Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Seretide 125 Evohaler 25 microgram/125 microgram/dose pressurised inhalation, suspension.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single actuation of Seretide provides:

25 micrograms of salmeterol (as salmeterol xinafoate) and 125 micrograms of fluticasone propionate (delivered from the valve). This is equivalent to 21 micrograms of salmeterol and 110 micrograms of fluticasone propionate delivered from the actuator (delivered dose).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Product imported from the UK:

Pressurised inhalation, suspension.
A moulded plastic outer with removable dust cover containing a canister. Canister contains a white to off white suspension

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Seretide is indicated in the regular treatment of asthma where use of a combination product (long-acting beta-2-agonist and inhaled corticosteroid) is appropriate:

- patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short acting beta-2-agonist

or
- patients already adequately controlled on both inhaled corticosteroid and long-acting beta-2-agonist.

4.2 Posology and method of administration

Seretide Evohaler is for inhalation use only.

Patients should be made aware that Seretide Evohaler must be used daily for optimum benefit, even when asymptomatic.

Patients should be regularly reassessed by a doctor, so that the strength of Seretide they are receiving remains optimal and is only changed on medical advice. **The dose should be titrated to the lowest dose at which effective control of symptoms is maintained. Where the control of symptoms is maintained with the lowest strength of the combination given twice daily then the next step could include a test of inhaled corticosteroid alone**. As an alternative, patients requiring a long acting beta-2-agonist could be titrated to Seretide given once daily if, in the opinion of the prescriber, it would be adequate to maintain disease control. In the event of once daily dosing when the patient has a history of nocturnal symptoms the dose should be given at night and when the patient has a history of mainly day-time symptoms the dose should be given in the morning.

Patients should be given the strength of Seretide containing the appropriate fluticasone propionate dosage for the severity of their disease. Note: Seretide 25/50 microgram strength is not appropriate in adults and children with severe asthma. Prescribers should be aware that, in patients with asthma, fluticasone propionate is as effective as other

inhaled steroids at approximately half the microgram daily dose.
For example, 100mcg of fluticasone propionate is approximately equivalent to 200mcg of beclomethasone dipropionate (CFC containing) or budesonide. If an individual patient should require dosages outside the recommended regimen, appropriate doses of beta-agonist and/or corticosteroid should be prescribed.

Recommended Doses:

Adults and adolescents 12 years and older:

Two inhalations of 25 micrograms salmeterol and 125 micrograms fluticasone propionate twice daily.

A short term trial of Seretide may be considered as initial maintenance therapy in adults or adolescents with moderate persistent asthma (defined as patients with daily symptoms, daily rescue use and moderate to severe airflow limitation) for whom rapid control of asthma is essential. In these cases, the recommended initial dose is two inhalations of 25 micrograms salmeterol and 50 micrograms fluticasone propionate twice daily. Once control of asthma is attained treatment should be reviewed and consideration given as to whether patients should be stepped down to an inhaled corticosteroid alone. Regular review of patients as treatment is stepped down is important.

A clear benefit has not been shown as compared to inhaled fluticasone propionate alone used as initial maintenance therapy when one or two of the criteria of severity are missing. In general inhaled corticosteroids remain the first line treatment for most patients. Seretide is not intended for the initial management of mild asthma. Seretide 25 micrograms/50 micrograms strength is not appropriate in adults and children with severe asthma; it is recommended to establish the appropriate dosage of inhaled corticosteroid before any fixed combination can be used in patients with severe asthma.

Children 4 years and older:

Two inhalations of 25 micrograms salmeterol and 50 micrograms fluticasone propionate twice daily.

The maximum licensed dose of fluticasone propionate delivered by Seretide inhaler in children is 100mcg twice daily.

There are no data available for use of Seretide inhaler in children aged under 4 years.

Children <12 years old may have difficulties synchronising aerosol actuation with inspiration of breath. Use of a spacer device with Seretide inhaler is recommended in patients who have, or are likely to have difficulties to coordinate actuation with inspiration. A recent clinical study has shown that paediatric patients using a spacer achieved exposure similar to adults not using spacer and paediatric patients using Accuhaler, confirming that spacers compensate for poor inhaler technique (see Section 5.2).

Either the Volumatic or AeroChamber Plus spacer device can be used (depending on National Guidance). Limited data are available that demonstrate an increase in systemic exposure when the AeroChamber Plus spacer device is used compared with the Volumatic spacer device (see section 4.4).

Patients should be instructed in the proper use and care of their inhaler and spacer and their technique checked to ensure optimum delivery of the inhaled drug to the lungs. **Patients should continue to use the same make of spacer device as switching between spacer devices can result in changes in the dose delivered to the lungs (see section 4.4).**

Re-titration to the lowest effective dose should always follow the introduction or change of a spacer device.

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 for use of Seretide in patients with hepatic impairment.

Instructions for Use:
Patients should be instructed in the proper use of their inhaler (see patient information leaflet)
During inhalation, the patient should preferably sit or stand. The inhaler has been designed for use in a vertical position.

Testing the inhaler:
Before using for the first time patients should remove the mouthpiece cover by gently squeezing the sides of the cover, shake the inhaler well, hold the inhaler between the fingers and thumb with your thumb at the base, below the mouthpiece and release puffs into the air until the counter reads 120 to make sure that it works. The inhaler should be shaken immediately before releasing each puff. If the inhaler has not been used for a week or more remove the mouthpiece cover, the patients should shake the inhaler well and release two puffs into the air. Each time the inhaler is activated the number on the counter will count down by one.

Use of the inhaler:
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.
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 mouth piece.
6. Just after starting to breathe in through their mouth, patients should press firmly down on the top of the inhaler to release Seretide, 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. Patients should continue holding their breath for as long as is comfortable.
8. To take a second inhalation, patients should keep the inhaler upright and wait about half a minute before repeating steps 3 to 7.
9. Patients should immediately replace the mouthpiece cover in the correct orientation by firmly pushing and snapping the cap into position. The cover does not require excessive force and it will click into position.

IMPORTANT
Patients should not rush stages 5, 6 and 7. It is important that patients 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.

Patients should consider getting a replacement when the counter shows the number 020. The counter will stop at 000 when all the recommended puffs have been used. Replace the inhaler when the counter reads 000.
Patients should never try to alter the numbers on the counter or detach the counter from the metal canister. The counter cannot be reset and is permanently attached to the canister.

Cleaning:

Your inhaler should be cleaned at least once a week.
1. Remove the mouth piece cover.
2. Do not remove the canister from the plastic casing.
3. Wipe the inside and outside of the mouthpiece and the plastic casing with a dry cloth or tissue.
4. Replace the mouthpiece cover in the correct orientation. The cover does not require excessive force and it will click into position.

DO NOT PUT THE METAL CONTAINER IN WATER.

4.3 Contraindications

Seretide is contraindicated in patients with hypersensitivity to any of the active substances or to the excipient.

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.

Seretide Evohaler should not be used to treat acute asthma symptoms for which a fast and short acting bronchodilator is required. Patients should be advised to have their medicinal product to be used for relief in an acute asthma attack available at all times.

Patients should not be initiated on Seretide during an exacerbation, or if they have significantly worsening or acutely deteriorating asthma.

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

Increasing use of short-acting bronchodilators to relieve asthma symptoms indicates deterioration of asthma control and patients should be reviewed by a physician.

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. The patient should also be medically reviewed where the current dosage of Seretide has failed to give adequate control of asthma. Consideration should be given to additional corticosteroid therapies.

Once asthma symptoms are controlled, consideration may be given to gradually reducing the dose of Seretide. Regular review of patients as treatment is stepped down is important. The lowest effective dose of Seretide should be used *(see section 4.2)*.

Treatment with Seretide should not be stopped abruptly.

As with all inhaled medication containing corticosteroids, Seretide should be administered with caution in patients with pulmonary tuberculosis.

Rarely, Seretide may cause cardiac arrhythmias e.g. supraventricular tachycardia, extrasystoles and atrial fibrillation, and a mild transient reduction in serum potassium at high therapeutic doses. Therefore Seretide should be used with caution in patients with severe cardiovascular disorders, heart rhythm abnormalities, diabetes mellitus, thyrotoxicosis, uncorrected hypokalaemia or patients predisposed to low levels of serum potassium.

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.

As with other inhalation therapy paradoxical bronchospasm may occur with an immediate increase in wheezing after dosing. Seretide Evohaler should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.

Care should be taken when transferring patients to Seretide therapy, particularly if there is any reason to suppose that adrenal function is impaired from previous systemic steroid therapy.

Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, decrease in bone mineral density, cataract and glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children). **It is important, therefore, that the patient is reviewed**

regularly and the dose of inhaled corticosteroid is reduced to the lowest dose at which effective control of asthma is maintained.

Prolonged treatment of patients with high doses of inhaled corticosteroids may result in adrenal suppression and acute adrenal crisis. Very rare cases of adrenal suppression and acute adrenal crisis have also been described with doses of fluticasone propionate between 500 and less than 1000mcg.
Situations, which could potentially trigger acute adrenal crisis, include trauma, surgery, infection or any rapid reduction in dosage. Presenting symptoms are typically vague and may include anorexia, abdominal pain, weight loss, tiredness, headache, nausea, vomiting, hypotension, decreased level of consciousness, hypoglycaemia, and seizures. Additional systemic corticosteroid cover should be considered during periods of stress or elective surgery.

Systemic absorption of salmeterol and fluticasone propionate is largely through the lungs. As the use of a spacer device with a metered dose inhaler may increase drug delivery to the lungs it should be noted that this could potentially lead to an increase in the risk of systemic adverse effects. Single dose pharmacokinetic data have demonstrated that the systemic exposure to salmeterol and fluticasone propionate may be increased as much as two-fold when the AeroChamber Plus spacer device is used with Seretide inhaler as compared with the Volumatic spacer device.

The benefits of inhaled fluticasone propionate therapy should minimise the need for oral steroids, but patients transferring from oral steroids may remain at risk of impaired adrenal reserve for a considerable time.
Patients who have required high dose emergency corticosteroid therapy in the past may also be at risk. This possibility of residual impairment should always be borne in mind in emergency and elective situations likely to produce stress, and appropriate corticosteroid treatment must be considered. The extent of the adrenal impairment may require specialist advice before elective procedures.

Ritonavir can greatly increase the concentration of fluticasone propionate in plasma. Therefore, concomitant use should be avoided, unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side-effects. There is also an increased risk of systemic side effects when combining fluticasone propionate with other potent CYP3A inhibitors *(see section 4.5).*

There was an increased reporting of lower respiratory tract infections (particularly pneumonia and bronchitis) in a 3 year study in patients with Chronic Obstructive Pulmonary Disease (COPD) receiving Seretide compared with placebo *(see section 4.8)* In a 3 year COPD study, older patients, patients with a lower body mass index (<25kg/m²) and patients with very severe disease (FEV1 <30% predicted) were at greatest risk of developing pneumonia regardless of treatment. Physicians should remain vigilant for the possible development of pneumonia and other lower respiratory tract infections in patients with COPD as the clinical features of such infections and exacerbation frequently overlap. If a patient with severe COPD has experienced pneumonia the treatment with Seretide should be re-evaluated.

Data from a large clinical trial (the Salmeterol Multi-Center Asthma Research Trial, SMART) suggested African-American patients were at 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 Seretide.

Concomitant use of systemic ketoconazole significantly increases systemic exposure 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).*

Paediatric Population

Children and adolescents <16years taking high doses of fluticasone propionate (typically ≥1000 microgram/day) may be at particular risk. Systemic effects may occur, particularly at high doses prescribed for long periods. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, acute adrenal crisis and growth retardation in children and adolescents and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression.

It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroid is regularly monitored. **The dose of inhaled corticosteroid should be reduced to the lowest dose at which effective control of asthma is maintained.**

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.

Concomitant use of other beta-adrenergic containing drugs can have a potentially additive effect.

Fluticasone Propionate

Under normal circumstances, low plasma concentrations of fluticasone propionate are achieved after inhaled dosing, due to extensive first pass metabolism and high systemic clearance mediated by cytochrome P450 3A4 in the gut and liver. Hence, clinically significant drug interactions mediated by fluticasone propionate are unlikely.

In an interaction study in healthy subjects with intranasal fluticasone propionate, ritonavir (a highly potent cytochrome P450 3A4 inhibitor) 100 mg b.i.d. increased the fluticasone propionate plasma concentrations several hundred fold, resulting in markedly reduced serum cortisol concentrations. Information about this interaction is lacking for inhaled fluticasone propionate, but a marked increase in fluticasone propionate plasma levels is expected. Cases of Cushing's syndrome and adrenal suppression have been reported. The combination should be avoided unless the benefit outweighs the increased risk of systemic glucocorticoid side-effects.

In a small study in healthy volunteers, the slightly less potent CYP3A inhibitor ketoconazole increased the exposure of fluticasone propionate after a single inhalation by 150%. This resulted in a greater reduction of plasma cortisol as compared with fluticasone propionate alone. Co-treatment with other potent CYP3A inhibitors, such as itraconazole, is also expected to increase the systemic fluticasone propionate exposure and the risk of systemic side-effects. Caution is recommended and long-term treatment with such drugs should if possible be avoided.

Salmeterol

Potent CYP3A4 inhibitors
Co-administration of ketoconazole (400 mg orally once daily) and salmeterol (50 mcg 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 (500mg orally three times a day) and salmeterol (50mcg 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

There are insufficient data on the use of salmeterol and fluticasone propionate during pregnancy and lactation in man to assess the possible harmful effects. In animal studies foetal abnormalities occur after administration of beta-2-adrenoreceptor agonists and glucocorticosteroids *(see section 5.3)*.

Administration of Seretide to pregnant women should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus.

The lowest effective dose of fluticasone propionate needed to maintain adequate asthma control should be used in the treatment of pregnant women.

There are no data available for human breast milk. Both salmeterol and fluticasone propionate are excreted into breast milk in rats. Administration of Seretide to women who are breastfeeding should only be considered if the expected benefit to the mother is greater than any possible risk to the child.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

As Seretide contains salmeterol and fluticasone propionate, the type and severity of adverse reactions associated with each of the compounds may be expected. There is no incidence of additional adverse events following concurrent administration of the two compounds.

Adverse events which have been associated with salmeterol/fluticasone propionate are given below, listed 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), very rare <1/1000), and not known) (cannot be estimated from the available data). Very common, common and uncommon events were derived from clinical trial data. The incidence in placebo was not taken into account. Very rare events were derived from post-marketing spontaneous data.

System Organ Class	Adverse Event	Frequency
Infections & Infestations	Candidiasis of the mouth and throat	Common
	Pneumonia	Common [1,3]
	Bronchitis	Common[1,3]
Immune System Disorders	Hypersensitivity reactions with the following manifestations:	
	Cutaneous hypersensitivity reactions	Uncommon
	Angioedema (mainly facial and oropharyngeal oedema), Respiratory symptoms (dyspnoea and/or bronchospasm), Anaphylactic reactions including anaphylactic shock	Very Rare
Endocrine Disorders	Cushing's syndrome, Cushingoid features, Adrenal suppression, Growth retardation in children and adolescents, Decreased bone mineral density,	Very Rare [4]
Metabolism & Nutrition Disorders	Hypokelaemia	Common [3]
	Hyperglycaemia	Very Rare[4]
Psychiatric Disorders	Anxiety, sleep disorders and behavioural	Very Rare

	changes, including hyperactivity and irritability (predominantly in children) Depression, aggression (predominantly in children**)**	Not Known
Nervous System Disorders	Headache Tremor	Very Common [1] Common
Eye Disorders	Cataract, Glaucoma	Very Rare[4]
Cardiac Disorders	Palpitations Tachycardia Cardiac arrhythmias (including atrial fibrillation, supraventricular tachycardia and extrasystoles).	Common Uncommon Very Rare
Respiratory, Thoracic & Mediastinal Disorders	Nasopharyngitis Throat irritation Hoarseness/dysphonia Sinusitis Paradoxical bronchospasm	Very Common [2,3] Common Common Common [1,3] Very Rare[4]
Skin and subcutaneous tissue disorders	Contusions	Common [1,3]
Musculoskeletal & Connective Tissue Disorders	Muscle cramps Traumatic fractures Arthralgia Myalgia	Common Common [1,3] Very Rare Very Rare

1. Reported commonly in placebo
2. Reported very commonly in placebo
3. Reported over 3 years in a COPD study
4. See section 4.4

Description of selected adverse reactions

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

Due to the fluticasone propionate component, hoarseness and candidiasis (thrush) of the mouth and throat can occur in some patients. Both hoarseness and incidence of candidiasis may be relieved by gargling with water after using the product. Symptomatic candidiasis can be treated with topical anti-fungal therapy whilst still continuing with the Seretide Evohaler.

Paediatric population

Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression and growth retardation in children and adolescents (see section 4.4). Children may also experience anxiety, sleep disorders and behavioural changes, including hyperactivity and irritability.

4.9 Overdose

There are no data available from clinical trials on overdose with Seretide, however data on overdose with both drugs are given below:

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. If Seretide therapy has to be withdrawn due to overdose of the beta agonist component of the drug, provision of appropriate replacement steroid therapy should be considered.
Additionally, hypokalaemia can occur and potassium replacement should be considered.

Acute: Acute inhalation of fluticasone propionate doses in excess of those recommended may lead to temporary suppression of adrenal function. This does not need emergency action as adrenal function is recovered in a few days, as verified by plasma cortisol measurements.

Chronic overdose of inhaled fluticasone propionate: Refer to *section 4.4: risk of adrenal suppression*. Monitoring of adrenal reserve may be necessary. In cases of fluticasone propionate overdose Seretide therapy may still be continued at a suitable dosage for symptom control.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Adrenergics and other anti-asthmatics.
ATC Code: R03AK06

Seretide Asthma clinical trials

A twelve month study (Gaining Optimal Asthma ControL, GOAL), in 3416 adult and adolescent patients with persistent asthma, compared the safety and efficacy of Seretide versus inhaled corticosteroid (Fluticasone Propionate) alone to determine whether the goals of asthma management were achievable. Treatment was stepped up every 12 weeks until **Total control was achieved or the highest dose of study drug was reached. GOAL showed more patients treated with Seretide achieved asthma control than patients treated with ICS alone and this control was attained at a lower corticosteroid dose
Well-Controlled asthma was achieved more rapidly with Seretide than with ICS alone. The time on treatment for 50% of subjects to achieve a first individual Well-Controlled week was 16 days for Seretide compared to 37 days for the ICS group. In the subset of steroid naive asthmatics the time to an individual Well Controlled week was 16 days in the Seretide treatment compared to 23 days following treatment with ICS.

The overall study results showed:

Percentage of Patients Attaining *Well Controlled (WC) and **Totally Controlled (TC) Asthma over 12 months				
	Salmeterol/FP		**FP**	
Pre-Study Treatment	**WC**	**TC**	**WC**	**TC**
No ICS (SABA alone)	78%	50%	70%	40%
Low dose ICS (≤500mcg BDP or equivalent/day)	75%	44%	60%	28%
Medium dose ICS (>500-1000mcg BDP or equivalent/day)	62%	29%	47%	16%
Pooled results across the 3 treatment levels	71%	41%	59%	28%

* Well controlled asthma; occasional symptoms or SABA use or less than 80% predicted lung function plus no night-time awakenings, no exacerbations and no side effects enforcing a change in therapy

** Total control of asthma; no symptoms, no SABA use, greater than or equal to 80% predicted lung function, no night-time awakenings, no exacerbations and no side effects enforcing a change in therapy
The results of this study suggest that Seretide 50/100mcg bd may be considered as initial maintenance therapy in patients with moderate persistent asthma for whom rapid control of asthma is deemed essential (see section 4.2).

A double-blind, randomised, parallel group study in 318 patients with persistent asthma aged ≥18 years evaluated the safety and tolerability of administering two inhalations twice daily (double dose) of Seretide for two weeks. The study showed that doubling the inhalations of each strength of Seretide for up to 14 days resulted in a small increase in beta-agonist-related adverse events (tremor; 1 patient [1%] vs 0, palpitations; 6 [3%] vs 1 [<1%], muscle cramps; 6[3%] vs 1 [<1%]) and a similar incidence of inhaled corticosteroid related adverse events (e.g. oral candidiasis; 6 [6%] vs 16 [8%], hoarseness; 2 [2%] vs 4 [2%]) compared to one inhalation twice daily. The small increase in beta-agonist-related adverse events should be taken into account if doubling the dose of Seretide is considered by the physician in adult patients requiring additional short-term (up to 14 days) inhaled corticosteroid therapy.

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 (50µg 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	10/6127	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 figures 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.

Mechanism of action:

Seretide contains salmeterol and fluticasone propionate which have differing modes of action.
The respective mechanisms of action of both drugs are discussed below.

Salmeterol:

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.
Salmeterol produces a longer duration of bronchodilation, lasting for at least 12 hours, than recommended doses of conventional short-acting beta-2-agonists.

Fluticasone propionate:

Fluticasone propionate given by inhalation at recommended doses has a glucocorticoid anti-inflammatory action within the lungs, resulting in reduced symptoms and exacerbations of asthma, with less adverse effects than when corticosteroids are administered systemically.

5.2 Pharmacokinetic properties

When salmeterol and fluticasone propionate were administered in combination by the inhaled route, the pharmacokinetics of each component were similar to those observed when the drugs were administered separately. For pharmacokinetic purposes therefore each component can be considered separately.

Salmeterol:

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 drug in plasma due to the low plasma concentrations at therapeutic doses (approximately 200 picogram/ml or less) achieved after inhaled dosing.

Fluticasone propionate:

The absolute bioavailability of a single dose of inhaled fluticasone propionate in healthy subjects varies between approximately 5-11% of the nominal dose depending on the inhalation device used. In patients with asthma a lesser degree of systemic exposure to inhaled fluticasone propionate has been observed.

Systemic absorption occurs mainly through the lungs and is initially rapid then prolonged. The remainder of the inhaled dose may be swallowed but contributes minimally to systemic exposure due to the low aqueous solubility and pre-systemic metabolism, resulting in oral availability of less than 1%. There is a linear increase in systemic exposure with increasing inhaled dose.

The disposition of fluticasone propionate is characterised by high plasma clearance (1150ml/min), a large volume of distribution at steady-state (approximately 300l) and a terminal half-life of approximately 8 hours.
Plasma protein binding is 91%.

Fluticasone propionate is cleared very rapidly from the systemic circulation. The main pathway is metabolism to an inactive carboxylic acid metabolite, by the cytochrome P450 enzyme CYP3A4. Other unidentified metabolites are also found in the faeces.
The renal clearance of fluticasone propionate is negligible. Less than 5% of the dose is excreted in urine, mainly as metabolites. The main part of the dose is excreted as faeces as metabolites and unchanged drug.

Paediatric population

The effect of 21 days of treatment with Seretide Inhaler 25/50mcg (2 inhalations twice daily with or without a spacer) or Seretide Accuhaler 50/100mcg (1 inhalation twice daily) was evaluated in 31 children aged 4 to 11 years with mild asthma. Systemic exposure to fluticasone propionate was similar for Seretide Inhaler with spacer (107pg hr/mL [95% CI: 45.7, 252.2]) and Seretide Accuhaler (138pg hr/mL [95% CI: 69.3, 273.2]), but lower for Seretide Inhaler (24pg hr/mL [95% CI: 9.6, 60.2]). Systemic exposure to salmeterol was similar for Seretide Inhaler, Seretide Inhaler with spacer, and Seretide Accuhaler (126 pg hr/mL [95% CI: 70, 225], 103 pg hr/mL [95% CI: 54, 200], and 110 pg hr/mL [95% CI: 55, 219], respectively).

5.3 Preclinical safety data

The only safety concerns for human use derived from animal studies of salmeterol xinafoate and fluticasone propionate given separately were effects associated with exaggerated pharmacological actions.

In animal reproduction studies, glucocorticosteroids have been shown to induce malformations (cleft palate, skeletal malformations). However, these animal experimental results do not seem to be relevant for man given recommended doses. Animal studies with salmeterol xinafoate have shown embryofoetal toxicity only at high exposure levels. Following co-administration, increased incidences of transposed umbilical artery and incomplete ossification of occipital bone were found in rats at doses associated with known glucocorticoid-induced abnormalities.
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 two years.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Norflurane (HFA 134a)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The shelf life expiry date of this product shall be the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Replace the mouthpiece cover firmly and snap it into position.
The canister contains a pressurised liquid. Do not store above 25° C. The container should not be punctured, broken or burnt even when apparently empty.
As with most inhaled medical products in pressurised containers, the therapeutic effect of this medicinal product may decrease when the container is cold.

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. The canister has a counter attached to it, which shows how many actuations of medicine are left. The number will show through a window in the back of the plastic actuator. One pressurised container delivers 120 actuations.
The device is available in a cardboard container, which holds: 1 x 120 actuations inhaler

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 PARALLEL PRODUCT AUTHORISATION HOLDER

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8 PARALLEL PRODUCT AUTHORISATION NUMBER

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15th of October 2010

10 DATE OF REVISION OF THE TEXT

May 2012