

IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PPA1473/022/001

Case No: 2059699

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

McDowell Pharmaceuticals

4 Altona Road, Lisburn, N. Ireland, BT27 5QB

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Ventolin Evohaler 100micrograms Pressurised Inhalation, suspension

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **15/05/2009**.

Signed on behalf of the Irish Medicines Board this

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ventolin Evohaler 100 micrograms Pressurised Inhalation, suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each metered dose contains 100 micrograms of Salbutamol (as sulphate)

For a full list of excipients see section 6.1

3 PHARMACEUTICAL FORM

Product imported from the UK

Pressurised inhalation suspension

Pressurised inhalation suspension supplied in an aluminium can with metering valve and a blue actuator.

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 administered by the inhaled route only, to be breathed in through the mouth.

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. Under these conditions a reassessment of the patient's therapy plan may be required and concomitant glucocorticosteroid therapy should be considered.

In patients who find co-ordination of a pressurised metered-dose inhaler difficult, a spacer may be used with Ventolin Evohaler. Babies and young children may benefit from use of the Babyhaler spacer device with Ventolin Evohaler.

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: 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: 200 micrograms before challenge.

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

Chronic therapy:

Adults: Up to 200 micrograms four times daily.

Children: Up to 200 micrograms four times daily.

Elderly: There is no need to adjust the dose in the elderly.

On demand use of Ventolin should not exceed four times daily. Reliance on such supplementary use or a sudden increase in dose indicates deteriorating asthma (see Special Warnings and Special 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 the drug to the lungs.

Testing your inhaler

Before using for the first time remove the mouthpiece cover by gently squeezing the sides of the cover, shake the inhaler well, and release two puffs into the air to make sure that it works. If it has not been used for several days shake it well and release one puff into the air to make sure that it works.

Using your inhaler

Remove the mouthpiece cover by gently squeezing the sides of the cover. Check inside and outside of the inhaler including the mouthpiece for the presence of loose objects. Shake the inhaler well to ensure that any loose objects are removed and that the contents of the inhaler are evenly mixed. Hold the inhaler upright between fingers and thumb with your thumb on the base, below the mouthpiece. Breathe out as far as is comfortable and then place the mouthpiece in your mouth between your teeth and close your lips around it but do not bite it. Just after starting to breathe in through your mouth press down on the top of the inhaler to release salbutamol while still breathing in steadily and deeply. While holding your breath, take the inhaler from your mouth and take your finger from the top of the inhaler. Continue holding your breath for as long as is comfortable. If you are to take further puffs keep the inhaler upright and wait about half a minute before repeating stages 3 to 7. Replace the mouthpiece cover by firmly pushing and snapping the cap into position.

IMPORTANT

Do not rush Stages 5, 6 and 7. It is important that you start to breathe in as slowly as possible just before operating your inhaler.

Practise in front of a mirror for the first few times. If you see 'mist' coming from the top of the inhaler or the sides of your mouth you should start again from stage 2.

If your doctor has been given you different instructions for using your inhaler, please follow them carefully. Tell your doctor if you have any difficulties.

Cleaning

Your inhaler should be cleaned at least once a week. Remove the metal canister from the plastic casing of the inhaler and remove the mouthpiece cover. Rinse the actuator thoroughly under warm running water. Dry the actuator THOROUGHLY inside and out. Replace the metal canister and mouthpiece cover.

DO NOT PUT THE METAL CANISTER INTO WATER.

4.3 Contraindications

Ventolin Evohaler is contra-indicated in patients with a history of hypersensitivity to any of its 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 toxemia of pregnancy, inhaled salbutamol presentations are not appropriate for managing premature labour. Salbutamol preparations should not be used for threatened abortion.

4.4 Special warnings and precautions for use

Ventolin 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 lung function tests. Severe asthma requires regular medical assessment as death may occur.

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 treatment (e.g. >1mg/day beclomethasone dipropionate) or oral corticosteroid therapy. With this primary background corticosteroid treatment, Ventolin 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.

Increasing use of short-acting inhaled β_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.

In the event of a previously effective dose of inhaled salbutamol failing to give relief for at least three hours, the patient should be advised to seek medical advice in order that any necessary additional steps may be taken.

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 concomitant treatment with xanthine derivatives, steroids, diuretics and by hypoxia. It is recommended that serum potassium levels are 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 in children.

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

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

Cardiovascular effects may be seen with sympathomimetic drugs, including salbutamol. There is some evidence from post-marketing data and published literature 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.

4.5 Interaction with other medicinal products and other forms of interaction

Salbutamol and non-selective beta-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 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.

Because no consistent pattern of defects can be discerned, and baseline rate 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 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.

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 ($\geq 1/10$), common ($\geq 1/100$ and $< 1/10$), uncommon ($\geq 1/1000$ and $< 1/100$), rare ($\geq 1/10,000$ 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 and very rare 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 β_2 agonist therapy.

Nervous system disorders

Uncommon: Tremor, headache

Very rare: Hyperactivity

Cardiac disorders

Common: Tachycardia

Uncommon: Palpitations

Very rare: Cardiac arrhythmias including atrial fibrillation, supraventricular tachycardis and extrasystoles

Unknown: Myocardial ischaemia* (see section 4.4).

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

Vascular disorders

Rare: Peripheral vasodilatation

Respiratory, thoracic and mediastinal disorders

Very rare: Paradoxical bronchospasm

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.

Gastrointestinal disorders

Uncommon: Mouth and throat irritation

Musculoskeletal and connective tissue disorders

Uncommon: Muscle cramps

4.9 Overdose

Symptoms and Signs

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

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

Treatment

Consideration should be given to discontinuation of treatment and appropriate symptomatic therapy such as cardioselective beta-blocking agents 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.

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, with little or no action on the β_1 adrenoceptors of the heart. With its fast onset of action, onset (within 5 minutes) in reversible airways obstruction due to asthma, chronic bronchitis and emphysema, it is particularly suitable for the management and prevention of attacks in mild asthma and for the treatment of acute exacerbations in moderate and severe asthma.

Ventolin should be used to relieve symptoms when they occur and to prevent them in those circumstances recognised by the patient to precipitate an asthmatic attack (e.g. before exercise or unavoidable allergen exposure).

Clinical experience over many years indicates continuing symptomatic benefit on airways obstruction on a long-term basis.

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. 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 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.

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 foetuses were found to have cleft palate, at 2.5 mg/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 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. A reproductive study in rabbits revealed cranial malformations in 37% of foetuses at 50mg/kg/day, 78 times the maximum human oral dose.

HFA 134a has been shown to be non-toxic 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 (Hydroflouralkane (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 label and outer carton of the product as marketed in the country of origin.

6.4 Special precautions for storage

Store below 30oC. Do not refrigerate or freeze.

The canister contains a pressurised liquid. Do not expose to temperatures higher than 50oC. Do not pierce the canister even when apparently empty.

6.5 Nature and contents of container

The suspension is contained in an aluminium alloy can, internally coated with fluoropolymer and sealed with a metering valve. Each canister is fitted into a plastic actuator incorporating an atomising nozzle and fitted with a dustcap. Each canister contains at least 200 metered doses.

6.6 Special precautions for disposal and other handling

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

7 Parallel Product Authorisation Holder

McDowell Pharmaceuticals,
4 Altona Road,
Lisburn
N.Ireland
BT27 5QB

8 Parallel Product Authorisation Number

PPA1473/022/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 15th May 2009

10 DATE OF REVISION OF THE TEXT