MONOGRAPH FOR HEALTH PROFESSIONALS

SALBUTAMOL ELIXIR 2 mg/5 mL

Salbutamol Sulphate B.P. 2.4 mg Equivalent to 2 mg Salbutamol Base

PRESCRIPTION ONLY MEDICATION

Bronchodilator
(beta$_2$-adrenergic stimulant)

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SALBUTAMOL ELIXIR 2 mg/5 mL

HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Oral liquid/ 2 mg per 5 mL	Methyl Hydroxybenzoate, Sodium Citrate, Citric acid, Sugar, Sorbitol Solution 70 %, Ethyl Alcohol, Amaranth Red, Talc Purified, Strawberry Flavour, Propyl Hydroxybenzoate and Purified water.

For a complete listing see Dosage Forms, Composition and Packaging section.

INDICATIONS AND CLINICAL USE

Salbutamol Elixir 2 mg/5 mL oral liquid is indicated for:

- The prevention or relief of bronchospasm due to bronchial asthma, chronic bronchitis and other chronic bronchopulmonary disorders in which bronchospasm is a complicating factor.

Pediatrics (< 2 years of age):
Salbutamol Elixir 2 mg/5 mL is not recommended in children under 2 years of age, until the dosage regimen and evidence concerning its safety have been established.

CONTRAINDICATIONS

- Patients with hypersensitivity to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the STORAGE/CONTENTS/ EXCIPIENTS STATEMENT section of the product monograph.
- In patients with tachyarrhythmias.

WARNINGS AND PRECAUTIONS

General
Patients should be advised to always carry their salbutamol aerosol or dry powder inhaler to use immediately if an episode of asthma is experienced. If therapy does not produce a significant improvement or if the patient's condition worsens, medical advice must be sought to determine a new plan of treatment. In the case of acute or rapidly worsening dyspnea, a doctor should be consulted immediately.

Use of Anti-Inflammatory Agents
In accordance with the present practice for asthma treatment, concomitant anti-inflammatory therapy should be part of the regimen if salbutamol needs to be used on a regular daily basis (see DOSAGE AND METHOD OF USE). It is essential that the physician instruct the patient in the need for further evaluation if the patient's asthma becomes worse.

Cardiovascular
In individual patients, any $beta_2$-adrenergic agonist, including salbutamol, may have a clinically significant cardiac effect. Care should be taken with patients suffering from cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias and hypertension. Special care and supervision are required in patients with idiopathic hypertrophic subvalvular aortic stenosis, in whom an increase in the pressure gradient between the left ventricle and the aorta may occur, causing increased strain on the left ventricle.

Fatalities have been reported following excessive use of inhaled sympathomimetic drugs in patients with asthma. The exact cause of death is unknown, but cardiac arrest following an unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected.

Endocrine and Metabolism

Metabolic Effects
In common with other beta-adrenergic agents, salbutamol can induce reversible metabolic changes such as potentially serious hypokalemia, particularly following nebulised or especially infused administration. Particular caution is advised in acute severe asthma since hypokalemia may be potentiated by concomitant treatment with xanthine derivatives, steroids and diuretics and by hypoxia. Hypokalemia will increase the susceptibility of digitalis treated patients to cardiac arrhythmias. It is recommended that serum potassium levels be monitored in such situations.

Care should be taken with patients with diabetes mellitus. Salbutamol can induce reversible hyperglycemia during oral or nebulised administration, or especially during infusions of the drug. 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.

Care should be taken with patients with hyperthyroidism.

Hypersensitivity
Immediate hypersensitivity reactions may occur after administration of salbutamol or salbutamol sulphate, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, hypotension, anaphylaxis, and oropharyngeal edema.

Care should be taken in patients who are unusually responsive to sympathomimetic amines.

Neurologic
Care should be taken with patients suffering from convulsive disorders.

USE IN SPECIAL POPULATIONS

Pregnant Women: Salbutamol has been in widespread use for many years in humans without apparent ill consequence. However, there are no adequate and well controlled studies in pregnant women and there is little published evidence of its safety in the early stages of human pregnancy. Administration of drugs during pregnancy should only be considered if the anticipated benefit to the expectant woman is greater than any possible risks to the fetus.

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 congential anomalies is 2 – 3 %, a relationship with salbutamol use cannot be established.

Labour and Delivery: Oral salbutamol has been shown to delay preterm labour in some reports but there are no well controlled studies which demonstrate that it will stop preterm labour or prevent labour at term. Therefore, cautious use of Salbutamol Elixir is required in pregnant patients when it is given for the relief of bronchospasm so as to avoid interference with uterine contractility.

Lactating Mothers: Since salbutamol is probably excreted in breast milk and because of its observed tumorigenicity in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the benefit of the drug to the mother. It is not known whether salbutamol in breast milk has a harmful effect on the neonate.

Pediatrics: Rarely, erythema multiforme and Stevens-Johnson syndrome have been associated with the administration of salbutamol sulphate in children.

Monitoring and Laboratory Tests
In accordance with the present practice for asthma treatment, patient response should be monitored clinically and by lung function tests.

Monitoring and Control of Asthma
Failure to respond to a previously effective dose of salbutamol indicates a deterioration of the condition and the physician should be contacted promptly. Patients should be warned not to exceed the recommended dose.

In worsening asthma it is inadequate to increase beta$_2$-agonist use only, especially over an extended period of time. Instead, a reassessment of the patient's therapy plan is required and concomitant anti inflammatory therapy should be considered. Sudden or progressive deterioration in asthma control is potentially life threatening; the treatment plan must be re-evaluated, and consideration be given to corticosteroid therapy. (see DOSAGE AND METHOD OF USE).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most frequent adverse reactions associated with Salbutamol Elixir are nervousness, and tremor. In some patients, Salbutamol Elixir may cause a fine tremor of skeletal muscle, particularly in the hands. This effect is common to all beta$_2$-adrenergic stimulants. Adaptation occurs during the first few days of dosing and the tremor usually disappears as treatment continues. A few patients experience a feeling of tension; this is also due to the effects on the skeletal muscle and not to direct CNS stimulation. Headache, tachycardia and palpitations, muscle cramps, insomnia, nausea, weakness and dizziness have also been reported.

Peripheral vasodilatation and a compensatory small increase in heart rate may occur in some patients. Cardiac arrhythmias (including atrial fibrillation, supraventricular tachycardia and extrasystoles) have been reported, usually in susceptible patients.

Rarely, potentially serious hypokalaemia may result from beta$_2$-agonist therapy, mainly from parenteral and nebulized administration. Other rarely reported adverse effects include drowsiness, flushing, restlessness, irritability, chest discomfort, difficulty in micturition, hypertension, angina, vomiting, vertigo, central nervous system stimulation, hyperactivity in children, unusual taste, and drying or irritation of the oropharynx.

Immediate hypersensitivity reactions including angioedema, urticaria, bronchospasm, hypotension, rash, oropharyngeal oedema, anaphylaxis and collapse have been reported very rarely.

DRUG INTERACTIONS

Drug-Drug Interactions

Table 1: Established or Potential Drug-Drug Interactions

salbutamol sulphate	Ref	Effect	Clinical comment
Monoamine oxidase inhibitors or tricyclic antideprssants.	CS	May potentiate action of salbutamol on cardiovascular system.	Salbutamol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants.
Other sympathomimetic bronchodilators or epinephrine.	CS	May lead to deleterious cardiovascular effects.	Other sympathomimetic bronchodilators or epinephrine should not be used concomitantly with salbutamol. If additional adrenergic drugs are to be administered by any route to the patient using salbutamol, the adrenergic drugs should be used with caution to avoid deleterious cardiovascular effects. Such concomitant use must be individualised and not given on a routine basis. If regular co-administration is required then alternative therapy must be considered.
Beta-blockers	CS	May effectively antagonise the action of salbutamol.	Beta-adrenergic blocking drugs, especially the non-cardioselective ones, such as propranolol, should not usually be prescribed together.
Diuretics	CS	May lead to ECG changes and/or hypokalemia, although the clinical significance of these effects is not known.	The ECG changes and/or hypokalemia that may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Caution is advised in the co-administration of beta-agonists with non potassium sparing diuretics.
Digoxin	CS	May lead to decrease in serum digoxin levels. The clinical significance of these findings for patients with obstructive airways disease who are receiving salbutamol and digoxin on a chronic basis is unclear.	Mean decreases of 16-22% in serum digoxin levels were demonstrated after single doses intravenous and oral administration of salbutamol, respectively, to normal volunteers who had received digoxin for 10 days. It would be prudent to carefully evaluate serum digoxin levels in patients who are currently receiving digoxin and salbutamol.

Legend: C = Case Study; CS = Class Statement; CT = Clinical Trial; T = Theoretical

DOSAGE AND METHOD OF USE

Dosing Considerations

Dosages should be individualised, and the patient's response should be monitored by the prescribing physician on an ongoing basis. If a previously effective dosage regimen fails to provide the usual relief, medical advice should be sought immediately; this is a sign of seriously worsening asthma that could require reassessment of therapy.

In accordance with current Canadian asthma guidelines, if salbutamol is required for relief of symptoms more than three times a week (not including its use to prevent exercise-induced bronchospasm); anti-inflammatory therapy (e.g., corticosteroid) should be part of the regimen.

Salbutamol Elixir is not intended for patients experiencing an acute episode of bronchospasm. Patients should always carry their salbutamol aerosol or dry powder inhaler to use immediately if an episode of asthma is experienced.

When Salbutamol Elixir is prescribed, the patient should be advised that the action of this medication may last for 6 to 8 hours. As there may be adverse effects associated with excessive dosing, the dosage or frequency of administration should only be increased upon medical advice.

Salbutamol Elixir is not to be used in children under two years of age.

Recommended Dose and Dosage Adjustment

Adults and children over 12 years of age: 5 to 10 mL (2 to 4 mg) 3 to 4 times daily.

Children (6 to 12 years of age): 5 mL (2 mg) 3 to 4 times daily.

Children (2 to 6 years of age): 0.25 mL (0.1 mg) per kg body weight 3 to 4 times daily.

The safety and efficacy of Salbutamol Elixir in children under 2 years of age, and for chronic therapy in children 2-6 years of age have not been established.

In elderly patients or in those known to be unusually sensitive to beta-adrenergic stimulant drugs, it is advisable to initiate treatment with 5 mL (2 mg) three or four times per day.

Missed Dose

If a dose of this medication is missed, it should be taken as soon as possible. However, if it is almost time for the next dose, skip the missed dose and go back to the regular dosing schedule.

Method of Use
Salbutamol Elixir is administered by the oral route only.
Dilution of Salbutamol Elixir with syrup BP or sorbitol solution is not recommended as this may result in precipitation of the cellulose thickening agent.

Salbutamol Elixir may be diluted with Purified Water BP 50% v/v. The resulting mixture should be protected from light and used within 28 days.

A 50% v/v dilution of Salbutamol Elixir has been shown to be adequately preserved against microbial contamination. However, to avoid the possibility of introducing excessive microbial contamination, the Purified Water used for dilution should be recently prepared or alternatively it should be boiled and cooled immediately before use.

Admixture of salbutamol elixir with other liquid preparation is not recommended.

OVERDOSAGE

Symptoms and Signs
The most common signs and symptoms of overdose with salbutamol are transient beta agonist pharmacologically mediated events. Overdosage may cause, peripheral vasodilation and increased irritability of skeletal muscle, hypokalemia, tachycardia, arrhythmia, hypertension and in extreme cases, sudden death. Serum potassium levels should be monitored.

Nausea, vomiting and hyperglycemia have been reported, predominantly in children and when salbutamol overdose has been taken via the oral route.

Treatment
Consideration should be given to discontinuation of treatment and appropriate symptomatic therapy. In case of overdosage, gastric lavage should be performed. In order to antagonise the effect of salbutamol, the use of a beta-adrenergic blocking agent preferably one of the relatively cardioselective ones (e.g. metoprolol, atenolol) may be considered, bearing in mind the danger of inducing an asthmatic attack.

PHARMACOLOGICAL INFORMATION

Mechanism of Action
Salbutamol produces bronchodilation through stimulation of $beta_2$-adrenergic receptors in bronchial smooth muscle, thereby causing relaxation of bronchial muscle fibres. This action is manifested by an improvement in pulmonary function as demonstrated by spirometric measurements.

A measurable decrease in airway resistance is typically observed 30 minutes after an oral dose of salbutamol sulphate. The maximum improvement in pulmonary function usually occurs after 2 to 3 hours, and significant bronchodilator activity has been observed to persist for 6 hours or longer.

STORAGE

Do not store above 30°C. Keep out of reach of children.

Protect from light.

CONTENTS

Salbutamol Elixir is a red, viscous liquid with an odour and flavour of strawberry, containing 2 mg salbutamol per 5 mL. Salbutamol Elixir is available in bottles of 120 mL.

EXCIPIENTS STATEMENT

Salbutamol Elixir contains salbutamol sulphate and the following excipients: Methyl Hydroxybenzoate, Sodium Citrate, Citric acid, Sugar, Sorbitol Solution 70 %, Ethyl Alcohol, Amaranth Red, Talc Purified, Strawberry Flavour, Propyl Hydroxybenzoate and Purified water.

PHARMACEUTICAL DRUG INFORMATION

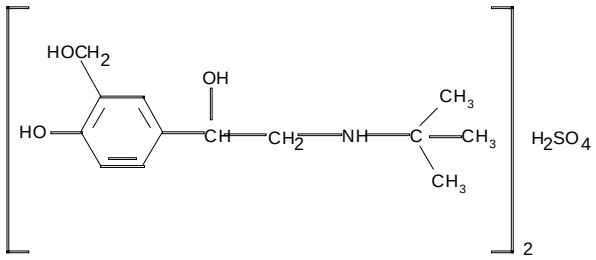
Drug Substance

Proper name: salbutamol sulphate

Chemical name: α^1-[(*tert*-butylamino)methyl]-4-hydroxy-*m*-xylene-α, α'-diol sulphate (2:1) (salt)

Molecular formula and molecular mass: $[C_{13}H_{21}NO_3]_2H_2SO_4$, 576.71

Structural Formula:



Physicochemical properties:

Description: White or almost white powder. It is odourless or almost odourless.

Solubility: Salbutamol sulphate is soluble in 4 parts of water; slightly soluble in ethanol (96%), in chloroform and in ether.

pH value: A 5% solution of salbutamol sulphate in distilled water has a pH value of 4.3

pKa values: Salbutamol has pKa values of 9.3 and 10.3.

Distribution Coefficient: The distribution coefficient of salbutamol between 2 phases of octanol and water, as determined by HPLC, is log D= -0.5 at pH 7.42 at room temperature.

Melting Point: Salbutamol melts at approximately 155^{o}C, with decomposition.

CLINICAL INFORMATION

Salbutamol has been used successfully in the management of severe acute asthma, constituting the standard emergency treatment for symptom relief and for the treatment of childhood asthma. Since children show a faster and more complete response to bronchodilators than adults, salbutamol constitutes the first-line treatment for all asthmatic children. Children, in fact, receive much higher doses of IV salbutamol per kg of weight than adults. In addition, those responses are complemented by a significantly low incidence of side effects when compared to adults, demonstrating a high level of tolerance.

There are several comparison effectiveness and safety studies of salbutamol and other bronchodilators as well as other asthma-class drugs. Salbutamol is more effective than isoprenaline, a non-selective β-adrenoreceptor agonist, and isoetarine, a selective β-adrenoreceptor agonist. Otherwise, it is quite similar to bitolterol, broxaterol, clenbuterol, fenoterol, metaproterenol, procaterol, terbutaline, and tulobuterol (all bronchodilators) from a clinical point of view. A clinical trial examined the bronchodilator response in adults with stable asthma following salbutamol and formoterol administration. The group of patients who took salbutamol showed a higher clinical response (forced expiratory volume, FEV). The efficacy and safety of levalbuterol (SABA with the more active R-enantiomer of salbutamol racemic mixture) compared to salbutamol have also been discussed. Jat et al. consider that levalbuterol is not clinically superior and should not be used over salbutamol for the treatment of acute asthma. According to a randomized placebo-controlled trial, no significant differences between levalbuterol and salbutamol in terms of FEV were documented. Regarding the comparison between IV salbutamol and IV aminophylline, it was observed that, in the doses and in the routes of administration targeted in the study, salbutamol was equally effective compared to aminophylline.

When comparing salbutamol and salmeterol, salmeterol has a prolonged bronchodilator effect in healthy adult volunteers. A similar statement was made for asthmatic patients: a comparative study of the dry powder formulations of salmeterol and salbutamol revealed that salmeterol is more successful in managing asthma. Likewise, a prolonged protective effect of salmeterol is observed. In patients with exercise-induced asthma, inhaled salmeterol exhibited a long-lasting effect, related to the compound's lipophilic property, which is responsible for the slow clearance of the molecules from the system. None of these drugs were associated with a worsening of the disease. However, a subsensitivity to salbutamol's bronchodilator effects induced by regular treatment with salmeterol in patients with asthma was reported.

The interaction of salbutamol with other drugs has also been explored. It is usually combined with ICSs, such as budesonide, fluticasone, and mometasone. In a randomized double-blind two-period single-dose crossover study, the authors sought to assess the efficacy and safety of salbutamol–budesonide compared with placebo in patients with asthma and EIB. Adolescents and adults who took this drug combination approximately 30 min before exercise displayed a more effective symptom relief than placebo. Additionally, Papi et al. supervised a clinical trial that compared the efficacy and safety of these two drugs. It was demonstrated that salbutamol alone increases the risk of severe asthma exacerbation, suggesting that combining salbutamol with budesonide is a better treatment strategy.

Indeed, the beneficial effects of this combination were proven in more than one study: another clinical trial confirmed that such a combination improves lung functions as well as anti-inflammatory and anti-allergic effects in patients with acute bronchial asthma. Siddiqui et al. have also studied the use of this SABA in conjunction with magnesium sulfate (MgSO4) in the management of acute asthma in Indian children. The authors concluded that the addition of nebulized MgSO4 to salbutamol did not enhance lung function. The findings of the clinical trial conducted by Sarhan et al., on the other hand, were rather different. They concluded that nebulized MgSO4 with salbutamol has a considerable bronchodilator effect, suggesting this form of treatment may be the best choice for the management of acute asthma exacerbations.

Increasing doses of salbutamol to salmeterol was the focus of the study published by Smyth et al. The data suggest that this interaction does not alter the beneficial or adverse effects of salbutamol in patients taking salmeterol. A double-blind placebo-controlled study was conducted with the purpose of uncovering the differences in the bronchodilator effects of salbutamol with or without sulfate in asthmatic patients. No clinically significant difference was found. Additionally, a therapy based on a combination of salbutamol and beclomethasone dipropionate improves asthma control more than increasing the dose of salbutamol. To examine the bronchodilator effects of three sets of treatments—salbutamol combined with oxitropium bromide, a low salbutamol dose, and a high salbutamol dose—Laitinen et al. conducted a controlled trial on adult asthmatic patients. Both the combination and high salbutamol dosage therapies showed more effectiveness than the low salbutamol dose treatment. Salbutamol administered with ipatropium bromide was the subject of a prospective randomized double-blind study in children aged 2–18 years with severe to moderate asthma. The goal was to determine if this drug combination impacted oxygenation, lung function, and the number of hospitalizations. In fact, there was a significant decrease in hospitalizations and an improvement in lung function in all children, particularly pronounced in children with severe asthma attacks. The therapeutic approach of combining nebulized salbutamol with salbutamol–ipatropium bromide has also been proven to be beneficial for treating acute asthma attacks in patients with moderate asthma. Another therapeutic approach in asthmatic children is to associate salbutamol and theophylline. A double-blind randomized controlled trial demonstrated that these drugs interact negatively, resulting in the occurrence of tachycardia. In addition to the aforementioned drug interactions, salbutamol has many other interactions; for example, with β-blockers (antagonists), corticosteroids, and diuretics.

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