Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Seretide 100 Diskus 50 microgram/100 microgram/dose inhalation powder, pre-dispensed

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single dose of Seretide contains 50 micrograms of salmeterol (as salmeterol xinafoate) and 100 micrograms of fluticasone propionate per actuation.

Excipients: Contains lactose monohydrate

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Inhalation powder, pre-dispensed

Imported product from UK:
A fine white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Asthma

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.

Note: Seretide 50 microgram/100 microgram strength is not appropriate in adults and children with severe asthma.

Chronic Obstructive Pulmonary Disease (COPD)

Seretide is indicated for the symptomatic treatment of patients with COPD, with a FEV_1 <60% predicted normal (pre-bronchodilator) and a history of repeated exacerbations, who have significant symptoms despite regular bronchodilator therapy.

4.2 Posology and method of administration

Seretide Diskus is for inhalation use only.
Patients should be made aware that Seretide Diskus 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. 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:

Asthma

Adults and adolescents 12 years and older:

One inhalation of 50 micrograms salmeterol and 100 micrograms fluticasone propionate twice daily.
or
One inhalation of 50 micrograms salmeterol and 250 micrograms fluticasone propionate twice daily.
or
One inhalation of 50 micrograms salmeterol and 500 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 one inhalation of 50 micrograms salmeterol and 100 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 50 microgram/100 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:

One inhalation of 50 micrograms salmeterol and 100 micrograms fluticasone propionate twice daily.

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

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

COPD

Adults:

One inhalation of 50 micrograms salmeterol and 500 micrograms fluticasone propionate twice daily.

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.

Using the Diskus:

The device is opened and primed by sliding the lever. The mouthpiece is then placed in the mouth and the lips closed round it. The dose can then be inhaled and the device closed.

4.3 Contraindications

Seretide is contraindicated in patients with hypersensitivity (allergy) to any of the active substances 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.

Seretide Diskus 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 symptoms indicates deterioration of 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.

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).

For patients with asthma or COPD, consideration should be given to additional corticosteroid therapies.

Treatment with Seretide should not be stopped abruptly in patients with asthma due to risk of exacerbation. Therapy should be down-titrated under physician supervision. For patients with COPD cessation of therapy may also be associated with symptomatic decompensation and should be supervised by a physician.

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 Diskus should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.

Seretide contains lactose up to 12.5 milligram /dose. This amount does not normally cause problems in lactose intolerant people.

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 prolonged 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.

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 the TORCH study in patients with COPD receiving Seretide 50/500 micrograms bd compared with placebo as well as in studies SCO40043 and SCO1000250 comparing the lower non-approved COPD dose of Seretide, 50/250 micrograms bd, to salmeterol 50 micrograms bd only (see section 4.8 and section 5.1). A similar incidence of pneumonia in the Seretide group was seen across all studies. In TORCH, older patients, patients with a lower body mass index ($<25 kg/m^2$) and patients with very severe disease (FEV_1<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 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 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 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), rare (≥1/10,000 to <1/1000), and very rare (<1/10,000) and not known (cannot be estimated from the available date). 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 Pneumonia Bronchitis	Common Common[1,3,5] Common[1,3]
Immune System Disorders	Hypersensitivity reactions with the following manifestations: Cutaneous hypersensitivity reactions Angioedema (mainly facial and oropharyngeal oedema), Respiratory symptoms	 Uncommon Very Rare

	(dyspnoea and/or bronchospasm), Anaphylactic reactions including anaphylactic shock	
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	Hypokalaemia Hyperglycaemia	Common[3] Very Rare[4]
Psychiatric Disorders	Anxiety, sleep disorders and behavioural changes, including hyperactivity and irritability (predominantly in children) Depression, aggression (predominantly in children)	Very Rare 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	Common

	Traumatic fractures	Common[1,3]
	Arthralgia	Very Rare
	Myalgia	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

5. See section 5.1.

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 Diskus.

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				
Pre-Study Treatment	**Salmeterol/FP**		**FP**	
	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.

Seretide COPD clinical trials

TORCH was a 3-year study to assess the effect of treatment with Seretide Diskus 50/500mcg bd, salmeterol Diskus 50 mcg bd, fluticasone propionate (FP) Diskus 500 mcg bd or placebo on all-cause mortality in patients with COPD. COPD patients with a baseline (pre−bronchodilator) FEV_1 <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 $p \leq 0.05$.

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, $p=0.248$.
Placebo-controlled clinical trials, over 6 and 12 months, have shown that regular use of Seretide 50/500 micrograms improves lung function and reduces breathlessness and the use of relief medication.

Studies SCO40043 and SCO100250 were randomised, double-blind, parallel-group, replicate studies comparing the effect of Seretide 50/250 micrograms bd (a dose not licensed for COPD treatment in the European Union) with salmeterol 50 micrograms bd on the annual rate of moderate/severe exacerbations in subjects with COPD with FEV1 less than 50% predicted and a history of exacerbations. Moderate/ severe exacerbations were defined as worsening symptoms that required treatment with oral corticosteroids and/or antibiotics or in patient hospitalisation.

The trials had a 4 week run-in period during which all subjects received open-label salmeterol/ FP 50/250 to standardize COPD pharmacotherapy and stabilise disease prior to randomisation to blinded study medication for 52 weeks. Subjects were randomised 1:1 to salmeterol/ FP 50/250 (total ITT n=776) or salmeterol (total ITT n=778). Prior to run-in, subjects discontinued use of previous COPD medications except short-acting bronchodilators. The use of concurrent inhaled long-acting bronchodilators (beta2-agonist and anticholinergic), ipratropium/salbutamol combination products, oral beta2-agonists, and theophylline preparations were not allowed during the treatment period. Oral corticosteroids and antibiotics were allowed for the acute treatment of COPD exacerbations with specific guidelines for use. Subjects used salbutamol on an as-needed basis throughout the studies.

The results of both studies showed that treatment with Seretide 50/250 resulted in a significantly lower annual rate of moderate/severe COPD exacerbations compared with salmeterol (SCO40043: 1.06 and 1.53 per subject per year, respectively, rate ratio of 0.70, 95% CI: 0.58 to 0.83, $p<0.001$; SCO100250: 1.10 and 1.59 per subject per year, respectively, rate ratio of 0.70, 95% CI: 0.58 to 0.83, $p<0.001$). Findings for the secondary efficacy measures (time to first moderate/severe exacerbation, the annual rate of exacerbations requiring oral corticosteroids, and pre-dose morning (AM) FEV1) significantly favoured Seretide 50/250 micrograms bd over salmeterol. Adverse event profiles were similar with the exception of a higher incidence of pneumonias and known local side effects (candidiasis and dysphonia) in the Seretide 50/250 micrograms bd group compared with salmeterol. Pneumonia-related events were reported for 55 (7%) subjects in the Seretide 50/250 micrograms bd group and 25 (3%) in the salmeterol group.

The increased incidence of reported pneumonia with Seretide 50/250 micrograms bd appears to be of similar magnitude to the incidence reported following treatment with Seretide 50/500 micrograms bd in TORCH.

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, without the adverse effects observed 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 or COPD 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 (1150 ml/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 in faeces as metabolites and unchanged drug.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate (which contains milk proteins)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The shelf life expiry date of this product is the date shown on the moulded plastic device and the outer carton of the product as marketed in the country of origin.

6.4 Special precautions for storage

Do not store above 30°C

6.5 Nature and contents of container

The inhalation powder is contained in blisters held on a formed PVC coated base, with a peelable foil laminate lid. The strip is contained in a moulded plastic device.

The plastic devices are available in overlabelled cardboard containers, which hold
1 x 60 dose Diskus

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

The Diskus releases a powder which is inhaled into the lungs. A dose indicator on the Diskus indicates the number of doses left. For detailed instructions for use see the Patient Information Leaflet.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

G & A Licensing Ltd
Ballymurray
Co. Roscommon

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 1447/87/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19th November 2010

10 DATE OF REVISION OF THE TEXT

January 2012