aqueous solution containing salbutamol 2.5 mg or 5 mg in 2.5 mL as Salbutamol Sulfate. The solutions are sterile, isotonic and preservative free.

*Salbutamol Inhalation Solution in bottles* is an aqueous solution containing salbutamol 5 mg/mL (0.5%w/v) as Salbutamol Sulfate and Benzalkonium Chloride as a preservative. It is available as 10 mL and 30 mL screw cap bottles.

AUST R 11354  Salbutamol Inhalation Solution 2.5 mg in Sterinebs® 2.5 mL (sterile) (30)

AUST R 11355  Salbutamol Inhalation Solution 5 mg in Sterinebs® 2.5 mL (sterile) (30)

AUST R 10799  Salbutamol Inhalation Solution 0.5% w/v 5 mg/mL (10 mL or 30 mL)

*Salbutamol Inhalation Solution in Sterinebs*: Store below 25°C. Protect from light. Protect from freezing. Use once only. Discard any remaining portion.

*Salbutamol Inhalation Solution in bottles*: Store upright below 25°C. Protect from light. Protect from freezing. Discard any remaining solution 3 months from opening.

The expiry date (month/year) is stated on the package after EXP.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine (S4)
DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS

AUST R 10799: 09 July 1991
AUST R 11354: 13 August 1991
AUST R 11355: 13 August 1991

DATE OF MOST RECENT AMENDMENT

22 March 2012

* Please note changes in Product Information

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Sterinebs® are plastic ampoules produced by Pfizer