IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA1077/049/014
Case No: 2054916

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 Tablets 4 mg

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 **30/10/2009**.

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 4 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 4mg salbutamol as salbutamol sulphate

Excipient: contains approximately 140.58mg lactose monohydrate per tablet

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

4mg - White tablet, round, flat-faced with bevelled edges, plain on one side and engraved with code “GX CN5” and a score line.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Ventolin Tablets are indicated for the relief of bronchospasm such as occurs with asthma, bronchitis and emphysema.

The management of uncomplicated premature labour during the third trimester of pregnancy following the control of uterine contractions with parenteral salbutamol.

4.2 Posology and method of administration

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.

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

Adults:- The usual total daily dose is 12 to 32mg in three or four divided doses.

In the management of premature labour, after uterine contractions have been controlled by intravenous infusion of Ventolin and the infusion has been withdrawn, maintenance therapy can be continued with oral Ventolin. The usual dosage is 4mg, three or four times daily.

Children:-
2 - 6 years: The usual total daily dose is 3 to 8mg in three or four divided doses.
6 - 12 years: The usual total daily dose is 6 to 8mg daily in divided doses.
Over 12 years: The usual total daily dose is 6 to 16mg daily in divided doses.

Special patient groups:
In elderly patients or in those known to be unusually sensitive to β-adrenergic stimulant drugs, it is advisable to initiate treatment with 2 milligrams salbutamol three or four times per day.

4.3 Contraindications

Ventolin Tablets 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, salbutamol presentations should not be used for threatened abortion.

Salbutamol should not be used as a tocolyte agent in patients with pre-existing ischaemic heart disease or those patients with significant risk factors for ischaemic heart disease.

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.

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.

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.

Patients should 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.

Salbutamol causes peripheral vasodilation which may result in reflex tachycardia and increased cardiac output.
Caution should be used in patients with angina, severe tachycardia or 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.

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.

As maternal pulmonary oedema and myocardial ischaemia have been reported during or following treatment of premature labour with β_2 agonists, careful attention should be given to fluid balance and cardio-respiratory function, including ECG, should be monitored. If signs of pulmonary oedema or myocardial ischaemia develop, discontinuation of treatment should be considered.

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

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, both in the respiratory and obstetric indications.

Tocolysis
Salbutamol should be used with caution in tocolysis and supervision of cardiorespiratory function, including ECG monitoring, should be considered. Treatment should be discontinued if signs of myocardial ischaemia (such as chest pain or ECG changes) develop. Salbutamol should not be used as a tocolytic agent in patients with significant risk factors for or pre-existing heart disease *(see section 4.3).*

Respiratory indications
Patients with underlying severe heart disease (e.g. ischaemic heart disease, arrhythmia 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.

Salbutamol has been in widespread use for many years in human beings without apparent ill consequence; this indicates 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 dose levels.

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 (<1/110,000) 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 beta-2 agonist therapy.

Nervous system disorders
Very common: Tremor
Common: Headache
Very rare: Hyperactivity

Cardiac disorders
Common: Tachycardia, palpitations

Uncommon: Myocardial ischaemia *(Obstetric Indications)
*In the management of pre-term labour with salbutamol injection/solution for infusion.

Unknown: Myocardial ischaemia* *(see section 4.4)* (Respiratory Indications)
*Reported spontaneously in post-marketing data therefore regarded as unknown.

Rare: Cardiac arrhythmias including atrial fibrillation, supraventricular tachycardia and extrasystoles.

Vascular disorders:
Rare: Peripheral vasodilatation.

Musculoskeletal and connective tissue disorders
Common: Muscle cramps
Very rare:Feeling of muscle tension.

4.9 Overdose

Symptoms and Signs
The most common signs and symptoms of overdose with salbutamol are transient beta agonist pharmacologically mediated events *(see Special Warnings and Precautions for Use and Undesirable Effects).*

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

Nausea, vomiting and hyperglycaemia have been reported, predominantly in children and when salbutamol overdose has been taken via the oral route.

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

Pharmacotherapeutic group: Selective beta-2-adrenoceptor agonist
ATC code:R03A C02

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. It is suitable for the management and prevention of attack in asthma.

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 oral administration, salbutamol 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. The bioavailability of orally administered salbutamol is about 50%.

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 2.5mg/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

Lactose monohydrate
Maize Starch
Starch, pregelatinised
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years.

6.4 Special precautions for storage

Do not store above 25^{o}C. Keep the container tightly closed to protect from moisture.

6.5 Nature and contents of container

Ventolin tablets are supplied in polyprolylene containers of 100 and 500 tablets, with a low density polyethylene (LDPE) closure.
Not all pack sizes may be marketed.

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

No special requirements.

7 MARKETING AUTHORISATION HOLDER

GlaxoSmithKline (Ireland) Limited,
Stonemasons Way,
Rathfarnham,
Dublin 16.

Trading as:
Allen & Hanburys

8 MARKETING AUTHORISATION NUMBER

PA 1077/49/14

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 10 November 1975

Date of last renewal: 05 August 2008

10 DATE OF REVISION OF THE TEXT

October 2009