IRISH MEDICINES BOARD ACT 1995

MEDICINAL PRODUCTS(LICENSING AND SALE)REGULATIONS, 1998

(S.I. No.142 of 1998)

PA1077/113/001
Case No: 2020328

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

Salmeterol Inhaler 25 micrograms per actuation 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 **25/08/2006** until **24/08/2011** .

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

Salmeterol Inhaler 25 micrograms per actuation pressurised inhalation suspension.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One metered dose (ex-valve) contains 25 micrograms salmeterol (as xinafoate). This is equivalent to a delivered dose (ex-actuator) of 21 micrograms salmeterol (as xinafoate).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Pressurised inhalation suspension.

White to off white suspension sealed in an aluminium canister in a green actuator.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Regular symptomatic add-on treatment of reversible airways obstruction in patients with asthma, including those with nocturnal asthma, who are inadequately controlled on inhaled corticosteroids in accordance with current treatment guidelines. Treatment of chronic obstructive pulmonary disease (COPD). Prevention of exercise-induced asthma.

4.2 Posology and method of administration

Salmeterol Inhaler is for inhalation use only.

Salmeterol Inhaler should be used regularly. The full benefits of treatment will be apparent after several doses of the medicinal product. As there may be adverse reactions associated with excessive dosing with this class of medicinal product, the dosage or frequency of administration should only be increased on medical advice.

Recommended Doses:

Asthma
Adults and adolescents 12 years and older:

Two actuations of 25 micrograms salmeterol twice daily.

In asthma patients with more severe airways obstruction up to four inhalations of 25 micrograms of salmeterol twice daily may be of benefit.

Children aged 4 years and older:

Two actuations of 25 micrograms salmeterol twice daily.

Children below 4 years of age:

Salmeterol Inhaler is not recommended for use in children below four years of age due to insufficient data on safety and efficacy.

COPD

Adults: Two actuations of 25 micrograms salmeterol twice daily.

Children: There is no relevant indication for use of Salmeterol Inhaler in children.

Special patient groups:

There is no need to adjust the dose in elderly patients or in those with renal impairment. There are no data available on the use of Salmeterol Inhaler in patients with hepatic impairment.

INSTRUCTIONS FOR USE:

Patients should be carefully instructed in the proper use of their inhaler (see Patient Information Leaflet).

1. Patients should remove the mouthpiece cover by gently squeezing the sides of the cover and check the mouthpiece inside and outside to see that it is clean.

2. Patients should shake the inhaler well. Before using for the first time or if the inhaler has not been used for a week patients should release one puff into the air to make sure that it works.

3. Patients should hold the inhaler upright between fingers and thumb with their thumb on the base, below the mouthpiece.

4. Patients should breathe out as far as is comfortable and then place the mouthpiece in their mouth between their teeth and close their lips around it. Patients should be instructed not to bite the mouthpiece.

5. Just after starting to breathe in through their mouth patients should press down on the top of the inhaler to release salmeterol while still breathing in steadily and deeply.

6. While holding their breath, patients should take the inhaler from their mouth and take their finger from the top of the inhaler. They should continue holding their breath for as long as is comfortable.

7. If patients are going to take a further puff, they should keep the inhaler upright and wait about half a minute before repeating steps 2 to 6.

8. After use patients should always replace the mouthpiece cover to keep out dust and fluff.

The mouthpiece cover is replaced by firmly pushing and snapping the cap into position.

Important:

Patients should not rush stages 4, 5 and 6. It is important that they start to breathe in as slowly as possible just before operating their inhaler.
Patients should practise in front of a mirror for the first few times. If they see "mist" coming from the top of their inhaler or the sides of their mouth they should start again from stage 2.

Salmeterol Inhaler should be used with a Volumatic spacer device by patients who find it difficult to synchronise aerosol actuation with inspiration of breath which is often the case for children and the elderly.

Cleaning:
The inhaler should be cleaned at least once a week by:

1. Removing the mouthpiece cover.
2. Wiping the inside and outside of the mouthpiece and the plastic casing with a dry cloth or tissue.
3. Replacing the mouthpiece cover.

The canister must not be removed from the plastic casing when cleaning the inhaler.

PATIENTS MUST NOT PUT THE METAL CANISTER INTO WATER.

4.3 Contraindications

Salmeterol Inhaler is contraindicated in patients with hypersensitivity to salmeterol xinafoate or to the excipient (see Section 6.1).

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.

Salmeterol 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 salmeterol.

Salmeterol should not be used to treat acute asthma symptoms for which a fast and short-acting inhaled bronchodilator is required. Patients should be advised to have their medicinal product to be used for the relief of acute asthma symptoms available at all times.

Increasing use of short-acting bronchodilators to relieve asthma symptoms indicates deterioration of asthma control. The patient should be instructed to seek medical advice if short-acting relief bronchodilator treatment becomes less effective or more inhalations than usual are required. In this situation the patient should be assessed and consideration given to the need for increased anti-inflammatory therapy (e.g. higher doses of inhaled corticosteroid or a course of oral corticosteroid). Severe exacerbations of asthma must be treated in the normal way.

Salmeterol should not be initiated in patients with significantly worsening or acutely deteriorating asthma. Sudden and progressive deterioration in control of asthma is potentially life-threatening and the patient should undergo urgent medical assessment. Consideration should be given to increasing corticosteroid therapy. Under these circumstances daily peak flow monitoring may be advisable. For maintenance treatment of asthma salmeterol should be given in combination with inhaled or oral corticosteroids. Long-acting bronchodilators should not be the only or the main treatment in maintenance asthma therapy (see Section 4.1).

Salmeterol should be administered with caution in patients with thyrotoxicosis.

There have been very rare reports of increases in blood glucose levels (see Section 4.8) and this should be considered when prescribing to patients with a history of diabetes mellitus.

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.

Potentially serious hypokalaemia may result from β_2 agonist therapy. Particular caution is advised in acute severe asthma as this effect may be potentiated by hypoxia and by concomitant treatment with xanthine derivatives, steroids and diuretics. Serum potassium levels should be monitored in such situations.

Patients should be instructed in the proper use of their inhaler and their technique checked to ensure optimum delivery of the inhaled medicinal product to the lungs.

As systemic absorption is largely through the lungs, the use of a spacer plus metered dose inhaler may vary the delivery to the lungs. It should be noted that this could potentially lead to an increase in the risk of systemic adverse effects so that dose adjustment may be necessary.

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 asthma unless there are compelling reasons for their use.

Potentially serious hypokalaemia may result from β_2 agonist therapy. Particular caution is advised in acute severe asthma as this effect may be potentiated by concomitant treatment with xanthine derivatives, steroids and diuretics.

4.6 Pregnancy and lactation

There are insufficient data on the use of salmeterol or this medicinal product during pregnancy and lactation in women to assess the possible harmful effects. In animal studies fetal abnormalities occur after administration of beta-2-adrenoreceptor agonists (see Section 5.3).

Use of Salmeterol Inhaler during pregnancy should only be considered if the expected benefit to the mother is greater than any possible risk to the fetus.

It is unknown whether salmeterol is excreted in human breast milk. Animal studies in rats have shown excretion of salmeterol in breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Salmeterol Inhaler should be made taking into account the benefit of breast-feeding to the child and the benefit of Salmeterol Inhaler therapy to the woman.

Studies of HFA-134a revealed no effects on the reproductive performance and lactation of adult or two successive generations of rats or on the fetal development of rats or rabbits.

4.7 Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Adverse reactions 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 on placebo was not taken into account. Very rare events are generally determined from post-marketing spontaneous data.

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

System Organ Class	*Adverse Reaction*	*Frequency*
Immune System Disorders	*Hypersensitivity reactions with the following manifestations:*	
	Rash (itching and redness)	*Uncommon*
	Anaphylactic reactions including oedema and angioedema, bronchospasm and anaphylactic shock	*Very Rare*
Metabolism & Nutrition Disorders	*Hypokalaemia*	*Rare*
	Hyperglycaemia	*Very Rare*
Psychiatric Disorders	*Nervousness*	*Uncommon*
	Insomnia	*Rare*
Nervous System Disorders	*Headache*	*Common*
	Tremor	*Common*
	Dizziness	*Rare*
Cardiac Disorders	*Palpitations*	*Common*
	Tachycardia	*Uncommon*
	Cardiac arrhythmias (including atrial fibrillation, supraventricular tachycardia and extrasystoles).	*Very Rare*
Respiratory, Thoracic & Mediastinal Disorders	*Oropharyngeal irritation*	*Very Rare*
	Paradoxical bronchospasm	*Very Rare*
Gastro-Intestinal Disorders	*Nausea*	*Very Rare*
Musculoskeletal & Connective Tissue Disorders	*Muscle cramps*	*Common*
	Arthralgia	*Very Rare*
General Disorders and Administration Site Conditions	*Non-specific chest pain*	*Very Rare*

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

As with other inhalational therapy paradoxical bronchospasm may occur with an immediate increase in wheezing and fall in peak expiratory flow rate (PEFR) after dosing. This should be treated immediately with a fast-acting inhaled bronchodilator. Salmeterol Inhaler should be discontinued immediately, the patient assessed, and if necessary alternative therapy instituted (see Section 4.4).

4.9 Overdose

The signs and symptoms of salmeterol overdose are tremor, headache and tachycardia. The preferred antidotes are cardioselective beta-blocking agents, which should be used with caution in patients with a history of bronchospasm

Additionally hypokalaemia can occur and therefore serum potassium levels should be monitored. Potassium replacement should be considered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Selective beta-2-adrenoreceptor agonists.

ATC Code: R03AC12

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 β_2 agonists. 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 salmeterol 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 salmeterol is prescribed.

Salmeterol has been studied in the treatment of conditions associated with COPD and has been shown to improve symptoms, pulmonary function and quality of life.

5.2 Pharmacokinetic properties

Salmeterol acts locally in the lung therefore plasma levels are not an indication of therapeutic effects. In addition there are only limited data available on the pharmacokinetics of salmeterol because of the technical difficulty of assaying the active substance in plasma due to the low plasma concentrations at therapeutic doses (approximately 200 picogram/ml or less) achieved after inhaled dosing.

5.3 Preclinical safety data

The only findings in animal studies with relevance for clinical use were the effects associated with exaggerated pharmacological activity.

In reproduction and development toxicity studies with salmeterol xinafoate there were no effects in rats. In rabbits, typical beta-2 agonist embryo fetal toxicity (cleft palate, premature opening of the eye lids, sternebral fusion and reduced ossification rate of the frontal cranial bones) occurred at high exposure levels (approximately 20 times the maximum recommended human daily dose based on the comparison of AUCs).

Salmeterol xinafoate was negative in a range of standard genotoxicity studies.

The non-CFC propellant, norflurane, has been shown to have no toxic effect 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 up to two years including no effects on the reproductive performance or embryofetal development.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Norflurane (HFA 134a), a hydrofluoroalkane (non-chlorofluorocarbon) propellant.

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years

6.4 Special precautions for storage

Do not store above 30° C.
The canister contains a pressurised liquid. Do not expose to temperatures higher than 50°C. Do not pierce the canister. Pressurised container. Do not puncture, break or burn even when apparently empty.

6.5 Nature and contents of container

The suspension is contained in an internally lacquered, 8ml aluminium alloy pressurised container sealed with a metering valve. The containers are fitted into plastic actuators incorporating an atomising mouthpiece and fitted with dustcaps. One pressurised container delivers 120 actuations.

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 (Trading as Allen & Hanburys)
Stonemasons Way
Rathfarnham
Dublin 16

8 MARKETING AUTHORISATION NUMBER

PA 1077/113/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 25th August 2006

10 DATE OF REVISION OF THE TEXT