IRISH MEDICINES BOARD ACT 1995

MEDICINAL PRODUCTS(LICENSING AND SALE)REGULATIONS, 1998

(S.I. No.142 of 1998)

PA1077/047/001
Case No: 2032319

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

GlaxoSmithKline (Ireland) Ltd

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

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

SEREVENT 25 Mcg/Acutuation 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 **19/01/2007** until .

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

Serevent Inhaler, 25 Micrograms, pressurised inhalation, suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Pressurised metered-dose inhaler delivering 25 micrograms of salmeterol as salmeterol xinafoate with each actuation.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Pressurised inhalation, suspension
Supplied in an aluminium can with metering value and actuator.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Adults
Salmeterol provides long-lasting (12 hour) bronchodilation in reversible airways obstruction due to asthma, chronic bronchitis, emphysema and COPD. It is suitable for long-term regular, twice-daily treatment to control symptoms, but in view of its slower onset of action (10 to 20 minutes), it should not be used to relieve acute asthmatic symptoms, for which a faster acting (within 5 minutes) inhaled bronchodilator (e.g. salbutamol) should be given.

Serevent is indicated when a regular bronchodilator is required, and to prevent night-time symptoms and/or day-time fluctuations caused by reversible airways obstruction (e.g. before exercise or unavoidable allergen challenge).

Serevent, as twice-daily regular treatment, can replace a short-acting (4 hour) inhaled bronchodilator (e.g. salbutamol), when it is required more than once a day, or an oral bronchodilator (e.g. salbutamol, theophylline).

There is no evidence that salmeterol is a replacement for corticosteroids and these should not be stopped or reduced when salmeterol is prescribed. In patients not already receiving anti-inflammatory therapy, this should be considered when starting salmeterol.

Patients must be warned not to stop steroid therapy or reduce it without medical advice, even if they feel better on Serevent.

Regular treatment of reversible airways obstruction in asthma including long-lasting prevention of exercise-induced bronchospasm.

Bronchodilators should not be the only or the main treatment in patients with severe or unstable asthma. Severe asthma requires regular medical assessment as death may occur. 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 optimal background steroid therapy, Serevent can offer additional symptomatic treatment. Sudden worsening of symptoms may require increased corticosteroid dosage which should be administered under urgent medical supervision.

4.2 Posology and method of administration

Salmeterol is administered by the inhaled route only.

It is intended that each prescribed dose is given by a minimum of 2 inhalations.

In order to gain full therapeutic benefit regular usage of salmeterol is recommended in the treatment of reversible airways obstruction due to asthma, Chronic Obstructive Pulmonary Disease (COPD) and chronic bronchitis. The onset of effective bronchodilation (>15% improvement in FEV_1) occurs within 10 to 20 minutes in asthma patients. The full benefits will be apparent after the first few doses of the drug. The bronchodilator effects of salmeterol usually last for 12 hours. This is particularly useful in the treatment of nocturnal symptoms in asthma, COPD and chronic bronchitis and in the management of exercise induced asthma.

Patients should be instructed not to take additional doses to treat symptoms but to take a short-acting inhaled beta-2-agonist.

In patients who find co-ordination of a pressurised metered-dose inhaler difficult a spacer may be used with Serevent Inhaler. Alternatively, Serevent Rotadisks using a Diskhaler inhaler or Serevent Diskus may be used.

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

The response to starting salmeterol is usually seen within a few days. If such improvement is not seen, the dose of salmeterol required may need to be increased to the maximum dose of 100 micrograms bd. If improvement is still not seen within 1 week of commencing therapy, salmeterol should be withdrawn and alternative therapy instituted.

Adults:
Treatment of asthma, COPD and chronic bronchitis:

Two inhalations (2 x 25 microgram of salmeterol) twice daily.

In patients with more severe airways obstruction in whom symptoms persist, up to four inhalations (4 x 25 microgram of salmeterol) twice daily may be of benefit.

Children:
There are insufficient clinical data at present to recommend the use of salmeterol in children.

Special patient groups:
There is no need to adjust the dose in elderly patients or in those with renal impairment.

4.3 Contraindications

Hypersensitivity to any ingredient of the preparation (see Pharmaceutical Particulars – List of excipients).

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.

Serevent should not be used (and is not sufficient) as the first treatment for asthma.

Sudden and progressive deterioration of asthma is potentially life-threatening and consideration should be given to starting or increasing corticosteroid therapy. In patients at risk, daily peak flow monitoring should be instituted.

Once asthma symptoms are controlled, consideration may be given to gradually reducing the dose of Serevent. Regular

review of patients as treatment is stepped down is important. The lowest effective dose of Serevent should be used.

Bronchodilators should not be the only or the main treatment in patients with severe or unstable asthma. Severe asthma requires regular medical assessment, including lung function testing, as patients are at risk of severe attacks and even death. Physicians should consider using oral corticosteroid therapy and/or maximum recommended dose of inhaled corticosteroid in these patients.

Increasing use of bronchodilators, in particular short-acting inhaled beta-2-agonists, to relieve symptoms indicates deterioration of asthma control. If patients find that short-acting relief bronchodilator treatment becomes less effective or they need more inhalations than usual, medical attention must be sought. In this situation patients should be reassessed and consideration given to the need for increased anti-inflammatory therapy (e.g. higher doses of inhaled corticosteroids or a course of oral corticosteroids). Severe exacerbations of asthma must be treated in the normal way with nebulised or parenteral bronchodilators and parenteral corticosteroids, together with other supportive measures.

Although Serevent may be introduces as add-on therapy when inhaled corticosteroids do not provide adequate control of asthma symptoms, patients should not be initiated on Serevent during an acute severe asthma exacerbation, or if they have significantly worsening or acutely deteriorating asthma.

Serious asthma-related adverse events and exacerbations may occur during treatment with Serevent. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation on Serevent.

Serevent is not a replacement for oral or inhaled corticosteroids. Its use is complementary to them. Patients must be warned not to stop steroid therapy and not to reduce it without medical advice even if they feel better on Serevent.

Serevent is not designed to relieve acute asthma symptoms, for which an inhaled short-acting bronchodilator (e.g. salbutamol) is required. Patients should be advised to have such relief medication available.

Data from a large clinical trial (the Salmeterol Multi-Center Asthma Research Trial, SMART) suggested African-American patients were at increased risk of serious respiratory-related events or deaths when using salmeterol compared with placebo (see section 5.1). It is not known if this was due to pharmacogenetic or other factors. Patients of black African or Afro-Caribbean ancestry should therefore be asked to continue treatment but to seek medical advice if asthma symptoms remained uncontrolled or worsen whilst using Serevent.

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.

There have been very rare reports of increases in blood glucose levels (see Adverse Reactions) and this should be considered when prescribing to patients with a history of diabetes mellitus.

Serevent should be administered with caution to patients with thyrotoxicosis.
Cardiovascular effects such as increases in systolic blood pressure and heart rate may occasionally be seen with all sympathomimetic drugs, especially at higher than therapeutic doses. For this reason, salmeterol should be used with caution in patients with pre-existing cardiovascular disease.

At transient decrease in serum potassium may occur with all sympathomimetic drugs at higher therapeutic doses. Therefore, salmeterol should be used with caution in patients predisposed to low levels of serum potassium.

4.5 Interaction with other medicinal products and other forms of interaction

Both non-selective and selective beta-blockers should be avoided in patients with reversible obstructive airways disease, unless there are compelling reasons for their use.

4.6 Pregnancy and lactation

In animal studies, some effects on the foetus, typical for a beta-2-agonist, occurred at exposure levels substantially

higher than those that occur with therapeutic use. Extensive experience with other beta-2-agonists has provided no evidence that such effects are relevant for women receiving clinical doses.

As yet, experience of the use of salmeterol during pregnancy is limited.
As with any medicine, use during pregnancy should be considered only if the expected benefit to the mother is greater than any possible risk to the foetus.

Plasma levels of salmeterol after inhaled therapeutic doses are negligible and therefore levels in milk should be correspondingly low. Nevertheless as there is limited experience of the use of salmeterol in nursing mothers its use in such circumstances should only be considered if the expected benefit to the mother is greater than any possible risk to the infant.

Studies in lactating animals support the view that salmeterol is likely to be secreted in only very small amounts into breast milk.

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. Common and uncommon events were generally determined from clinical trial data. The incidence of placebo was not taken into account. Very rare events were generally determined from post-marketing spontaneous data.

The following frequencies are estimated at the standard dose of 50 micrograms twice daily. Frequencies at the higher dose of 100 micrograms twice daily have also been taken to account where appropriate.

Immune system disorders:
Hypersensitivity reactions:
Uncommon: Rash.
Very rare: Anaphylactic reactions including oedema and angioedema, bronchospasm and anaphylactic shock.

Metabolism and nutrition disorders:
Very rare: Hyperglycaemia.

Nervous system disorders:
Common: Tremor and headache.

The pharmacological side effects of beta-2-agonist treatment, such as tremor and headache, have been reported, but tend to be transient and to reduce with regular therapy. Tremor occurs more commonly when administered at doses higher than 50 micrograms twice daily.

Cardiac disorders:
Common: Palpitations.

The pharmacological side-effects of beta-2-agonist treatment, subjective palpitations, have been reported, but tend to be transient and to reduce with regular therapy.

Uncommon: Tachycardia.

Tachycardia occurs more commonly when administered at doses higher than 50 micrograms twice daily.

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

Respiratory, thoracic and mediastinal disorders:
Very rare: Oropharyngeal irritation and paradoxical bronchospasm.

As with other inhalational therapy, paradoxical bronchospasm may occur with an immediate increase in wheezing after dosing. This should be treated immediately with a fast-acting inhaled bronchodilator. Serevent Inhaler should be discontinued immediately, the patient assessed, and if necessary alternative therapy instituted.

Musculoskeletal and connective tissue disorders:
Common: Muscle cramps.
Very rare: Arthralgia.

4.9 Overdose

The expected symptoms and signs of salmeterol overdosage are those typical of excessive beta-2-adrenergic stimulation, including tremor, headache, tachycardia, increases in systolic blood pressure and hypokalaemia. The preferred antidote for overdosage with Serevent Inhaler is a cardioselective beta-blocking agent. Cardioselective beta-blocking drugs should be used with caution in patients with history of bronchospasm.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action:
Salmeterol is a selective long-acting (12 hour) beta-2-adrenoceptor agonist with a long side-chain which binds to the exo-site of the receptor.

These pharmacological properties of salmeterol offer more effective protection against histamine-induced bronchoconstriction and produce a longer duration of bronchodilation, lasting for at least 12 hours, than recommended doses of conventional short-acting beta-2-agonists. *In vitro* tests have shown salmeterol is a potent and long-lasting inhibitor of the release, from human lung, of mast cell mediators, such as histamine, leukotrienes and prostaglandin D_2.
In man salmeterol inhibits the early and late phase response to inhaled allergen; the latter persisting for over 30 hours after a single dose when the bronchodilator effect is no longer evident. Single dosing with salmeterol attenuates bronchial hyper-responsiveness.

These properties indicate that Serevent has additional non-bronchodilator activity, but the full clinical significance is not yet clear. The mechanism is different from the anti-inflammatory effect of corticosteroids, which should not be stopped or reduced when Serevent is prescribed.

The Salmeterol Multi-center Asthma Research Trial (SMART):

SMART was a multi-centre, randomised, double-blind, placebo-controlled, parallel group 28-week study in the US which randomised 13,176 patients to salmeterol (50 micrograms twice daily) and 13,179 patients to placebo in addition to the patients' usual asthma therapy. Patients were enrolled if ≥ 12 years of age, with asthma and if currently using asthma medication (but not a Long Acting Beta-Agonist (LABA)). Baseline Intercostal Space (ICS) use at study entry was recorded, but not required in the study. The primary endpoint in SMART was the combined number of respiratory-related deaths and respiratory-related life-threatening experiences.

Key findings from SMART: primary endpoint

Patient group	Number of primary endpoint events/number of patients		Relative Risk (95% confidence intervals)
	salmeterol	placebo	
All patients	50/13,176	36/13,179	1.40 (0.91, 2.14)
Patients using inhaled steroids	23/6,127	19/6,138	1.21 (0.66, 2.23)
Patients not using inhaled steroids	27/7,049	17/7,041	1.60 (087, 2.93)
African-American patients	**20/2,366**	**5/2.319**	**4.10 (1.54, 10.90)**

(Risk in bold is statistically significant at the 95% level.)

Key findings from SMART by inhaled steroid use at baseline: secondary endpoints

	Number of secondary endpoint events/number of patients		Relative Risk (95% confidence intervals)
	salmeterol	placebo	
Respiratory-related death			
Patients using inhaled steroids	10/6127	5/6138	2.01 (0.69, 5.86)
Patients not using inhaled steroids	14/7049	6/7041	2.28 (0.88, 5.94)
Combined asthma-related death or life threatening experience			
Patients using inhaled steroids	16/6127	13/6138	1.24 (0.60, 2.58)
Patients not using inhaled steroids	**21/7049**	**9/7041**	**2.39 (1.10, 5.22)**
Asthma-related death			
Patients using inhaled steroids	4/6127	3/6138	1.35 (0.30, 6.04)
Patients not using inhaled steroids	9/7049	0/7041	*

(* = could not be calculated because of no events in placebo group. Risk in bold is statistically significant at the 95% level. The secondary endpoints in the table above reached statistical significance in the whole population). The secondary endpoints of combined all-cause death or life-threatening experience, all cause death, or all cause hospitalisation did not reach statistical significance in the whole population.

5.2 Pharmacokinetic properties

Salmeterol acts locally in the lung therefore plasma levels are not predictive of therapeutic effect. In addition there are only limited data available on the pharmacokinetics of salmeterol because of the technical difficulty of assaying the drug in plasma because of the very low plasma concentrations (approximately 200 pg/ml or less) achieved after inhaled dosing. After regular dosing with salmeterol xinafoate, hydroxynaphthoic acid can be detected in the systemic circulation, reaching steady state concentrations of approximately 100 ng/ml. These concentrations are up to 1000 fold lower than steady state levels observed in toxicity studies and, in long-term regular dosing (more than 12 months) in patients with airways obstruction, have been shown to produce no ill effects.

5.3 Preclinical safety data

In reproduction studies in animals, some effects on the foetus, typical of a beta-2-agonist, have been observed at very high doses.
Salmeterol xinafoate produced no genetic toxicity in a range of studies using either prokaryotic or eukaryotic cell systems *in vitro* or *in vivo* in the rat.
Long-term studies with salmeterol xinafoate, induced class related benign tumours of smooth muscle in the mesovarium of rats and the uterus of mice. The scientific literature and our own pharmacological studies provide good evidence that these effects are species specific and have no relevance for clinical use.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Soya lecithin
Dichlorodifluoromethane
Trichlorofluoromethane

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years.

6.4 Special precautions for storage

Do not store above 30°C.

Do not refrigerate or freeze. Store in the original container.

The canister contains a pressurised liquid. Do not pierce the canister.
The canister should not be broken, punctured or burnt, even when apparently empty.

As with most inhaled medications in pressurised metered-dose inhalers, the therapeutic effect of this medication may decrease when the canister is cold.

6.5 Nature and contents of container

An aluminium can closed with a metering valve. The filled canister is fitted into a polypropylene actuator to form a complete inhaler. Each inhaler is packed into a carton.

Each canister provides 60 or 120 actuations.

Not all packs 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

See Patient Information Leaflet.
Patients should be carefully instructed in the correct use of the inhaler.

7 MARKETING AUTHORISATION HOLDER

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Stonemason's Way
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Trading As: Allen & Hanburys.

8 MARKETING AUTHORISATION NUMBER

PA 1077/47/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13 October 1992

Date of last renewal: 13 October 2002

10 DATE OF REVISION OF THE TEXT

August 2006