1. Name of the Medicinal Product

Ventomac 100

Salbutamol Pressurized Inhalation BP 100 mcg

2. Qualitative and Quantitative Composition

Each actuation from the valve delivers:

Salbutamol Sulfate BP/Ph.Eur.

equivalent to Salbutamol .....100 mcg

Suspended in Propellant HFA 134a.....q.s.

For Excipients see point 6.1

3. Pharmaceutical Form

Metered dose inhaler

4. Clinical Particulars

4.1 Therapeutic indications

Salbutamol is indicated in adults, adolescents and children aged 4 to 11 years.

It provides short-acting (4 to 6 hour) bronchodilation with fast onset (within 5 minutes) in reversible airways obstruction.

It is particularly suitable for the relief and prevention of asthma symptoms. It should be used to relieve symptoms when they occur, and to prevent them in those circumstances recognised by the patient to precipitate an asthma attack (e.g. before exercise or unavoidable allergen exposure).

It is particularly valuable as relief medication in mild, moderate or severe asthma, provided that reliance on it does not delay the introduction and use of regular inhaled corticosteroid therapy.

4.2 Posology and method of administration

Salbutamol is for oral inhalation use only.

Adults (including the elderly): 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, two inhalations should be taken 10-15 minutes before challenge.

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

Paediatric Population:

Relief of acute bronchospasm:

The usual dosage for children under the age of 12 years: one inhalation (100 micrograms). The dose may be increased to two inhalations if required.

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

Prevention of allergen or exercise-induced bronchospasm:

The usual dosage for children under the age of 12 years: one inhalation (100 micrograms) before challenge or exertion. The dose may be increased to two inhalations if required.

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

Chronic therapy

The usual dosage for children under the age of 12 years: up to two inhalations 4 times daily.

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

On-demand use of Salbutamol 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.

4.3 Contraindications

Hypersensitivity to the active substance or any of the excipients.

Although intravenous salbutamol, and occasionally salbutamol tablets, are used in the management of premature labour uncomplicated by conditions such as placenta praevia, ante-partum haemorrhage or toxaemia of pregnancy, inhaled salbutamol preparations are not appropriate for managing premature labour. Salbutamol preparations should not be used for threatened abortion.

4.4 Special warnings and precautions for use

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.

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.

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.

Increasing use of bronchodilators, in particular short-acting inhaled β_2-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.

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.

Salbutamol should be administered cautiously to patients with thyrotoxicosis.

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.

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. Salbutamol should be discontinued immediately, the patient assessed, and if necessary, a different fast-acting bronchodilator instituted for on-going use.

4.5 Interaction with other medicinal products and other forms of interaction

Other short-acting sympathomimetic aerosol bronchodilators or epinephrine should not be used concomitantly with Salbutamol. If additional adrenergic drugs are to be administered by any route, they should be used with caution to avoid deleterious cardiovascular effects.

Monoamine Oxidase Inhibitors or Tricyclic Antidepressants: Salbutamol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of Salbutamol on the vascular system may be potentiated.

Beta-Blockers: Beta-adrenergic receptor blocking agents not only block the pulmonary effect of beta-agonists, such as Salbutamol Pressurized Inhalation, but may produce severe bronchospasm in asthmatic patients. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with asthma. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

Diuretics: The ECG changes and/or hypokalemia that may result from the administration of nonpotassium-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. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta-agonists with nonpotassium-sparing diuretics.

Digoxin: Mean decreases in serum digoxin levels occur after single-dose intravenous and oral administration of Salbutamol. The clinical significance of these findings for patients with obstructive airway disease who are receiving Salbutamol and digoxin on a chronic basis is unclear. Nevertheless, it would be prudent to carefully evaluate the serum digoxin levels in patients who are currently receiving digoxin and Salbutamol.

4.6 Pregnancy and Lactation

Pregnancy:

Safety in pregnant women has not been established. No controlled clinical trials with salbutamol have been conducted in pregnant women. Rare reports of various congenital anomalies following intrauterine exposure to salbutamol (including cleft palate, limb defects and cardiac disorders) have been received. Some of the mothers were taking multiple medications during their pregnancies. Salbutamol should not be used during pregnancy unless clearly necessary.

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.

4.7 Effects on ability to drive and use machines

Not available.

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.

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

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

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.

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.

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

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Salbutamol is a selective β_2-adrenoceptor agonist. At therapeutic doses it acts on the β_2-adrenoceptors of bronchial muscle providing short acting (4-6 hour) bronchodilation with a fast onset (within 5 minutes) in reversible airways obstruction.

In vitro studies and in vivo pharmacologic studies have demonstrated that Salbutamol has a preferential effect on beta$_2$-adrenergic receptors compared with isoproterenol. While it is recognized that beta$_2$-adrenergic receptors are the predominant receptors in bronchial smooth

muscle, data indicate that there is a population of beta$_2$-receptors in the human heart existing in a concentration between 10% and 50%. The precise function of these receptors has not been established.

The pharmacologic effects of beta-adrenergic agonist drugs, including salbutamol, are at least in part attributable to stimulation through beta-adrenergic receptors of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels are associated with relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

Salbutamol is longer acting than isoproterenol in most patients by any route of administration because it is not a substrate for the cellular uptake processes for catecholamines nor for catechol-*O*-methyl transferase.

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-sulfate (phenolic sulfate) 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 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. 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 β_2-receptor agonists, salbutamol has been shown to be teratogenic in mice when given subcutaneously. In a reproductive study, 9.3% of fetuses were found to have cleft palate at 2.5mg/kg, 4 times the maximum human oral dose. In rats, treatment at the levels of 0.5, 2.32, 10.75 and 50mg/kg/day orally throughout pregnancy resulted in no significant fetal abnormalities. The only toxic effect was an increase in neonatal mortality at the highest dose level as the result of lack of maternal care. A reproductive study in rabbits revealed

cranial malformations in 37% of fetuses at 50mg/kg/day, 78 times the maximum human oral dose.

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

1,1,1,2 Tetrafluoroethane (Propellant HFA 134A)

6.2 Incompatibilities

None

6.3 Shelf life

36 months from the manufacturing date.

Never use after the expiry date clearly indicated on the outer packaging.

6.4 Special precautions for storage

Store below 30°C, Do not freeze. Protect from frost and direct sunlight.

Store the inhaler with the mouth piece down.

6.5 Nature and contents of container

Pressurised metered dose inhaler containing suspension aerosol filled in aluminum canister fitted with suitable metered valve and 19ml actuator 0.48mm orifice, dark blue coloured cap and light blue body. Each Canister is been labeled and further packed in a carton along with Patient Information Leaflet.

6.6 Special Precaution for disposal

None.

7. MARKETED BY,

Macleod's Pharmaceuticals Limited

Off: Atlanta Arcade, Church Road,
Andheri-Kurla Road, Andheri (East)
Mumbai - 400 059, INDIA

Manufactured By;
Oxalis Labs ,
Village Theda, P.O.Lodhimajra,
Tehsil Baddi , Dist.Solan,
Himachal Pradesh,India-174101

8. Who Reference Number (Prequalification Programme)

9. Date of first Prequalification/ last renewal

10. Date of Revision of the Text:

References:

1]http://www.rxlist.com/ventolin-solution-drug/.htm

2]https://www.medicines.org.uk/emc/medicine/99/SPC/Ventolin+Evohaler/