Certificate Number: PP10186913

SUMMARY OF PRODUCT CHARACTERISTICS

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1. NAME OF THE MEDICINAL PRODUCT

Ventolin Respirator Solution 5 mg/ml.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Aqueous, colourless to light yellow solution, pH 3.5, providing 5 mg/ml of salbutamol (as Salbutamol Sulfate BP).

Excipients with known effect: Benzalkonium chloride (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for nebulisation.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ventolin Respirator Solution is indicated in adults, adolescents and children aged 4 to 11 years. For babies and children under 4 years of age, see Section 4.2.

Ventolin Respirator Solution is indicated for use in the routine management of chronic bronchospasm unresponsive to conventional therapy, and in the treatment of acute severe asthma.

4.2 Posology and method of administration

Ventolin Respirator Solution is for inhalation use only, to be breathed in through the mouth, under the direction of a physician, using a suitable nebuliser. The solution should not be injected or swallowed. Ventolin Respirator Solution may be administered intermittently or continuously. Salbutamol has a duration of action of 4 to 6 hours in most patients.

Private purchase of nebuliser devices for use at home to deliver rescue therapy for the acute treatment of asthma in children and adolescents is not recommended.

Only specialists in respiratory medicine should initiate and clinically manage use of nebulisers and associated nebulised medicines at home for acute treatment of asthma in children and adolescents.

Children should be trained in the correct use of their device to deliver rescue therapy and use should be supervised by a responsible adult.

Urgent medical assistance should be sought if worsening asthma symptoms are not relieved by rescue medicines, even if there is short-term recovery following use of prescribed nebulised medication.

Intermittent administration

Adults: Ventolin Respirator solution 0.5 ml (2.5 mg of salbutamol) should be diluted to a final volume of 2 ml with sterile normal saline. This may be increased to 1 ml (5 mg of salbutamol) diluted to a final volume of 2.5 ml. The resulting solution is inhaled from a suitably driven nebuliser until aerosol generation ceases. Using a correctly matched nebuliser and driving source this should take about ten minutes.

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Ventolin Respirator Solution may be used undiluted for intermittent administration. For this, 2 ml of Ventolin Respirator Solution (10 mg of salbutamol) is placed in the nebuliser and the patient allowed to inhale the nebulised solution until bronchodilation is achieved. This usually takes 3 - 5 minutes. Some adult patients may require higher doses of salbutamol up to 10 mg, in which case nebulisation of the undiluted solution may continue until aerosol generation ceases.

Paediatric Population

The same mode of administration for intermittent administration is also applicable to children. The minimum starting dosage for children under the age of 12 years is 0.5 ml (2.5 mg of salbutamol) diluted to 2 to 2.5 ml with sterile normal saline. Some children (over the age of 18 months) may, however, require higher doses of salbutamol up to 5 mg. Intermittent treatment may be repeated up to four times daily.

Children aged 12 years and over: Dose as per adult population.

In infants under 18 months the clinical efficacy of nebulised salbutamol is uncertain. As transient hypoxaemia may occur supplemental oxygen therapy should be considered.

Other pharmaceutical forms may be more appropriate for administration in children under 4 years old.

Continuous administration

Ventolin Respirator Solution is diluted with sterile normal saline to contain 50-100 micrograms of salbutamol per ml, (1-2 ml solution made up to 100 ml with diluent). The diluted solution is administered as an aerosol by a suitably driven nebuliser. The usual rate of administration is 1-2 mg per hour.

4.3 Contraindications

Hypersensitivity to the active substance or any of the excipients listed in section 6.1.

Non-IV formulations of salbutamol must not be used to arrest uncomplicated premature labour or threatened abortion.

4.4 Special warnings and precautions for use

Ventolin Respirator Solution must only be used by inhalation, to be breathed in through the mouth, and must not be injected or swallowed.

Bronchodilators should not be the only or main treatment in patients with severe or unstable asthma. Severe asthma requires regular medical assessment, including lung-function testing, as patients are at risk of severe attacks and even death. Physicians should consider using the maximum recommended dose of inhaled corticosteroid and/or oral corticosteroid therapy in these patients.

Patients receiving treatment at home should be warned to seek medical advice if treatment with Ventolin Respirator Solution becomes less effective. As there may be adverse effects associated with excessive dosing the dosage or frequency of administration should only be increased on medical advice.

Patients being treated with Ventolin Respirator Solution may also be receiving other dosage forms of short-acting inhaled bronchodilators to relieve symptoms.

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Patients who are prescribed regular anti-inflammatory therapy (e.g., inhaled corticosteroids) should be advised to continue taking their anti-inflammatory medication even when symptoms decrease, and they do not require Ventolin Respirator Solution.

Increasing use of bronchodilators, in particular short-acting inhaled β2-agonists, to relieve symptoms, indicates deterioration of asthma control, and patients should be warned to seek medical advice as soon as possible. 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).

Overuse of short-acting beta-agonists may mask the progression of the underlying disease and contribute to deteriorating asthma control, leading to an increased risk of severe asthma exacerbations and mortality.

Patients who take more than twice a week "as needed" salbutamol, not counting prophylactic use prior to exercise, should be re-evaluated (i.e., daytime symptoms, night-time awakening, and activity limitation due to asthma) for proper treatment adjustment as these patients are at risk for overuse of salbutamol.

Severe exacerbations of asthma must be treated in the normal way.

Cardiovascular effects may be seen with sympathomimetic drugs, including salbutamol. There is some evidence from post-marketing data and published literature of rare occurrences of myocardial ischaemia associated with salbutamol. Patients with underlying severe heart disease (e.g. ischaemic heart disease, arrhythmia or severe heart failure) who are receiving salbutamol should be warned to seek medical advice if they experience chest pain or other symptoms of worsening heart disease. Attention should be paid to assessment of symptoms such as dyspnoea and chest pain, as they may be of either respiratory or cardiac origin.

Ventolin Respirator Solution should be used with care in patients known to have received large doses of other sympathomimetic drugs.

Potentially serious hypokalaemia may result from β_2-agonist therapy, mainly from parenteral and nebulised administration. Particular caution is advised in acute severe asthma as this effect may be potentiated by hypoxia and by concomitant treatment with xanthine derivatives, steroids and diuretics. Serum potassium levels should be monitored in such situations.

In common with other β-adrenoceptor agonists, salbutamol can induce reversible metabolic changes such as increased blood glucose levels. Diabetic patients may be unable to compensate for the increase in blood glucose and the development of ketoacidosis has been reported. Concurrent administration of corticosteroids can exaggerate this effect.

Lactic acidosis has been reported 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 Section 4.8). 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.

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.

Salbutamol should be administered cautiously to patients suffering from thyrotoxicosis.

Ventolin Respirator Solution contains 0.1 mg/ml Benzalkonium chloride in each dosage unit. Benzalkonium chloride may cause bronchospasm, especially in patients with asthma.

As with other inhalation therapy, paradoxical bronchospasm may occur with an immediate increase in wheezing after dosing. This should be treated immediately with an alternative presentation or a different fast-acting inhaled bronchodilator. Ventolin Respirator Solution should be discontinued immediately, the patient assessed, and if necessary a different fast-acting bronchodilator instituted for on-going use.

4.5. Interactions with other medicinal products and other forms of interaction

Should not normally be prescribed with non-selective β-blocking drugs such as propranolol.

4.6 Fertility, pregnancy and lactation

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. As with the majority of drugs, there is little published evidence of the safety of salbutamol in the early stages of human pregnancy, but in animal studies there was evidence of some harmful effects on the foetus at very high dose levels.

Breast-feeding

As salbutamol is probably secreted in breast milk, its use in nursing mothers requires careful consideration. It is not known whether salbutamol has a harmful effect on the neonate, and 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.

Fertility:

There is no information on the effects of salbutamol on human fertility. There were no adverse effects on fertility in animals (*see section 5.3*).

4.7. Effects on ability to drive and use machines

None reported.

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 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000) and very rare (<1/10,000). 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.

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Potentially serious hypokalaemia may result from beta$_2$ agonist therapy.

Unknown: Lactic acidosis (see section 4.4)

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
Unknown: Myocardial ischaemia* (see section 4.4)

Vascular disorders
Rare: Peripheral vasodilatation.

Respiratory, thoracic and mediastinal disorders
Very rare: Paradoxical bronchospasm.

Gastrointestinal disorders
Uncommon: Mouth and throat irritation.

Musculoskeletal and connective tissue disorders
Uncommon: Muscle cramps.

* reported spontaneously in post-marketing data therefore frequency regarded as unknown

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

The most common signs and symptoms of overdose with salbutamol are transient beta agonist pharmacologically mediated events, including tachycardia, tremor, hyperactivity and metabolic effects including hypokalaemia and lactic acidosis (see sections 4.4 and 4.8).

Hypokalaemia may occur following overdose with salbutamol. Serum potassium levels should be monitored. Lactic acidosis has been reported in association with high therapeutic doses as well as overdoses of short-acting beta-agonist therapy, therefore monitoring for elevated serum lactate and consequent metabolic acidosis (particularly if there is persistence or worsening of tachypnea despite resolution of other signs of bronchospasm such as wheezing) may be indicated in the setting of overdose.

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5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Andrenergics, inhalants. Selective beta-2-andrenoreceptor agonists
ATC code: R03AC02

Salbutamol is a selective β2-agonist providing short-acting (4-6 hour) bronchodilation with a fast onset (within 5 minutes) in reversible airways obstruction. At therapeutic doses it acts on the β_2-adrenoceptors of bronchial muscle. With its fast onset of action, it is particularly suitable for the management and prevention of attack in 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'-0-sulfate (phenolic sulfate) which is also excreted primarily in the urine. The faeces are a minor route of excretion. 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%.

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 sulfate.

The swallowed portion of an inhaled dose is absorbed from the gastrointestinal tract and undergoes considerable first-pass metabolism to the phenolic sulfate. Both unchanged drug and conjugate are excreted primarily in the urine.

5.3 Preclinical safety data

In an oral fertility and general reproductive performance study in rats at doses of 2 and 50 mg/kg/day, with the exception of a reduction in number of weanlings surviving to day 21 post partum at 50 mg/kg/day, there were no adverse effects on fertility, embryofetal development, litter size, birth weight or growth rate.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Preservative: Benzalkonium chloride
Sulphuric acid if required to adjust to pH 3.5.
Purified water

6.2. Incompatibilities

None known.

6.3. Shelf life

Unopened: 3 years. Following opening for the first time: 28 days.

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6.4. Special precautions for storage
Store below 25°C. Protect from light. Discard any contents remaining one month after opening the bottle.

6.5 Nature and contents of container
Screw-capped 10 ml amber glass bottle.
Screw-capped 20 ml amber glass bottle.

6.6 Special precautions for disposal
Inhalation use only, using a suitable nebuliser.

The nebulised solution may be inhaled through a face mask, "T" piece or via an endotracheal tube. Intermittent positive pressure ventilation (IPPV) may be used, but is rarely necessary. When there is a risk of anoxia through hypoventilation, oxygen should be added to the inspired air.

As many nebulisers operate on a continuous flow basis, it is likely that nebulised drug will be released into the local environment. Ventolin Respirator Solution should therefore be administered in a well ventilated room, particularly in hospitals when several patients may be using nebulisers at the same time.

Ventolin Respirator Solution may be diluted with sterile normal saline (see section 4.2).

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

7 MARKETING AUTHORISATION HOLDER
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