京卫制药
JEWIM PHARMA

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Salbutamol Pressurised Inhalation

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The product is a pressurised inhalation suspension, each actuation delivers 100 mcg of salbutamol.

3. PHARMACEUTICAL FORM

Inhalation aerosol

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

It is indicated for the relief of bronchospasm in patients with asthma or chronic obstructive pulmonary disease (reversible obstructive airway disease), and for acute prophylaxis against exercise-induced asthma or other stimuli known to induce bronchospasm.

4.2 Posology and method of administration

The product is for oral inhalation use only. It may be used with a spacer device by patients who find it difficult to synchronise aerosol actuation with inspiration of breath.

Adults:

For the relief of acute asthma symptoms including bronchospasm: one inhalation (100 micrograms) may be administered as a single minimum starting dose. This may be increased to two inhalations if necessary.

To prevent allergen- or exercise-induced symptoms: it should be taken 10-15 minutes before challenge. For chronic therapy, two inhalations up to four times a day.

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.

Paediatric population:

For the relief of acute asthma symptoms including bronchospasm or before challenge or exertion: one inhalation (100 micrograms) may be administered as recommended dose, the dose may be increased to two inhalations if required.

For chronic therapy, two inhalations up to four times a day.

The spacer device may be used to facilitate administration to children under 5 years of

age.

Impaired hepatic function:

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

Impaired renal function:

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

On-demand use of the product should not exceed 8 inhalations in any 24 hours. Reliance on such frequent supplementary use, or a sudden increase in dose, indicates poorly controlled or deteriorating asthma, overdose of the drug can cause adverse reactions. Therefore, the dosage or frequency of administration should only be increased on medical advice (see warnings and precautions).

4.3 Contraindications

It is contra-indicated in patients with a history of hypersensitivity to any of the components.

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. Bronchodilators should not be the only or main treatment in patients with severe or unstable asthma. 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. Increasing use of bronchodilators, in particular short-acting inhaled β2-agonists, to relieve symptoms, indicates deterioration of asthma control. The patient should be instructed to seek medical advice if short-acting relief bronchodilator treatment becomes less effective, or more inhalations than usual are required. In this situation the patient should be assessed and consideration given to the need for increased anti-inflammatory therapy (e.g. higher doses of inhaled corticosteroid or a course of oral corticosteroid). Severe exacerbations of asthma must be treated in the normal way. In patients considered at risk, daily peak flow monitoring may be instituted.

Animal studies suggest that cardiac effects may occur with high dosages of some sypathomimetic 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.

The product contains hydrofluoroalkane (norflurane) propellant. In animal studies, norflurane has been shown to have no significant pharmacological effects, except at very high exposure concentrations when narcosis and a relatively weak sensitisation to the arrhythmogenic effects of catecholamines were found. The potency of the cardiac sensitisation is less than that of trichlorofluoromethane (CFC-11).

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 β2-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 should be monitored in such situations.

The possibility of cardiac arryhthmias arising as a consequence of salbutamol induced hypokalaemia should be borne in mind, especially in digitalised patients, following the administration of salbutamol injection.

Patients inhaler technique should be checked to make sure that aerosol actuation is synchronised with inspiration of breath for optimum delivery of drug to the lungs. Patients should be warned that they may experience a different taste upon inhalation compared to their previous inhaler.

The dosage or frequency of administration should only be increased on medical advice. If a previously effective dose of inhaled salbutamol fails to give relief lasting at least three hours, the patient should be advised to seek medical advice.

Caution use for athlete.

Please keep out of the reach of children.

4.5 Interaction with other medicinal products and other forms of interaction

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

Care is recommended if it is proposed to administer salbutamol in concomitant therapy with other sympathomimetic amines as excess sympathetic stimulation may occur.

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

4.6 **Fertility, pregnancy and lactation**

Administration of the drug to pregnancy women should only be considered if the expected benefits to the expectant woman are greater than any possible risks to the foetus. Like most other drugs, there is only little published evidence of its safety in the early stages of human pregnancy.

Animal studies have shown that it will cause some dangers to foetus when the dose is very high. Large scale animal reproductive toxicity studies show that the norflurane propellant, HFA-134a, has no damage to the fetal development.

No teratogenic effect was found in the teratogenic study at the comparable high doses which can appear teratogenic effect for beta-2 agonist, however, safety during pregnancy and lactatio n has not been established.

As salbutamol is probably secreted in breast milk, so its use should be restricted to situations where it is felt that the expected benefit to the mother is likely to outweigh any potential risk to the neonate. It is not known whether salbutamol has a harmful effect on the neonate, and its use in nursing mothers requires careful consideration.

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 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.

4.7 Effects on ability to drive and use machines

No report.

4.8 Undesirable effects

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥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, very rare and unknown 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.

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).

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. Tachycardia may occur in some patients.

Rare	Peripheral vascular dilatation

Respiratory, thoracic and mediastinal disorders

Very rare	Paradoxical bronchospasm.

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

Gastrointestinal disorders

Uncommon	Mouth and throat irritation

Musculoskeletal and connective tissue disorders

Uncommon	Muscle cramps

A fine tremor of skeletal muscle has been reported in some patients when salbutamol is administered orally or 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 CNC stimulation.

Note: The incidence and severity of particular side effects depends on the dosage and route of administration. Salbutamol does not cause difficulty in micturition because, unlike sympathomimetic drugs such as ephedrine, therapeutic doses have no alpha-adrenergic receptor stimulant activity.

4.9 Overdose

The most common signs and symptoms of overdose with salbutamol are transient beta agonist pharmacologically mediated events (see Warnings and precautions for Use and Adverse reaction).

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

Consideration should be given to discontinuation of treatment and appropriate symptomatic treatment such as a cardio-selective beta-blocking agent, in patients

presenting with cardiac symptoms (e.g. tachycardia, palpitations). Beta-blocking drugs should be used with caution in patients with a history of bronchospasm.

The signs of salbutamol overdosage are significant tachycardia and/or significant muscle tremor.

It should be noted that the salbutamol from the forty 100 microgram puffs of the inhaler contain as much salbutamol as one 4 milligram salbutamol tablet.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Salbutamol is a selective beta-2 adrenoreceptor agonist, which can selectively stimulate beta-2 adrenoceptors of bronchial muscle and hence bronchodilation. This is thought to be due to stimulation of adenyl cyclase, resulting in increased levels of cyclic AMP within cells, thereby relaxing smooth muscle, and inhibition of mast cells and other sensitized cells to release allergic reaction medium, thereby relieving bronchospasm. The product is used for bronchial asthma.

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.

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. Most 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%.

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 2.5 mg/kg. 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. Reproductive studies in the rabbit at doses of 50mg/kg/day orally (i.e. much higher than the normal human dose) have shown fetuses with treatment related changes; these included open eyelids (ablepharia), secondary palate clefts (palatoschisis), changes in ossification of

the frontal bones of the cranium (cranioschisis) and limb flexure. Reformulation of the product has not altered the known toxicological profile of salbutamol.

The non-CFC propellant, HFA 134a, has been shown to have no toxic effect 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

Ethanol

Oleic acid

Norflurane

6.2 Incompatibilities

None reported.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30°C. Protect from frost and direct sunlight.

6.5 Nature and contents of container

An inhaler comprising an aluminium canister sealed with a metering valve, actuator and dust cap. Salbutamol Pressurised Inhalation delivers 100 micrograms of salbutamol per inhalation, 200 doses.

6.6 Special precautions for disposal

The aerosol spray is inhaled through the mouth into the lungs. After shaking the inhaler, the patient should exhale, the mouthpiece should be placed in the mouth and the lips closed around it. The actuator is depressed to release a spray, which must coincide with inspiration of breath.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

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