Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Serevent Evohaler 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 the 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

Asthma
Serevent Evohaler is indicated for the regular symptomatic add-on treatment of reversible airways obstruction in patients with asthma, including those with nocturnal asthma, who are inadequately controlled on inhaled corticosteroidsin accordance with current treatment guidelines.

Serevent Evohaler is also indicated in the prevention of exercise-induced asthma.

Chronic Obstructive Pulmonary Disease (COPD)
Serevent Evohaler is indicated in the treatment of patients with COPD.

4.2 Posology and method of administration

Posology

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

COPD

Adults aged 18 years and over:
Two actuations of 25 micrograms salmeterol twice daily.

Paediatric population
There is no relevant indication for use of Serevent Evohaler in the paediatric population in the indication for COPD.

Special populations
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 Serevent Evohaler in patients with hepatic impairment.

Method of administration
Serevent Evohaler is for inhalation use only.
Serevent Evohaler 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.

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.
2. Patients should check inside and outside of the inhaler including the mouthpiece for the presence of loose objects.
3. Patients should shake the inhaler well to ensure that any loose objects are removed and that the contents of the inhaler are evenly mixed. Before using for the first time or if the inhaler has not been used for a week patients should release two puffs into the air to make sure that it works.
4. Patients should hold the inhaler upright between fingers and thumb with their thumb on the base, below the mouthpiece.
5. 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.
6. 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.
7. 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.
8. If patients are going to take a further puff, they should keep the inhaler upright and wait about half a minute before repeating steps 3 to7.
9. After use patients should always replace the mouthpiece cover to keep out dust and fluff.
10. Patients should replace the mouthpiece cover by firmly pushing and snapping the cap into position.

Important:

Patients should not rush stages 5, 6 and 7. 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.

Serevent Evohaler 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

Hypersensitivity to salmeterol xinafoate or any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

The management of asthmashould normally follow a stepwise programme.

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

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

Increasing use of short-acting bronchodilators to relieve asthma symptoms indicates deterioration of asthma control. In this case, the patient should be instructed to seek medical advice.

Although Serevent Evohaler may be introduced as add-on therapy when inhaled corticosteroids do not provide adequate control of asthma symptoms, patients should not be initiated on Serevent Evohaler 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 Evohaler. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation on Serevent Evohaler.

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).

Once asthma symptoms are controlled, consideration may be given to gradually reducing the dose of Serevent Evohaler Regular review of patients as treatment is stepped down is important. The lowest effective dose of Serevent Evohaler should be used.

Paradoxical bronchospasm
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. Serevent Evohaler should be discontinued immediately, the patient assessed, and if necessary alternative therapy instituted (see section 4.8).

The pharmacological side effects of beta-$_2$ agonist treatment, such as tremor, subjective palpitations and headache have been reported, but tend to be transient and to reduce with regular therapy (see section 4.8).

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

Thyrotoxicosis
Serevent Evohaler should be administered with caution in patients with thyrotoxicosis.

Blood glucose levels
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.

Hypokalaemia

Potentially serious hypokalaemia may result from beta$_2$ 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.

Respiratory-related events
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 Evohaler.

Ketoconazole
Concomitant use of systemic ketoconazole significantlyincreases systemicexposure to salmeterol. This may lead to an increase in the incidence of systemic effects (e.g. prolongation in the QTc interval and palpitations). Concomitant treatment with ketoconazole or other potent CYP3A4 inhibitors should therefore be avoided unless the benefits outweigh the potentially increased risk of systemic side effects of salmeterol treatment (see section 4.5).

Inhaler technique
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

Beta- adrenergic blockers may weaken or antagonise the effect of salmeterol. Both non- selective and selective beta- blockers should be avoided unless there are compelling reasons for their use.

Potentially serious hypokalaemia may result from beta$_2$ 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.

Potent CYP3A4 inhibitors
Co- administration of ketoconazole (400 mg orally once daily) and salmeterol (50 micrograms inhaled twice daily) in 15 healthy subjects for 7 days resulted in a significant increase in plasma salmeterol exposure (1.4- fold Cmax and 15-fold AUC). This may lead to an increase in the incidence of other systemic effects of salmeterol treatment (e.g. prolongation of QTc interval and palpitations) compared with salmeterol or ketoconazole treatment alone (see section 4.4).

Clinically significant effects were not seen on blood pressure, heart rate, blood glucose and blood potassium levels. Co-administration with ketoconazole did not increase the elimination half-life of salmeterol or increase salmeterol accumulation with repeat dosing.

The concomitant administration of ketoconazole should be avoided, unless the benefits outweigh the potentially increased risk of systemic side effects of salmeterol treatment. There is likely to be a similar risk of interaction with other potent CYP3A4 inhibitors (e.g. itraconazole, telithromycin, ritonavir).

Moderate CYP 3A4 inhibitors
Co-administration of erythromycin (500 mg orally three times a day) and salmeterol (50 micrograms inhaled twice daily) in 15 healthy subjects for 6 days resulted in a small but non-statistically significant increase in salmeterol exposure (1.4-fold Cmax and 1.2-fold AUC). Co-administration with erythromycin was not associated with any serious adverse effects.

4.6 Fertility, pregnancy and lactation

Pregnancy
A moderate amount of clinical data on pregnant women (between 300 to 1000 pregnancy outcomes) indicate no malformative or feto/ neonatal toxicity of salmeterol.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity with the exception of evidence of some harmful effects on the fetus at very high dose levels (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of Serevent Evohaler during pregnancy.

Breast-feeding
Available pharmacodynamic/toxicological data in animals have shown excretion of salmeterol in milk. A risk to the suckling child cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Serevent Evohaler therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for 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 foetal 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 MedDRA system organ class. The frequency of adverse reactions is defined as: very common (≥ 1/10), common (≥1/100 to <1/10), uncommon (≥1/1 000 to <1/100), rare (≥1/10, 000 to <1/1 000) 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 50 micrograms twice daily. Frequencies at the higher dose of 100 micrograms 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 and nutrition disorders	Hypokalaemia	Rare
	Hyperglycaemia	Very rare
Psychiatric disorders	Nervousness	Uncommon
	Insomnia	Rare
Nervous system disorders	Headache (see section 4.4)	Common
	Tremor (see section 4.4)	Common
	Dizziness	Rare
Cardiac disorders	Palpitations (see section 4.4)	Common
	Tachycardia	Uncommon
	Cardiac arrhythmias (including atrial fibrillation, supraventricular tachycardia and extrasystoles).	Very rare
Respiratory, thoracic and mediastinal disorders	Oropharyngeal irritation	Very rare
	Paradoxical bronchospasm (see section 4.4)	Very rare
Gastrointestinal disorders	Nausea	Very rare
Musculoskeletal and 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 50 micrograms twice daily.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; e-mail: medsafety@hpra.ie

4.9 Overdose

Symptoms and signs

The signs and symptoms of salmeterol overdose are those typical of excessive beta$_2$-adrenergic stimulation including dizziness, increases in systolic blood pressure,tremor, headache and tachycardia. Additionally hypokalaemia can occur and therefore serum potassium levels should be monitored. Potassium replacement should be considered.

Treatment
If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary. Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

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) beta2-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 beta2 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.

Asthma clinical trials

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 LABA). Baseline 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 (0.87, 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	10/6,127	5/6,138	2.01 (0.69, 5.86)
Patients not using inhaled steroids	14/7,049	6/7,041	2.28 (0.88, 5.94)
Combined asthma-related death or life-threatening experience			
Patients using inhaled steroids	16/6,127	13/6,138	1.24 (0.60, 2.58)
Patients not using inhaled steroids	**21/7,049**	**9/7,041**	**2.39 (1.10, 5.22)**
Asthma-related death			
Patients using inhaled steroids	4/6,127	3/6,138	1.35 (0.30, 6.04)
Patients not using inhaled steroids	9/7,049	0/7,041	*

(*=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 hospitalisations did not reach statistical significance in the whole population.

COPD clinical trials

TORCH study

TORCH was a 3-year study to assess the effect of treatment with Seretide Diskus 50/500 micrograms bd, salmeterol Diskus 50 micrograms bd, fluticasone propionate (FP) Diskus 500 micrograms bd or placebo on all-cause mortality in patients with COPD. COPD patients with a baseline (pre-bronchodilator) FEV1 <60% of predicted normal were randomised to double-blind medication. During the study, patients were permitted usual COPD therapy with the exception of other inhaled corticosteroids, long-acting bronchodilators and long-term systemic corticosteroids. Survival status at 3 years was determined for all patients regardless of withdrawal from study medication. The primary endpoint was reduction in all cause mortality at 3 years for Seretide vs Placebo.

	Placebo N = 1524	Salmeterol 50 N = 1521	FP 500 N = 1534	Seretide 50/500 N = 1533
All cause mortality at 3 years				
Number of deaths (%)	231 (15.2%)	205 (13.5%)	246 (16.0%)	193 (12.6%)
Hazard Ratio vs Placebo (CIs) p value	N/A	0.879 (0.73, 1.06) 0.180	1.060 (0.89, 1.27) 0.525	0.825 (0.68, 1.00) 0.052[1]
Hazard Ratio Seretide 50/500 vs components (CIs) p value	N/A	0.932 (0.77, 1.13) 0.481	0.774 (0.64, 0.93) 0.007	N/A

1. Non significant P value after adjustment for 2 interim analyses on the primary efficacy comparison from a log-rank analysis stratified by smoking status

There was a trend towards improved survival in subjects treated with Seretide compared with placebo over 3 years however this did not achieve the statistical significance level p≤0.05.
The percentage of patients who died within 3 years due to COPD-related causes was 6.0% for placebo, 6.1% for salmeterol, 6.9% for FP and 4.7% for Seretide.

The mean number of moderate to severe exacerbations per year was significantly reduced with Seretide as compared with treatment with salmeterol, FP and placebo (mean rate in the Seretide group 0.85 compared with 0.97 in the salmeterol group, 0.93 in the FP group and 1.13 in the placebo). This translates to a reduction in the rate of moderate to severe exacerbations of 25% (95% CI: 19% to 31%; p<0.001) compared with placebo, 12% compared with salmeterol (95% CI: 5% to 19%, p=0.002) and 9% compared with FP (95% CI: 1% to 16%, p=0.024). Salmeterol and FP significantly reduced exacerbation rates compared with placebo by 15% (95% CI: 7% to 22%; p<0.001) and 18% (95% CI: 11% to 24%; p<0.001) respectively.

Health Related Quality of Life, as measured by the St George's Respiratory Questionnaire (SGRQ) was improved by all active treatments in comparison with placebo. The average improvement over three years for Seretide compared with placebo was -3.1 units (95% CI: -4.1 to -2.1; p<0.001), compared with salmeterol was -2.2 units (p<0.001) and compared with FP was -1.2 units (p=0.017). A 4-unit decrease is considered clinically relevant.

The estimated 3-year probability of having pneumonia reported as an adverse event was 12.3% for placebo, 13.3% for salmeterol, 18.3% for FP and 19.6% for Seretide (Hazard ratio for Seretide vs placebo: 1.64, 95% CI: 1.33 to 2.01, p<0.001). There was no increase in pneumonia related deaths; deaths while on treatment that were adjudicated as primarily due to pneumonia were 7 for placebo, 9 for salmeterol, 13 for FP and 8 for Seretide. There was no significant difference in probability of bone fracture (5.1% placebo, 5.1% salmeterol, 5.4% FP and 6.3% Seretide; Hazard ratio for Seretide vs placebo: 1.22, 95% CI: 0.87 to 1.72, p=0.248.

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

Replace the mouthpiece cover firmly and snap it into position.

Do not store above 30° C.

Pressurised container. Do not expose to temperatures higher than 50°C. 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 and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

GlaxoSmithKline (Ireland) Limited
12 Riverwalk
Citywest Business Campus
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8 MARKETING AUTHORISATION NUMBER

PA1077/047/005

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10 DATE OF REVISION OF THE TEXT