Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ventolin Evohaler

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each metered dose actuation provides100 micrograms of salbutamol (as the sulphate).

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Pressurised inhalation, suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Ventolin Evohaler is indicated for the prophylaxis and treatment of airways obstruction due to bronchial asthma and chronic obstructive airways disease.

4.2 Posology and method of administration

Ventolin Evohaler is for oral inhalation use only. A Volumatic$_{TM}$ spacer device may be used in patients who find it difficult to synchronise aerosol actuation with inspiration of breath. The Babyhaler$_{TM}$ spacer device may be used to facilitate administration to children under 5 years of age.

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

Increasing use of β_2 agonists may be a sign of worsening asthma. In such circumstances, 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.

Relief of acute bronchospasm
Adults (including the elderly): 100 or 200 micrograms.

Children: 100 micrograms, the dose may be increased to 200 micrograms if required.

Prevention of recognised allergen- or exercise- induced bronchospasm:
Adults (including the elderly): 200 micrograms before challenge.

Children: 100 micrograms before challenge, the dose may be increased to 200micrograms if required.

Chronic therapy:
Adults (including the elderly): Up to 200 micrograms four times daily.

Children: Up to 200 micrograms four times daily.

On-demand use of Ventolin Evohaler 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 (see *Special warnings and precautions for use*).

4.3 Contraindications

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

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.

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

The management of asthma should normally follow a stepwise programme, and patient response should be monitored clinically and by using lung function tests.

Severe asthma requires regular medical assessment, including lung-function testing, as patients are at risk of severe attacks and even death. Bronchodilators should not be the only or main treatment in patients with severe or unstable asthma. Patients with severe asthma have constant symptoms and frequent exacerbations, with limited physical capacity, and PEF values below 60% predicted at baseline with greater than 30% variability, usually not returning entirely to normal after a bronchodilator. These patients will require high dose inhaled steroid therapy or oral corticosteroid therapy.

With this primary background corticosteroid treatment, salbutamol provides essential rescue medication for a severe asthmatic in treating acute exacerbations. Failure to respond promptly or fully to such rescue medication signals a need for urgent medical advice and treatment.

As there may be adverse effects associated with excessive dosing, 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). 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.

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

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.

Patients requiring long-term management with bronchodilators should be kept under regular surveillance.

A responsible adult should supervise the use of the inhaler by children.

4.5 Interaction with other medicinal products and other forms of interaction

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

Salbutamol is not contra-indicated in patients under treatment with monoamine oxidase inhibitors (MAOIs). However, the effects of salbutamol may be altered by guanethidine, reserpine, methyldopa and tricyclic antidepressants.

Caution should be exercised during the concurrent use of anaesthetic agents such as chloroform, cyclopropane, halothane and other halogenated agents.

4.6 Pregnancy and lactation

Administration of drugs during pregnancy should only be considered if the expected benefit to the mother is greater than any possible risk 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 for congenital anomalies is 2-3%, a relationship with salbutamol use cannot be established.

As salbutamol is probably secreted in breast milk, its use in nursing mothers is not recommendedunless 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.

4.7 Effects on ability to drive and use machines

There are no known effects on the ability to drive and use machines.

4.8 Undesirable effects

Ventolin Evohaler may cause a fine tremor of skeletal muscle, usually the hands are most obviously affected. This effect is dose-related and is common to all -adrenergic stimulants.

Headaches have occasionally been reported.

Tachycardia, with or without peripheral vasodilatation, may rarely occur. In common with other β_2-agonists, cardiac arrhythmias (including atrial fibrillation, supraventricular tachycardia and extrasystoles) have been reported in association with the use of salbutamol, usually in susceptible patients.

Hypersensitivity reactions including angioedema, urticaria, bronchospasm, hypotension and collapse have been reported very rarely.

There have been very rare reports of muscle cramps

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 Evohaler should be discontinued immediately, the patient assessed, and, if necessary, alternative therapy instituted.

Potentially serious hypokalaemia may result from β_2-agonist therapy.

As with other β_2-agonists hyperactivity in children has been reported rarely.

Mouth and throat irritation may occur with inhaled salbutamol.

Use with caution in diabetic patients as salbutamol may cause an increase in blood sugar level.

Salbutamol should not cause difficulty in micturition because unlike sympathomimetic drugs such as ephedrine, it does not stimulate α-adrenoceptors. However, there have been reports of difficulty in micturition inpatients with prostatic enlargement.

4.9 Overdose

The preferred antidote for overdosage with salbutamol is a cardioselective β-blocking agent, but β-blocking drugs should be used with caution in patients with a history of bronchospasm.

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

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) bronchodilatation with a fast onset (within 5 minutes) in reversible airways obstruction.

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 β_2-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 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. 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 Ventolin Evohaler 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

Norflurane [Hydro-fluoralkane (HFA) 134a].

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

The shelf life expiry date of this product is the date shown on the container and outer carton of the product as marketed in the country of origin.

6.4 Special precautions for storage

Do not store above 30°C.

Protect from frost and direct sunlight.

As with most inhaled medications in aerosol canisters, the therapeutic effect of this medication may decrease when the canister is cold.

The canister should not be broken, punctured or burnt, even when apparently empty.

6.5 Nature and contents of container

An inhaler comprising an aluminium alloy can sealed with a metering valve, actuator and dust cap. Each canister contains 200 metered actuations providing 100 micrograms of salbutamol (as salbutamol sulphate) per actuation.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Patients should be carefully instructed in the correct use of the inhaler.

For detailed instructions for use refer to the Patient Information Leaflet in every pack.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

PRIMECROWN LTD
28 Sarum Complex
Uxbridge
Middlesex
UB8 2RZ
England

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 1071/007/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 May 2003