IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA1077/049/006
Case No: 2057329

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

GlaxoSmithKline (Ireland) Limited

Stonemasons Way, **Rathfarnham**, **Dublin 16**, **Ireland**

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

Ventolin Respirator Solution 5 mg/ml, 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 **23/01/2009**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ventolin Respirator Solution 5 mg/ml, Nebuliser Solution.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of aqueous solution contains 5mg Salbutamol (as Sulphate)
Each ml of solution also contains 100 micrograms Benzalkonium Chloride

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Nebuliser solution.
A clear, colourless to pale yellow liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Ventolin Respirator Solution is indicated for the treatment of acute severe asthma (status asthmaticus) and for routine management of chronic bronchospasm unresponsive to conventional therapy.

4.2 Posology and method of administration

Ventolin Respirator Solution is to be used as respirator or nebuliser, only under the direction of a physician.

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

The solution must not be injected, or swallowed.

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.

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

1. By intermittent administration:

Adults and children over 12 years:
Ventolin Respirator Solution 0.5-1.0 ml (2.5-5.0 milligrams of salbutamol) should be diluted to a final volume of 2.0 or 2.5 ml (0.1-0.2% of salbutamol) with sterile normal saline as a diluent. 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.

The solution may be used undiluted in a nebuliser using 2ml (10 milligrams salbutamol) over 3-5 minutes or until aerosol generation ceases.

Children under 12 years:

The usual dose is 0.5 ml (2.5 milligrams salbutamol) diluted to a final volume of 2.0 or 2.5 ml with sterile normal saline .

2. By continuous administration:

Ventolin Respirator Solution is diluted with sterile normal saline to give a 100ml solution containing 50-100 micrograms of salbutamol per ml and administration by a suitably driven nebuliser delivering 1-2 milligrams drug/hour via face mask, 'T' piece or endotracheal tube.

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 Respirator Solution is contraindicated 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 toxaemia of pregnancy, inhaled salbutamol preparations are not appropriate for managing premature labour. Salbutamol presentations should not be used for threatened abortion during the first or second trimester of pregnancy.

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 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.

Respirator solution 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 Respirator Solution 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.

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

Salbutamol should be administered cautiously to patients suffering from thyrotoxicosis, hypertension, coronary insufficiency and cardiac arrhythmias.

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 anti-cholinergics should therefore be used cautiously. Patients should receive adequate instruction and be warned not to let the solution or mist enter the eye.

For intermittent administration the product should not be used more frequently than every three hours.

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.

In common with other β-adrenoceptor agonists, Ventolin can induce reversible metabolic changes, for example

increased blood sugar levels. The diabetic patients 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 section 4.8, Undesirable effects)*. 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.

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

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

Caution should be exercised during the concurrent use of anaesthetic agents such as chloroform, cyclopropane, halothane and other halogenated agents. The effects of this product may be altered by guanethidine, reserpine, methyldopa, tricyclic anti-depressants. Salbutamol is not contraindicated in patients under treatment with monoamine oxidase inhibitors (MAOIs).

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.

Salbutamol has been in widespread use for many years in human beings without apparent ill consequence, this includes its well-established use in the management of premature labour. However, as with the majority of drugs, there is little published evidence of its safety in the early stages of human pregnancy, but in animal studies there was evidence of some harmful effects on the foetus at very high doses.

During world-wide 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 risks. 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

Not applicable.

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 disorder
Rare: Hypokalaemia.
Potentially serious hypokalaemia may result from beta-2-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.
Unknown: Myocardial ischaemia* (*see section 4.4, Special warnings and precautions for use)*.

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

Vascular disorders
Rare: Peripheral vasodilatation.
Peripheral vasodilatation and a compensatory small increase in heart rate may occur in some patients.

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 Respirator Solution 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

During continuous administration of Ventolin Respirator Solution, any signs of overdosage can usually be counteracted by withdrawal of the drug.

Symptoms and Signs
The most common signs and symptoms of overdose with salbutamol are transient beta agonist pharmacologically mediated events *(see section 4.4, Special Warnings and Precautions for use and 4.8, Undesirable effects).*

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 cardio-selective 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 adrenoreceptor agonist. At therapeutic doses it acts on the β_2 adrenoreceptors of bronchial muscle, with little or no action on the β-1 adrenoreceptors 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 the 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 2.5milligrams/kg, i.e. 4 times the maximum oral dose.

In rats, treatment at the levels of 0.5, 2.32, 10.75 and 50 milligrams/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 50 milligrams/kg/day, i.e. 78 times the maximum human oral dose.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium Chloride Solution.
Dilute Sulphuric Acid (for pH adjustment)
Purified water

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6

6.3 Shelf Life

As package for sale, 3 years.
After first opening, one month

6.4 Special precautions for storage

Do not store above 25 ºC.
Keep bottle in the outer carton.

6.5 Nature and contents of container

Ventolin Respirator Solution is supplied in amber glass vials with polypropylene screw caps containing 20ml of solution.

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

Dilution:
Ventolin Respirator Solution may be diluted with sterile normal saline.
Any unused solution in the chamber of the nebuliser must be discarded.

7 MARKETING AUTHORISATION HOLDER

GlaxoSmithKline (Ireland) Limited
Stonemasons Way
Rathfarnham
Dublin 16
Trading as: Allen & Hanburys

8 MARKETING AUTHORISATION NUMBER

PA 1077/049/006

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23rd January 1984

Date of last renewal: 23rd January 2009

10 DATE OF REVISION OF THE TEXT

March 2009