Ventolin™ Oral Liquid
Salbutamol sulphate

QUALITATIVE AND QUANTITATIVE COMPOSITION

Ventolin oral liquid: Salbutamol BP 2 mg as sulphate in each 5 ml of a fruit-flavoured, sugar free oral liquid. Contains sodium benzoate.

PHARMACEUTICAL FORM

Oral Liquid.

CLINICAL PARTICULARS

Indications

Salbutamol is a selective beta-$_2$ adrenoceptor agonist indicated for the treatment or prevention of bronchospasm. It provides short acting bronchodilation in reversible airways obstruction due to asthma, chronic bronchitis and emphysema.

Bronchodilators should not be the only or main treatment in patients with persistent asthma. In patients with persistent asthma unresponsive to *VENTOLIN*, treatment with inhaled corticosteroids is recommended to achieve and maintain control. Failing to respond to treatment with *VENTOLIN* may signal a need for urgent medical advice or treatment.

VENTOLIN oral liquid is indicated for the relief of bronchospasm in bronchial asthma of all types, chronic bronchitis and emphysema.

VENTOLIN oral liquid is suitable oral therapy for children or for those adults who prefer liquid medicines.

Dosage and Administration

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

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.

As there may be adverse effects associated with excessive dosing, the dosage or frequency of administration should only be increased on medical advice.

***Adults*:**
The usual effective dose is 4 mg of salbutamol (10 ml of oral liquid) 3 or 4 times per day. If adequate bronchodilation is not obtained each single dose may be gradually increased to as much as 8 mg of salbutamol (20 ml of oral liquid).
However, it has been established that some patients obtain adequate relief with 2 mg of salbutamol 3 or 4 times daily.

***Children*:**
The following doses should be administered 3 or 4 times daily:
2-6 years: 1-2 mg salbutamol as 2.5-5 ml of oral liquid.
6-12 years: 2 mg salbutamol as 5 ml of oral liquid.
Over 12 years: 2-4 mg salbutamol as 5-10ml of oral liquid.
The drug is well tolerated by children so that, if necessary, these doses can be cautiously increased.

Special patient groups:
In elderly patients or in those known to be unusually sensitive to beta-adrenergic stimulant drugs, it is advisable to initiate treatment with 2 mg salbutamol 3 or 4 times per day.

Contraindications

VENTOLIN oral liquid is contra-indicated in patients with a history of hypersensitivity to any of its components.

Non-i.v. formulations of *VENTOLIN* must not be used to arrest uncomplicated premature labour or threatened abortion.

Warnings and Precautions

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 should be warned that if either the usual relief is diminished or the usual duration of action is reduced, they should not increase the dose or its frequency of administration, but should seek medical advice.

VENTOLIN should be administered cautiously to patients with thyrotoxicosis.

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-adrenoceptors agonists, *VENTOLIN* 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.

VENTOLIN oral liquid is not indicated for obstetric use.

Obstetric use only:

As maternal pulmonary oedema and myocardial ischaemia have been reported during or following treatment of premature labour with beta-$_2$ agonists, careful attention should be given to fluid balance and cardio-respiratory function, including ECG should be monitored. If signs of pulmonary oedema or myocardial ischaemia develop, discontinuation of treatment should be considered.

Interactions

VENTOLIN and non-selective beta-blocking drugs, such as propranolol, should not usually be prescribed together.

VENTOLIN is not contraindicated in patients under treatment with monoamine oxidase inhibitors (MAOIs).

Pregnancy and Lactation

Fertility

There is no information on the effects of salbutamol on human fertility. There were no adverse effects on fertility in animals (see *Pre-clinical Safety Data*).

Pregnancy

Administration of drugs 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.

As no consistent pattern of defects can be discerned, and baseline rate for congenital anomalies is 2- to 3%, a relationship with salbutamol use cannot be established.

Lactation

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.

Effects on Ability to Drive and Use Machines

None Reported.

Adverse Reactions

Adverse reactions are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000) and very rare (<1/10,000) including isolated reports. Very common and common reactions were generally determined from clinical trial data. Rare and very rare reactions 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 beta-2 agonist therapy.

Nervous system disorders

Very common:	Tremor.
Common:	Headache.
Very rare:	Hyperactivity.

Cardiac disorders

Common:	Tachycardia, palpitations.
Uncommon:	Myocardial ischaemia*

*In the management of pre-term labour with Ventolin injection/solution for infusion.

Rare:	Cardiac arrhythmias including atrial fibrillation, supraventricular tachycardia and extrasystoles.

Vascular disorders

Rare: Peripheral vasodilatation.

Musculoskeletal and connective tissue disorders

Common: Muscle cramps.
Very rare: Feeling of muscle tension.

Overdose

The most common signs and symptoms of overdose with *VENTOLIN* are transient beta agonist pharmacologically mediated events (see *Warnings and Precautions* and *Adverse Reactions*).

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

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 Reaction* 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.

Nausea, vomiting and hyperglycaemia have been reported, predominantly in children and when *VENTOLIN* overdose has been taken via the oral route.

Treatment

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

Salbutamol is a selective beta-$_2$ adrenoceptor agonist. At therapeutic doses it acts on the beta-$_2$ receptors of bronchial muscle providing short acting (4 to 6 hour) bronchodilation in reversible airways obstruction.

Pharmacokinetics

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'-0- 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 oral administration, salbutamol 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. The bioavailability of orally administered salbutamol is about 50%.

Pre-Clinical 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 fetuses are found to have cleft palate, at 2.5 mg/kg, 4 times the maximum human oral dose. In rats, treatment-related effects observed were an increase in neonatal mortality at the high dose (50 mg/kg.day) in an oral study, as a result of lack of maternal care, and a dose-related inhibition of fetal development in oral and subcutaneous studies. A reproductive study in rabbits revealed cranial malformations in 37% of fetuses at 50 mg/kg/day, 78 times the maximum human oral dose.

Reproduction studies in rats demonstrated no evidence of impaired fertility at oral doses of *VENTOLIN* up to 50 mg/kg.

PHARMACEUTICAL PARTICULARS

List of Excipients

Sodium Citrate
Citric Acid Monohydrate
Hydroxpropyl Methylcellulose 2910
Sodium Benzoate
Saccharin Sodium
Orange Flavour
Sodium Chloride
Purified Water

Incompatibilities

Sugar-free formulation:

Dilution of *VENTOLIN* Syrup with Syrup BP or Sorbitol solution is not recommended as this may result in precipitation of the cellulose thickening agent.

Shelf Life

3 years (sugar-free formulation). The expiry date is indicated on the packaging.

Special Precautions for Storage

VENTOLIN oral liquid should be protected from light and stored below 30^{o}C (Sugar-free formulation).

Nature and Contents of Container

VENTOLIN oral liquid is supplied in bottles of 1 litre and 100 ml.

Not all presentations are available in every country.

Instructions for Use/Handling

Dilution:
Sugar-free formulation:

VENTOLIN oral liquid does not contain sugars. It 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 *VENTOLIN* oral liquid has been shown to be adequately preserved against microbial contamination. However, to avoid 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. Dilution of *VENTOLIN* oral liquid with Syrup BP or Sorbitol solution is not recommended as this may be result in precipitation of the cellulose thickening agent. Admixture of *VENTOLIN* oral liquid with other liquid preparations is not recommended.

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