IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PPA0465/064/002
Case No: 2054664

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

PCO Manufacturing Limited

Unit 10, Ashbourne Business Park, **Rath**, **Ashbourne**, **Co. Meath**, **Ireland**

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

Ventolin Nebules 2.5 mg nebuliser solution

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 **20/10/2008** until **04/01/2012**.

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 Nebules 2.5mg Nebuliser Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The concentration of salbutamol is 0.1%

Each Nebule contains 2.5mg Salbutamol (as sulphate).

Each ml of solution contains 1mg Salbutamol (as sulphate).

For a full list of excipients, see 6.1.

3 PHARMACEUTICAL FORM

Nebuliser Solution.

Product imported from the UK:
A clear colourless to pale yellow sterile, isotonic, aqueous solution

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Ventolin Nebules 2.5mg are indicated for the routine management of chronic bronchospasm, unresponsive to conventional therapy.

They are also indicated in the treatment of acute severe asthma (status asthmaticus).

4.2 Posology and method of administration

Salbutamol inhaled formulations are 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.
Ventolin Nebules are intended to be used undiluted. However, if prolonged delivery time is desirable (more than 10 minutes) dilution using sterile normal saline as a diluent may be required.
Ventolin Nebules are to be used with a nebuliser, under the direction of a physician.
The solution must not be injected, or swallowed.
Increasing use of β2 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.

Delivery of the aerosol may be by facemask, 'T' piece or via an endotracheal tube. Intermittent positive pressure ventilation 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 there may be adverse effects associated with excessive dosing, the dosage or frequency of administration should only be increased on medical advice.

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

Adults and Children: -
A suitable starting dose of salbutamol by wet inhalation is 2.5 milligrams.
This may be increased to 5 milligrams. Treatment may be repeated up to four times daily. In adults higher dosing, up to 40 milligrams per day, can be given under strict medical supervision in hospital for the treatment of severe airways obstruction.
Clinical efficacy of nebulised salbutamol in infants under 18 months is uncertain.
As transient hypoxaemia may occur, supplemental oxygen therapy should be considered.

4.3 Contraindications

Ventolin Nebules are contraindicated in patients with a history of hypersensitivity to sympathomimetics or any component of the preparation.

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 presentations should not be used for threatened abortion.

4.4 Special warnings and precautions for use

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 β2 agonists to control symptoms indicates deterioration of asthma control. Under these conditions, the patient's therapy plan should be reassessed.

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 (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.

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

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

Patients receiving treatment at home with Ventolin Nebules must be warned that if either the usual relief is diminished or the usual duration of action reduced, they should not increase the dose or its frequency of administration but should seek medical advice.

A responsible adult should supervise the treatment with Ventolin Nebules in children.

Ventolin Nebules should be used with caution in patients known to have received large doses of other sympathomimetic drugs.

Salbutamol should be administered cautiously to patients with thyrotoxicosis.

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.

Potentially serious hypokalaemia may result from β2 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 β-adrenoceptor 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 ketacidosis has been reported. Concurrent administration of corticosteroids can exaggerate this effect.

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.

Salbutamol should not cause difficulty in micturition because unlike sympathomimetic drugs such as ephedrine, it does not stimulate alpha-adrenoceptors. However, there have been reports of difficulty in micturition in patients with prostatic enlargement. Use with caution in diabetic patients as salbutamol may cause an increase in blood sugar level.

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, tachyarrhythmia or severe heart failure) who are receiving salbutamol for respiratory disease, 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 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 in its use with 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 (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. 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 β2 agonist therapy.

Very rare: Lactic acidosis.
Lactic acidosis has been reported very rarely in patients receiving intravenous and nebulised salbutamol therapy for the treatment of acute asthma exacerbation.

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).

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 Nebules 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.

Unknown* : Myocardial ischaemia
*Reported spontaneously in post marketing data therefore frequency regarded as unknown.

4.9 Overdose

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Salbutamol is a selective β2 adrenoceptor agonist. At therapeutic doses it acts on the β2 adrenoceptors of bronchial muscle, with little or no action on the β-1 adrenoceptors of cardiac muscle.

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 β2 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 2.5mg/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 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Dilute sulphuric acid
Water

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 package of the product on the market in the country of origin.

After opening outer foil packaging: 3 months.
Once nebule is opened, use immediately

6.4 Special precautions for storage

Do not store above 30°C. Keep nebules in the outer carton.

6.5 Nature and contents of container

The Nebules consist of low-density polyethylene (LDPE). Five Nebules are linked together in a strip. Each strip of five Nebules is packaged in a laminated aluminium foil blister pack consisting of a base foil bay and foil lidding material.

Ventolin Nebules are available in packs of 20 Nebules.

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

Note the date of opening.
Add 3 months to this date. This will be the ‘discard after’ date.
Write the ‘discard after’ date on the foil pack lid in the space provided.
Do not use any unused Ventolin Nebules remaining in the tray after the ‘discard after’ date but return them to you pharmacist for destruction.

Dilution: Ventolin nebules may be diluted with sterile normal saline.
Do not use the product if discoloured.
Any unused solution in the chamber for the nebuliser must be discarded.

7 Parallel Product Authorisation Holder

PCO Manufacturing Limited
Unit 10, Ashbourne Business Park
Rath
Ashbourne
Co. Meath

8 Parallel Product Authorisation Number

PPA465/64/2

8 MARKETING AUTHORISATION NUMBER

PPA 465/64/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation 5th January 2007

10 DATE OF REVISION OF THE TEXT

October 2008