

PRODUCT INFORMATION

SERETIDE[®] ACCUHALER[®] AND MDI

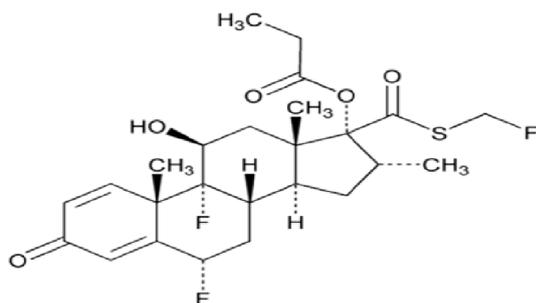
NAME OF THE MEDICINE

Fluticasone propionate/ Salmeterol xinafoate

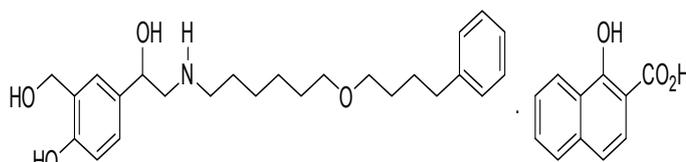
The chemical name of fluticasone propionate is S-Fluoromethyl 6 α , 9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -propionyloxy-androsta-1, 4-diene-17 β -carbothioate. It has a molecular formula of C₂₅H₃₁F₃O₅S and a molecular weight of 500.6.

The chemical name of salmeterol xinafoate is (\pm)-4-Hydroxy- α ¹-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-*m*-xylene- α,α' -diol 1-hydroxy-2-naphthoate (salt). It has a molecular formula of C₂₅H₃₇NO₄·C₁₁H₈O₃ and a molecular weight of 603.8.

The structural formula of fluticasone propionate is:



The structural formula of salmeterol xinafoate is:



CAS Registry Number:

Fluticasone propionate: 80474-14-2

Salmeterol xinafoate: 94749-08-3

DESCRIPTION

Seretide Accuhaler and Seretide Metered Dose Inhaler (MDI) contain the active ingredients fluticasone propionate and salmeterol (as xinafoate).

Fluticasone propionate is a white to off-white powder. It is freely soluble in dimethyl sulfoxide and dimethylformamide, sparingly soluble in acetone, dichloromethane, ethyl acetate and chloroform, slightly soluble in methanol and 95% ethanol, and practically insoluble in water.

Salmeterol xinafoate is a white to off-white crystalline powder. It is freely soluble in methanol, slightly soluble in ethanol, chloroform, and isopropanol, and sparingly soluble in water.

Seretide Accuhaler also contains the excipient lactose (which contains milk protein).

Seretide Metered Dose Inhaler (MDI) also contains the excipient norflurane (HFA 134a) which is a CFC-free propellant.

PHARMACOLOGY

Seretide contains fluticasone propionate and salmeterol xinafoate which have differing modes of action. Salmeterol provides symptomatic relief, while fluticasone propionate improves lung function and prevents exacerbations of the condition. Seretide can offer a more convenient regimen for patients on concurrent long-acting beta-agonist and inhaled corticosteroid therapy. The respective mechanisms of action of both drugs are discussed below.

Fluticasone propionate:

Fluticasone propionate given by inhalation at recommended doses has potent glucocorticoid activity in the airway. The potent anti-inflammatory action improves the symptomatic control of asthma, allows reduction of other drugs, such as rescue bronchodilators, and may limit the risk of decline in lung function over time. The low systemic bioavailability of fluticasone propionate provides a better risk: benefit outcome without the adverse effects that accompany systemically administered corticosteroids.

Salmeterol:

Salmeterol is a selective long-acting beta-2-adrenoceptor agonist and at dosages of less than 100 microgram twice daily has little measurable cardiovascular effect. Salmeterol xinafoate is a racemate, the R-enantiomer being active.

The pharmacological properties of salmeterol offer a slower onset of action, but more effective protection against histamine-induced bronchoconstriction and a longer duration of bronchodilation (lasting for approximately 12 hours) than recommended doses of conventional short-acting beta-2 agonists. The onset of effective bronchodilation (> 15% improvement in FEV₁) occurs within 10 to 30 minutes and peak effect occurs between 3 to 4 hours.

In vitro tests have shown salmeterol is a potent and long-lasting inhibitor of the release of mast cell mediators, such as histamine, leukotrienes and prostaglandin D₂, from human lung fragments. In one study 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 hyperresponsiveness. 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.

Pharmacokinetics

There is no evidence in animal or human subjects that the administration of fluticasone propionate and salmeterol together by the inhaled route affects the pharmacokinetics of either component. For pharmacokinetic purposes therefore each component can be considered separately.

Even though plasma levels of Seretide are very low, potential interactions with other substrates and inhibitors of CYP 3A4 cannot be excluded.

Fluticasone propionate:

Following oral administration 87-100% of the dose is excreted in the faeces, up to 75% as parent compound depending on the dose. There is a non-active major metabolite. Following intravenous administration there is rapid plasma clearance suggestive of extensive hepatic extraction. The plasma elimination half-life is approximately 3 hours. The volume of distribution is approximately 250 litres. Doses delivered by the dry powder inhalers and metered-dose inhalers may not have the same systemic bioavailability; however, there is no difference in clinical efficacy between the inhalers in controlled studies.

The absolute bioavailability of fluticasone propionate for each of the available inhaler devices has been estimated from within and between study comparisons of inhaled and intravenous pharmacokinetic data based on AUC(0-infinity) data. In healthy adult subjects the absolute bioavailability has been estimated for fluticasone propionate Accuhaler (8%), fluticasone propionate Diskhaler (9%) and fluticasone propionate Inhaler (10.9%) respectively. The absolute bioavailability from Seretide Accuhaler and Inhaler are approximately 6%.

Salmeterol:

Salmeterol acts locally in the lung, therefore plasma levels are not predictive of therapeutic effect. In addition there are only limited data available on the pharmacokinetics of salmeterol because of the technical difficulty of assaying very low plasma concentrations (approximately 200 pg/mL or less) of the drug after inhaled dosing.

Following administration, salmeterol xinafoate is extensively bound (95-98%) to plasma proteins. Elimination of radioactivity from plasma following oral administration of radiolabelled salmeterol xinafoate is slow (mean $t_{1/2}$ is 67 hours). Excretion is predominantly through the faeces and to a lesser extent urine. Aliphatic hydroxylation appears to be the major route of metabolism in humans.

After regular dosing with salmeterol xinafoate, the xinafoate moiety, hydroxynaphthoic acid, can be detected in the systemic circulation, reaching steady state concentrations of approximately 100 ng/mL. These concentrations are up to 1000-fold lower than steady state levels observed in toxicity studies and in longer-term regular dosing (more than 12 months) trials in patients with airways obstruction, there have not been adverse effects attributable to hydroxynaphthoic acid reported.

In a placebo-controlled, crossover drug interaction study in 20 healthy subjects, co-administration of salmeterol (50 micrograms twice daily inhaled) and the CYP3A4 inhibitor ketoconazole (400 mg once daily orally) for 7 days resulted in a significant increase in plasma salmeterol exposure (1.4-fold C_{max} and 15-fold AUC). There was no increase in salmeterol accumulation with repeat dosing. Three subjects were withdrawn from salmeterol and ketoconazole co-administration due to QTc prolongation or palpitations with sinus tachycardia. The increase in the QTc interval observed with the co-administration of salmeterol and ketoconazole compared with salmeterol and placebo administration was not statistically significant. There were no clinically significant effects seen in heart rate or blood potassium levels, which were the primary endpoints of the study (see **PRECAUTIONS** and **INTERACTIONS WITH OTHER MEDICINES**).

CLINICAL TRIALS

Asthma

Seretide Accuhaler

Clinical trials have investigated the safety and efficacy data of fluticasone propionate/salmeterol (Seretide) at three dose strengths (100/50 micrograms, 250/50 micrograms and 500/50 micrograms) in the treatment of patients with reversible obstructive airways disease and asthma. Six studies of 12 or 28 week duration have been carried out in a total of 2080 patients (1671 adults, 152 adolescents and 257 children), of which 769 were treated with Seretide.

Three studies used the 100/50 micrograms dose strength (338 patients), two the 250/50 micrograms dose strength (264 patients) and one the 500/50 micrograms dose strength (167 patients). All studies were of double blind, randomised, parallel group design, and aimed to demonstrate superiority of the combination product over its constituent drugs at each dose

strength, or equivalence of the combination product compared to the two drugs taken concurrently from separate inhalers (concurrent therapy).

Seretide vs. salmeterol alone or fluticasone propionate alone:

In two studies using the 100/50 micrograms and 250/50 micrograms doses, the primary efficacy variables were probability of remaining in the study, mean change from baseline in morning pre-dose FEV₁ at endpoint, and mean serial FEV₁ AUC at Week 1. Patients were symptomatic and demonstrated room for improvement in lung function. Seretide was significantly more effective (p<0.001) than placebo or salmeterol alone in all primary efficacy comparisons. In addition Seretide was significantly more effective than fluticasone propionate alone in all primary efficacy comparisons (p≤0.007) except for probability of remaining in the study for the 100/50 micrograms dose (p=0.084). Effects of Seretide were maintained over the treatment period. FEV₁ results measured over 12 hours after 1 week of treatment or after 12 weeks of treatment were similar but higher than those seen after the first dose of Seretide. Seretide produced clinically significant improvements in quality of life (>0.5 as assessed by the Asthma Quality of Life Questionnaire) in both studies.

In a third study, Seretide 500/50 micrograms was significantly more effective than fluticasone propionate alone (p<0.001). Higher mean changes in morning PEF were seen in the Seretide group for Weeks 1-12 (95% confidence intervals for the treatment difference were -29 L/min to -12 L/min). As well as the marked improvements in lung function seen with Seretide, reductions in rescue salbutamol use and an increase in the percentage of symptom-free days were seen. Significant differences compared with placebo and with salmeterol alone or fluticasone propionate alone were seen in most of these parameters. Improvements were noted over the first week of dosing.

Seretide vs. concurrent therapy:

Four double-blind, double-dummy studies assessed clinical equivalence of Seretide with concurrent therapy with salmeterol and fluticasone propionate. Three were conducted in symptomatic adults and adolescents and one in paediatric patients.

In all studies, large increases in mean morning PEF were seen over Weeks 1-12 in both treatment groups. Improvements were already apparent over Week 1.

Results for the primary efficacy variable (mean morning PEF over Weeks 1-12 in the Intent-to-Treat Population) met the criterion for clinical equivalence (90% confidence limits for the difference between treatments contained within ±15 L/min) in three of the four studies. In one study, the data suggested Seretide had slightly greater efficacy compared to concurrent administration of salmeterol and fluticasone propionate (difference -9 L/min; 90% confidence limits -17, 0 L/min; 95% confidence limits -19, 2 L/min).

Both Seretide and concurrent therapy improved symptom scores, decreased rescue salbutamol usage and increased the percentage of symptom free days and nights. Effects of the two treatments appeared to be similar on these parameters with statistical comparisons generally showing no clinically relevant differences between treatments.

Clinic measures of FEV₁ were made at each clinic visit. Improvements seen at 2 weeks were similar to those seen after 12 weeks treatment. In a 28-week study, efficacy, as measured by FEV₁, was maintained throughout the duration of treatment. Results were not dependent on the type of pre-study corticosteroid used.

Seretide MDI

Two 12 week, double blind, double dummy, randomised, parallel group clinical studies were performed in 1006 adult and adolescent patients aged ≥ 12 years. The first study compared the 50/25 micrograms strength fluticasone propionate/salmeterol metered dose inhaler (MDI);

165 patients) with the corresponding 100/50 micrograms Accuhaler (167 patients), while the second study compared the 250/25 micrograms strength MDI (176 patients) with the 500/50 micrograms Accuhaler (161 patients). The dosing regimen for the MDI is two inhalations twice daily whilst the Accuhaler is one inhalation twice daily, ensuring the total daily dose of each active ingredient is the same for both formulations. Both studies also included a comparison with CFC fluticasone propionate MDI alone, at the same fluticasone propionate dose as the combination, to reaffirm the superiority of the combination over fluticasone propionate alone despite the change in formulation. All patients had reversible obstructive airways disease and were symptomatic on inhaled corticosteroids, with room for improvement in lung function. No clinical trial was performed with the 125/25 micrograms MDI strength because pharmaceutical and clinical pharmacology data have demonstrated dose proportionality across the three strengths of the fluticasone propionate component.

The primary efficacy variable was change in mean morning PEF over weeks 1-12, and this met the criterion for clinical equivalence between the MDI and Accuhaler combination formulations (95% confidence limits for the difference between treatments contained within ± 15 L/min) in both studies. Comparable results were also seen for other time points in both studies, with almost all 95% confidence intervals falling within ± 15 L/min. In no cases were the confidence intervals greater than ± 16 L/min. Large increases in mean PEF were seen over weeks 1-12 in both the MDI and the Accuhaler combination groups.

In both studies, fluticasone propionate/salmeterol MDI was significantly more effective than fluticasone propionate MDI alone in change from baseline in mean morning PEF throughout the treatment period. This was manifest as early as week 1 ($p < 0.001$). Mean treatment differences were greater than 15 L/min. These results demonstrate clinical superiority of the MDI combination over the FP CFC formulation alone, reaffirming the superiority of the combination over fluticasone propionate alone, despite the change in formulation. While a statistical comparison of fluticasone/salmeterol Accuhaler was not conducted, the differences between these 2 treatment groups were of similar magnitude to those observed for the combination MDI.

Both the Seretide MDI and Accuhaler formulations improved symptoms scores, decreased rescue salbutamol usage and increased the percentage of symptom free days and nights. Effects of the two treatments on these parameters were similar.

Initial Maintenance Therapy – Moderate Persistent Asthma

Moderate persistent asthma is characterised by daily symptoms over a prolonged period of time or nocturnal asthma more than once a week, a peak expiratory flow rate (PEFR) or FEV₁ of 60-80% of predicted and a variability in PEFR or FEV₁ of $> 30\%$.

Seretide 100/50 micrograms vs FP 100 micrograms bd

The data of four randomised, double blind, controlled, parallel group studies, SAS30001 (n=168), SAS30003 (n=86), SAS30017 (n=150) and SAM40027 Stratum 1 Addendum (n=404) were integrated to examine the safety and efficacy of Seretide 100/50 micrograms bd as initial maintenance therapy over a 12 week treatment period in subjects aged ≥ 12 years with moderate persistent asthma. The results showed that the mean improvement from baseline in morning pre-dose PEF over Weeks 1-12 and Endpoint (primary endpoint – defined as the mean of the last available 7 days of on-treatment data for each subject) were significantly higher with Seretide 100/50 micrograms bd than with FP 100 micrograms bd (treatment difference vs FP: 23.8 L/min and 24.0 L/min respectively, $p < 0.001$).

Seretide was also superior for the secondary endpoints, including pre-dose FEV₁; serial FEV₁; % of days with no asthma symptoms; % of nights with no awakenings; and % of rescue free

days. Additionally, a higher proportion of patients achieved 'Well controlled' asthma over Weeks 5-12 with Seretide 100/50 micrograms bd vs FP 100 micrograms bd (46% vs 29%, respectively, odds ratio 2.04 in favour of Seretide, $p < 0.001$).

This integrated analysis demonstrated both statistical and clinical superiority of Seretide 100/50 micrograms bd compared with FP 100 micrograms bd in improving lung function, reducing symptoms and attaining asthma control.

Furthermore, one of the key studies, SAM40027 Stratum 1 Addendum, demonstrated that initial maintenance therapy with Seretide brought about significantly more rapid asthma control compared with FP alone. Specifically, this study showed that in the first twelve weeks of treatment, the time taken for 50% of subjects to achieve the first week of 'Well-controlled' asthma was 16 days for Seretide 100/50 micrograms bd, compared to 30 days with FP 100 micrograms bd alone ($p = 0.003$).

Subgroup analyses: Additional subgroup analyses were undertaken of all Seretide 100/50 micrograms bd studies in the target population to explore/further define patients who were likely to benefit most from treatment with Seretide as initial maintenance therapy. The greatest incremental benefit in the percentage of subjects with 'well-controlled' asthma on Seretide versus FP alone was demonstrated in subjects exhibiting all three clinical features: daily symptoms, daily use of rescue medication, moderate/severe airflow limitation (ie. $FEV_1 \leq 80\%$). In this population, 43% of subjects on Seretide achieved 'well controlled' asthma as compared with 23% on FP alone over the first 12 weeks of treatment. This represents a 2.6-fold difference (95% confidence interval: 1.87, 3.62) in favour of Seretide, and is a greater margin of difference than previously demonstrated in the overall data (integrated data: odds ratio 2.04).

In patients with all three stated baseline features, significant treatment differences were seen between Seretide and FP alone for PEF, symptoms and rescue use. Improvement in PEF was 26 L/min greater with Seretide than with FP alone (95% CI 19.3, 32.6) and patients treated with Seretide were twice as likely to be symptom-free than patients treated with FP alone over the first 12 weeks of treatment (odds ratio Seretide/FP 2.05, 95% CI 1.54, 2.74, $p < 0.001$). Likewise, the Seretide group had significantly more rescue-free days compared with FP alone ($p < 0.001$).

Additionally in this group of patients the time to first achieving 'well controlled' asthma was significantly shorter with Seretide compared with FP alone (median time to first week of 'well controlled' asthma was 9 days for Seretide and 16 days for FP, $p < 0.001$).

Dosage adjustment with Seretide vs FP

Two studies, SAS30040 ($n = 484$) and SAM40027 Stratum 1 Addendum ($n = 404$) demonstrated Seretide to be a superior option to FP alone in two situations, (i) dosing step-down once control has been achieved with Seretide and (ii) dosing step-up where the patient failed to achieve control with the initial doses of medication.

For patients who have achieved control with a maintenance dose of Seretide 250/50 micrograms bd, SAS30040 demonstrated that stepping down the dose to Seretide 100/50 micrograms bd is more effective than removing the LABA component, and switching patients to FP 250 μ g bd. This study showed PEF values to be maintained over 12 weeks after stepping down to Seretide 100/50 micrograms, but a decline in PEF values was noted with FP 250 micrograms during the same period (treatment difference of 12.9 L/min in favour of Seretide, $p < 0.001$).

For patients in whom control was not achieved with an initial dose of Seretide or FP as initial maintenance therapy, SAM40027 Stratum 1 Addendum demonstrated the benefits of dosing

step-up with Seretide compared with FP alone. The study confirmed that subjects in the Seretide group had 1.67 greater chance of achieving 'Well-controlled' asthma at the same or lower ICS doses compared to FP alone (odds ratio 1.67, p=0.006). The fact that more patients were achieving control at the earlier treatment steps with Seretide indicated that, overall, control was achieved earlier in the study with Seretide than with FP alone, highlighting the time superiority of the combination.

Chronic Obstructive Pulmonary Disease (COPD)

Three randomised, double blind, placebo-controlled trials have investigated the safety and efficacy of Seretide Accuhaler in the treatment of patients with COPD. The studies used two Seretide dose strengths (250/50 micrograms and 500/50 micrograms). All studies comprised four treatment arms: Seretide, salmeterol, fluticasone propionate, placebo. Salmeterol is currently registered for the treatment of COPD.

Seretide vs salmeterol alone: The primary efficacy variable for the three studies was mean change in morning pre-dose FEV₁. In the ITT analysis, a statistically significant difference in the primary endpoint in favour of Seretide was seen across all three studies. For multiple measured secondary endpoints, Seretide 500/50 micrograms was superior by a clinically significant degree only for dyspnoea vs salmeterol alone. In addition, Seretide 250/50 micrograms was statistically significantly superior to salmeterol for % days without use of reliever medication and % of nights without awakening.

Post-hoc subgroup analyses were performed for those patients with severe COPD (FEV₁<50% predicted normal). There were 1724 patients in the severe subgroup, of whom 415 received Seretide. A statistically significant treatment difference in favour of Seretide (both doses) was seen in the primary endpoint in two of the three studies. The clinical significance of these results is uncertain. For multiple measured secondary endpoints, Seretide 500/50 micrograms produced a clinically significant improvement in breathlessness and a clinically significant reduction in % of days without use of reliever medication (1 time per day) compared with salmeterol alone.

INDICATIONS

For the regular treatment of asthma, where the use of a combination product is appropriate. This may include:

- Patients on effective maintenance doses of long-acting beta-2 agonists and inhaled corticosteroids
- Patients who are symptomatic on current inhaled corticosteroid therapy
- Initiation of maintenance therapy in those patients with moderate persistent asthma not adequately controlled on 'as needed' reliever medication, and who have moderate/severe airway limitation and daily symptoms requiring reliever medication every day (see **CLINICAL TRIALS**).

For the symptomatic treatment of patients with severe COPD (FEV₁<50% predicted normal) and a history of repeated exacerbations who have significant symptoms despite regular beta-2 agonist bronchodilator therapy. Seretide is not indicated for the initiation of bronchodilator therapy in COPD.

CONTRAINDICATIONS

Seretide is contraindicated in patients with a history of hypersensitivity to any ingredients of the preparation (see **DESCRIPTION**).

PRECAUTIONS

The management of asthma should normally follow a stepwise program and patient response should be monitored clinically and by lung function tests. Treatment of asthma should be in accordance with current National asthma treatment guidelines.

Seretide is not for relief of acute symptoms for which a fast- and short-acting inhaled bronchodilator (e.g. salbutamol) is required. Patients should be advised to have their relief medication available at all times.

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 be reviewed by a physician. Consideration should be given to increasing corticosteroid therapy. Also, where the current dosage of Seretide has failed to give adequate control of asthma, the patient should be reviewed by a physician. For patients with asthma or COPD, consideration should be given to additional corticosteroid therapies and administration of antibiotics if an exacerbation is associated with infection.

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

There was an increased reporting of pneumonia in studies of patients with COPD receiving Seretide (see **ADVERSE EFFECTS**). Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of pneumonia and exacerbation frequently overlap.

As with all medications containing corticosteroids, Seretide should be administered with caution in patients with active or quiescent pulmonary tuberculosis.

Seretide should be administered with caution in patients with thyrotoxicosis.

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

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

Rare instances of glaucoma and increased intraocular pressure have been reported following administration of inhaled corticosteroids.

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.

Seretide should not be initiated in patients with unstable or acutely deteriorating asthma, which may be a life-threatening condition. Serious acute respiratory events, including fatalities, have been reported when salmeterol has been initiated in this situation. Although it is not possible from these reports to determine whether salmeterol contributed to these adverse events or failed to relieve the deteriorating asthma, the use of salmeterol in this setting is inappropriate.

Seretide should not be used to transfer patients from oral to inhaled steroids.

In rare cases inhaled therapy may unmask underlying eosinophilic conditions (e.g. Churg Strauss syndrome). These cases have usually been associated with reduction or withdrawal of oral corticosteroid therapy. A direct causal relationship has not been established.

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

A drug interaction study in healthy subjects has shown that ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can greatly increase fluticasone propionate plasma concentrations, resulting in markedly reduced serum cortisol concentrations. During post-marketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing's syndrome and adrenal suppression. Therefore, concomitant use of fluticasone propionate and ritonavir should be avoided, unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side-effects.

Data from a large US study (SMART) comparing the safety of salmeterol (a component of Seretide) or placebo added to usual therapy showed a significant increase in asthma-related deaths in patients receiving salmeterol. Data from this study suggested that African-American patients may be at greater risk of serious respiratory-related events or deaths when using salmeterol compared to placebo. It is not known if this was due to pharmacogenetic or other factors. The SMART study was not designed to determine whether concurrent use of inhaled corticosteroids modifies the risk of asthma-related death.

It was observed in a drug interaction study that concomitant use of systemic ketoconazole increases exposure to salmeterol. This may lead to prolongation in the QTc interval. Due to the potential increased risk of cardiovascular adverse events, the concomitant use of salmeterol with strong CYP3A4 inhibitors (e.g. ketoconazole, atazanavir, ritonavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir) is not recommended (see **INTERACTIONS WITH OTHER MEDICINES** and **Pharmacokinetics**).

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

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 may reduce with regular therapy.

Spacer Devices:

Most patients will benefit from the consistent use of a spacer device with their metered dose inhaler (MDI or 'puffer'), particularly those with poor inhaler technique. Use of a spacer will also decrease the amount of drug deposited in the mouth and back of the throat, and therefore reduce the incidence of local side effects such as 'thrush' and a hoarse voice.

A change in the make of spacer may be associated with alterations in the amount of drug delivered to the lungs. The clinical significance of these alterations is uncertain. However, in these situations, the person should be monitored for any loss of asthma control.

If using a spacer, the patient should be instructed to actuate the inhaler into the spacer and then slowly breathe in as far as possible. Hold your breath for as long as comfortable, before breathing out slowly. This should be repeated for each actuation of the drug into the spacer. Any delays between actuation and inhalation should be kept to a minimum.

Static on the walls of the spacer may cause variability in drug delivery. Patients should be instructed to wash the spacer in warm water and detergent and allow it to air dry without rinsing or drying with a cloth. This should be performed before initial use of the spacer and at least monthly thereafter.

Possible systemic effects, including Adrenocortical function, Bone density and Growth:

Inhaled steroids are designed to direct glucocorticoid delivery to the lungs in order to reduce overall systemic glucocorticoid exposure and side effects. With sufficient doses however, all inhaled steroids can have adverse effects; possible systemic effects include Cushing's syndrome, Cushingoid features, depression of the hypothalamic-pituitary adrenal (HPA) axis, reduction of bone mineral density, cataract, glaucoma and retardation of growth rate in children and adolescents (see **OVERDOSAGE**).

The lowest dose of inhaled fluticasone that causes suppression of the HPA axis (as indicated by the 24 hour urinary cortisol concentrations), effects on bone mineral density or growth retardation in children has not yet been established. Some depression of plasma cortisol may occur in a small number of adult patients on higher doses (e.g. >1 mg/day). However, adrenal function and adrenal reserve usually remain within normal range on inhaled fluticasone propionate therapy. To minimise the systemic effects of inhaled corticosteroids, including fluticasone propionate, each patient should be titrated down to the lowest dose that effectively controls his/her asthma (see **DOSAGE AND ADMINISTRATION**).

Data regarding the effect of long term use of inhaled fluticasone on bone mineral density in elderly patients are limited.

Patients in a medical or surgical emergency, who in the past have required high doses of inhaled steroids and/or intermittent treatment with oral steroids, remain at risk of impaired adrenal reserve for a considerable time. The extent of the adrenal impairment may require specialist advice before elective procedures. The possibility of residual impaired adrenal response should always be borne in mind in emergency and elective situations likely to produce stress and appropriate corticosteroid treatment must be considered (see **OVERDOSAGE**).

Fertility:

Neither fluticasone propionate nor salmeterol xinafoate alone show significant effects on fertility. Studies to detect such effects with co-administration have not been conducted.

Use in Pregnancy:

Pregnancy Category B3

There are limited data from clinical trials in pregnant women. However, extensive clinical experience with drugs in this class has revealed no evidence of adverse effects on the mother or foetus at relevant therapeutic doses of ICS. As with any medication, administration during pregnancy should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus.

An observational retrospective epidemiological cohort study utilising electronic health records from the United Kingdom was conducted to evaluate the risk of major congenital malformations (MCMs) following first trimester exposure to inhaled fluticasone propionate alone and salmeterol-fluticasone propionate relative to non-fluticasone propionate containing inhaled corticosteroids. No placebo comparator was included in this study.

Within the asthma cohort of 5362 first trimester inhaled corticosteroid-exposed pregnancies, 131 diagnosed MCMs were identified; 1612 (30%) were exposed to fluticasone propionate or salmeterol-fluticasone propionate of which 42 diagnosed MCMs were identified. The adjusted odds ratio for MCMs diagnosed by 1 year was 1.1 (95%CI: 0.5 – 2.3) for fluticasone propionate exposed vs non-fluticasone propionate inhaled corticosteroid exposed women with moderate asthma and 1.2 (95%CI: 0.7 – 2.0) for women with considerable to severe asthma. No difference in the risk of MCMs was identified following first trimester exposure to fluticasone propionate alone versus salmeterol-fluticasone propionate. Absolute risks of MCM across the asthma severity strata ranged from 2.0 to 2.9 per 100 fluticasone propionate-exposed pregnancies which is comparable to results from a study of 15,840 pregnancies unexposed to asthma therapies in the General Practice Research Database (2.8 MCM events per 100 pregnancies).

Results from the retrospective epidemiological study did not find an increased risk of MCMs following exposure to fluticasone propionate when compared to other inhaler corticosteroids, during the first trimester of pregnancy.

Reproductive toxicity studies in animals, either with single drug or in combination, revealed the foetal effects expected at excessive systemic exposure levels of a potent beta-2-adrenoceptor agonist and glucocorticosteroid – however these findings may not be relevant to humans taking inhaled steroids and beta-2 agonist at the recommended dose.

Use in Lactation:

Fluticasone propionate and salmeterol concentrations in plasma after inhaled doses are very low and therefore concentrations in human breast milk are likely to be correspondingly low. Studies in lactating animals support this for salmeterol xinafoate, although after subcutaneous administration of radiolabelled fluticasone propionate to lactating rats, levels of radioactivity in milk were 3 to 7 times plasma levels. There are no data available for human breast milk.

Administration during lactation should only be considered if the expected benefit to the mother is greater than any possible risk to the child.

Paediatric Use:

The growth of paediatric patients receiving corticosteroids, including fluticasone propionate, should be monitored. The potential growth effects of prolonged treatment should be weighed against the clinical benefits obtained. To minimise the systemic effects of inhaled corticosteroids, including fluticasone propionate, each patient should be titrated down to the lowest dose that effectively controls his/her asthma (see **DOSAGE AND ADMINISTRATION**).

In children taking recommended doses of inhaled fluticasone propionate, adrenal function and adrenal reserve usually remain within the normal range. However, the possible effects of previous or intermittent treatment with oral steroids should not be discounted. Nevertheless, the benefits of inhaled fluticasone propionate should minimise the need for oral steroids.

Genotoxicity:

Neither fluticasone propionate nor salmeterol xinafoate showed evidence of mutagenic potential when tested alone in a standard battery of genotoxicity assays. No studies

examining the potential interaction of fluticasone propionate and salmeterol xinafoate to cause genetic toxicity when co-administered have been conducted.

The non-CFC propellant, norflurane (HFA134a), 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.

Carcinogenicity:

No studies on the carcinogenic potential of the combined formulation of fluticasone propionate:salmeterol xinafoate have been conducted in animals. With fluticasone alone, no evidence of a tumorigenic effect was observed in either a 2 year study in rats receiving doses of fluticasone propionate up to 57 mg/kg/day by inhalation or in an 18 month study in mice receiving oral doses of fluticasone propionate up to 1 mg/kg/day. With salmeterol xinafoate alone, oral administration to mice at 0.2, 1.4 or 10 mg/kg/day for 18 months resulted in the development of smooth muscle tumours (leiomyomas and possibly leiomyosarcomas) in the uterus. In rats, combined oral / inhalational administration for 24 months at total dose levels of 0.2, 0.7 and 2.6 mg/kg/day resulted in leiomyomas in the suspensory ligament of the ovaries, as well as an increased incidence of benign pituitary tumours. The smooth muscle tumours in both species are thought to result from chronic stimulation of beta-adrenoceptors in these tissues, whereas the mechanism involved in the development of the pituitary tumours is unknown.

Preclinical Safety Data:

Fluticasone propionate and salmeterol xinafoate have been extensively evaluated in animal toxicity tests. Significant toxicities occurred only at doses in excess of those recommended for human use and were those expected for a potent beta-2-adrenoreceptor agonist and glucocorticosteroid.

Co-administration of fluticasone propionate and salmeterol resulted in some cardiovascular lesions not seen upon dosing with the individual drugs (mild atrial myocarditis and focal coronary arteritis in rats and papillary muscle necrosis in dogs). However, these high dose changes were not consistently observed across studies and are unlikely to be of clinical relevance.

Co-administration did not modify other class-related toxicities in animals.

Effects on ability to drive and use machinery:

Seretide is unlikely to produce an effect.

INTERACTIONS WITH OTHER MEDICINES

Both non-selective and selective beta-blockers should be avoided unless there are compelling reasons for their use.

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.

A drug interaction study in healthy subjects has shown that ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can greatly increase fluticasone propionate plasma concentrations, resulting in markedly reduced serum cortisol concentrations. During post-

marketing use, there have been reports of clinically significant drug interactions in patients receiving intranasal or inhaled fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing's syndrome and adrenal suppression. Therefore, concomitant use of fluticasone propionate and ritonavir should be avoided, unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side-effects.

Studies have shown that other inhibitors of cytochrome P450 3A4 produce negligible (erythromycin) and minor (ketoconazole) increases in systemic exposure to fluticasone propionate without notable reductions in serum cortisol concentrations. Nevertheless, care is advised when co-administering potent cytochrome P450 3A4 inhibitors (e.g. ketoconazole) as there is potential for increased systemic exposure to fluticasone propionate.

Co-administration of ketoconazole and salmeterol resulted in a significant increase in plasma salmeterol exposure (1.4-fold C_{max} and 15-fold AUC). This increase in plasma salmeterol may cause a prolongation of QTc interval (see **PRECAUTIONS** and **Pharmacokinetics**).

ADVERSE EFFECTS

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

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common ($\geq 1/10$), common ($\geq 1/100$ and $< 1/10$), uncommon ($\geq 1/1000$ and $< 1/100$), rare ($\geq 1/10,000$ and $< 1/1000$) and very rare ($< 1/10,000$).

Clinical Trial Data

Infections and infestations

Common: Candidiasis of mouth and throat, pneumonia (in COPD patients).

Such patients may find it helpful to rinse out their mouth with water after inhalation. Symptomatic candidiasis can be treated with topical anti-fungal therapy whilst still continuing with the fluticasone propionate.

Rare: Oesophageal candidiasis

Immune system disorders

Hypersensitivity Reactions:

Uncommon: Cutaneous hypersensitivity reactions, dyspnoea.

Rare: Anaphylactic reactions

Endocrine disorders

Possible systemic effects include (see **PRECAUTIONS**):

Uncommon: Cataract

Rare: Glaucoma

Metabolism and nutrition disorders

Uncommon: Hyperglycaemia.

Psychiatric disorders

Uncommon: Anxiety, sleep disorders.

Rare: Behavioural changes, including hyperactivity and irritability (predominantly in children).

Nervous system disorders

Very common: Headache (see **PRECAUTIONS**).

Uncommon: Tremor (see **PRECAUTIONS**).

Cardiac disorders

Common: Palpitations (see **PRECAUTIONS**).

Uncommon: Tachycardia, atrial fibrillation.

Rare: Cardiac arrhythmias including supraventricular tachycardia and extrasystoles.

Peripheral vasodilation and a compensatory small increase in heart rate may occur in some patients.

Respiratory, thoracic and mediastinal disorders

Common: Hoarseness/dysphonia, throat irritation.

Skin and subcutaneous tissue disorders

Uncommon: Contusions.

Musculoskeletal and connective tissue disorders

Common: Muscle cramps, arthralgia.

Postmarketing Data

Immune system disorders

Hypersensitivity reactions manifesting as:

Uncommon: Cutaneous hypersensitivity reactions.

Rare: Angioedema (mainly facial and oropharyngeal oedema) and respiratory symptoms (dyspnoea and/or bronchospasm), anaphylactic reactions

Endocrine disorders

Possible systemic effects include (see **PRECAUTIONS**):

Rare: Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decreased bone mineral density.

Metabolism and nutrition disorders

Uncommon: Hyperglycaemia.

Psychiatric disorders

Uncommon: Anxiety, sleep disorders.

Rare: Behavioural changes, including hyperactivity and irritability (predominantly in children).

Respiratory, thoracic and mediastinal disorders

Rare: Paradoxical bronchospasm (see **PRECAUTIONS**)

DOSAGE AND ADMINISTRATION

Seretide Accuhaler and MDI are for inhalation only.

Seretide Accuhaler and MDI must be used regularly for optimum benefit, even when asymptomatic.

Patients should be regularly assessed by a doctor, so the dose of Seretide they are receiving remains optimal. Strength of dose should only be increased or decreased on medical advice.

The use of one puff bd of the MDI has not been investigated in clinical trials.

Seretide Accuhaler:

The Accuhaler releases a powder that is inhaled into the lungs. The device is opened and primed by sliding the lever. The mouthpiece is then placed in the mouth and the lips closed around it. The dose can then be inhaled and the device closed. A dose counter on the Accuhaler indicates the number of doses left.

For more detailed instructions for use refer to the patient information leaflet.

Seretide MDI:

Seretide MDI is available with or without a counter. The MDI comprises a suspension of fluticasone propionate and salmeterol in a CFC-free propellant. The suspension is contained in an aluminium alloy canister sealed with a metering valve. The canisters are fitted into plastic actuators incorporating an atomising orifice and fitted with dustcaps. For Seretide MDI with counter, the canister has a counter attached to it, which shows how many actuations of medicine are left. The number of actuations left will show through a window in the back of the plastic actuator.

For more detailed instructions for use refer to the patient information leaflet.

Asthma

The dose of fluticasone propionate should be titrated to the lowest dose at which effective control of symptoms is maintained.

Patients should be given the dose of Seretide containing the appropriate fluticasone propionate dosage for the severity of their disease.

Adults and children over 12 years:

The recommended dose for regular asthma management is 100/50 micrograms to 500/50 micrograms fluticasone propionate/salmeterol twice daily:

Seretide Accuhaler: One inhalation (100/50 micrograms to 500/50 micrograms) twice daily.

Seretide MDI: Two inhalations (50/25 micrograms to 250/25 micrograms) twice daily.

The recommended dose for **initiation of maintenance therapy** in moderate persistent asthma is 100/50 micrograms fluticasone propionate/salmeterol twice daily:

Seretide Accuhaler: One inhalation (100/50 micrograms) twice daily.

Seretide MDI: Two inhalations (50/25 micrograms) twice daily.

Patients commenced on Seretide as initial maintenance therapy should be reviewed after 6-12 weeks. In patients whose asthma is well controlled and stable, cessation of salmeterol and transfer to maintenance therapy with an inhaled corticosteroid alone should be considered.

Children 4 years and over:

The recommended dose for regular asthma management is 100/50 micrograms fluticasone propionate/salmeterol twice daily:

Seretide Accuhaler: One inhalation (100/50 micrograms) twice daily.

Seretide MDI: Two inhalations (50/25 micrograms) twice daily.

The safety and efficacy of Seretide for the initiation of maintenance treatment in this age group has not been established. There are no data available for use of Seretide in children aged under 4 years.

Special patient groups:

There is no need to adjust the dose in elderly patients or in those with renal or hepatic impairment.

COPD

Adults:

The recommended dose is 250/50 micrograms or 500/50 micrograms fluticasone propionate/salmeterol twice daily:

Seretide Accuhaler: One inhalation 500/50 micrograms twice daily.

OR

One inhalation 250/50 micrograms twice daily may be a consideration in patients who are at a greater risk of inhaled corticosteroid adverse effects (see **CLINICAL TRIALS** and **DOSAGE AND ADMINISTRATION**).

Seretide MDI: Two inhalations 250/25 micrograms twice daily.

OR

Two inhalations 125/25 micrograms twice daily may be a consideration in patients who are at a greater risk of inhaled corticosteroid adverse

effects (see **CLINICAL TRIALS** and **DOSAGE AND ADMINISTRATION**).

OVERDOSAGE

For information on the management of overdose contact the Poison Information Centre on 131126 (Australia)

The available information on overdose with Seretide, fluticasone and/or salmeterol is given below:

It is not recommended that patients receive higher than approved doses of Seretide. It is important to review therapy regularly and titrate down to the lowest dose at which effective control of disease is maintained (see **DOSAGE AND ADMINISTRATION**).

Symptoms and Signs

The expected symptoms and signs of salmeterol overdose are those typical of excessive beta-2-adrenergic stimulation, including tremor, headache, tachycardia, increases in systolic blood pressure, hypokalaemia and raised blood glucose levels.

Acute inhalation of fluticasone propionate doses in excess of those approved may lead to temporary suppression of the hypothalamic-pituitary–adrenal axis. This does not usually require emergency action as normal adrenal function typically recovers within a few days.

If higher than approved doses of Seretide are continued over prolonged periods, significant adrenocortical suppression is possible. There have been very rare reports of acute adrenal crisis, mainly occurring in children exposed to higher than approved doses over prolonged periods (several months or years). Presenting symptoms are typically vague and may include anorexia, abdominal pain, weight loss, tiredness, headache, nausea, vomiting, decreased levels of consciousness, hypoglycaemia and seizures. Situations which could potentially trigger acute adrenal crisis include exposure to trauma, surgery, infection or any rapid reduction in the dosage of the inhaled fluticasone propionate component. Additional systemic corticosteroid cover should be considered during periods of stress or elective surgery.

Treatment

There is no specific treatment for an overdose of salmeterol and fluticasone propionate. If overdose occurs, the patient should be treated supportively with appropriate monitoring necessary.

PRESENTATION AND STORAGE CONDITIONS

Seretide Accuhaler

Moulded plastic device containing a foil strip with 28 or 60 regularly placed blisters each containing a powder formulation of 100 micrograms of fluticasone propionate and 50 micrograms of salmeterol (as xinafoate).

Moulded plastic device containing a foil strip with 28 or 60 regularly placed blisters each containing a powder formulation of 250 micrograms of fluticasone propionate and 50 micrograms of salmeterol (as xinafoate).

Moulded plastic device containing a foil strip with 28 or 60 regularly placed blisters each containing a powder formulation of 500 micrograms of fluticasone propionate and 50 micrograms of salmeterol (as xinafoate).

Seretide Accuhaler should be stored in a dry place below 30°C.

Not all pack sizes may be marketed.

Seretide MDI

Seretide 50/25 micrograms MDI delivers 50 micrograms of fluticasone propionate and 25 micrograms of salmeterol (as xinafoate) per inhalation. Packs of 120 metered doses.

Seretide 125/25 micrograms MDI delivers 125 micrograms of fluticasone propionate and 25 micrograms of salmeterol (as xinafoate) per inhalation. Packs of 120 metered doses.

Seretide 250/25 micrograms MDI delivers 250 micrograms of fluticasone propionate and 25 micrograms of salmeterol (as xinafoate) per inhalation. Packs of 120 metered doses.

Seretide MDI is available with or without a counter (see **DOSAGE AND ADMINISTRATION**).

Seretide MDI should be stored below 30°C. Protect from frost and direct sunlight.

Replace the mouthpiece cover firmly and snap it into position.

As with most inhaled medications in pressurised canisters, the therapeutic effect of this Seretide MDI may decrease when the canister is cold. The canister should not be punctured, broken or burnt even when apparently empty.

NAME AND ADDRESS OF THE SPONSOR

GlaxoSmithKline Australia Pty Ltd
Level 4
436 Johnston Street
Abbotsford
Victoria 3067

POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (ARTG): 8 February 2000

DATE OF MOST RECENT AMENDMENT: 14 September 2016

Seretide and Accuhaler are registered trade marks of the GlaxoSmithKline group of companies.

Version 7.0