

DATA SHEET

SERETIDE™ Accuhaler™

***Salmeterol xinafoate 50mcg and Fluticasone propionate
(100mcg, 250mcg or 500mcg)***

Qualitative and quantitative composition

Moulded plastic device containing a foil strip with 60 regularly placed blisters each containing 50mcg of salmeterol xinafoate and 100mcg of fluticasone propionate.

Moulded plastic device containing a foil strip with 60 regularly placed blisters each containing 50mcg of salmeterol xinafoate and 250mcg of fluticasone propionate.

Moulded plastic device containing a foil strip with 60 regularly placed blisters each containing 50mcg of salmeterol xinafoate and 500mcg of fluticasone propionate.

Pharmaceutical form

Inhalation powder.

Clinical particulars

Therapeutic Indications

Reversible Obstructive Airways Disease (ROAD)

SERETIDE is indicated in the regular treatment of reversible obstructive airways disease (ROAD), including asthma in children and adults, where use of a combination (bronchodilator and inhaled corticosteroid) is appropriate.

This may include:

Patients on effective maintenance doses of long-acting β -agonists and inhaled corticosteroids.

Patients who are symptomatic on current inhaled corticosteroid therapy.

Patients who are symptomatic on "as needed" short-acting beta-agonists, as an alternative to initiation of maintenance therapy with moderate or high doses of inhaled corticosteroid alone.

Chronic Obstructive Pulmonary Disease (COPD)

The symptomatic treatment of patients with moderate to severe COPD (pre-bronchodilator FEV₁<60% predicted normal), who have significant symptoms despite bronchodilator therapy.

Posology and Method of Administration

SERETIDE Accuhaler is for inhalation only.

Patients should be made aware that SERETIDE Accuhaler must be used regularly 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.

Reversible Obstructive Airways Disease (ROAD)

The dose should be titrated to the lowest dose at which effective control of symptoms is maintained. Where effective control of symptoms is maintained with twice daily SERETIDE, titration to the lowest effective dose could include SERETIDE given once daily.

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

Recommended Doses:-

Adults and adolescents 12 years and older.

One inhalation (50mcg salmeterol and 100mcg fluticasone propionate) twice daily.

or

One inhalation (50mcg salmeterol and 250mcg fluticasone propionate) twice daily.

or

One inhalation (50mcg salmeterol and 500mcg fluticasone propionate) twice daily.

Children 4 years and older:-

One inhalation (50mcg salmeterol and 100mcg fluticasone propionate) twice daily.

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

Chronic Obstructive Pulmonary Disease (COPD)

The recommended starting dose for adults is 1 inhalation 50/250mcg twice daily. For patients who require additional symptomatic control replace the 50/250mcg strength with the 50/500mcg strength. The maximum daily dose is 1 inhalation of 50/500mcg twice daily (see Salmeterol/fluticasone propionate clinical trials).

Special patient groups:-

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

Contra-indications

SERETIDE is contraindicated in patients with a history of hypersensitivity to any of the ingredients (see Pharmaceutical Particulars – List of Excipients).

Special Warnings and Special Precautions for Use

The management of ROAD should normally follow a stepwise programme and patient response should be monitored clinically and by lung function tests.

SERETIDE Accuhaler is not for relief of acute symptoms for which a fast and short-acting 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 ROAD, the patient should be reviewed by a physician.

For patients with asthma or COPD, consideration should be given to additional corticosteroid therapies, and to including administration of antibiotics if an infection is present.

Treatment with SERETIDE 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 Undesirable 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 inhaled medication 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.

Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods; these effects are much less likely to occur than with oral corticosteroids (see Overdose). Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma. It is important, therefore, for ROAD patients, that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control is maintained.

The possibility of impaired adrenal response should always be borne in mind in emergency and elective situations likely to produce stress and appropriate corticosteroid treatment considered (see Overdose).

It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroid is regularly monitored.

Certain individuals can show greater susceptibility to the effects of inhaled corticosteroid than do most patients.

Because of the possibility of impaired adrenal response, patients transferring from oral steroid therapy to inhaled fluticasone propionate therapy should be treated with special care, and adrenocortical function regularly monitored.

Following introduction of inhaled fluticasone propionate, withdrawal of systemic therapy should be gradual and patients encouraged to carry a steroid warning card indicating the possible need for additional therapy in times of stress.

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

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 (see Interaction with Other Medicinal Products and Other Forms of Interaction).

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.

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. Caution should be exercised when strong CYP3A4 inhibitors (e.g. ketoconazole) are co-administered with salmeterol. (see Interactions, and Pharmacokinetic Properties).

Use During Pregnancy and Lactation

Administration of medicines during pregnancy and lactation should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus or child.

There is insufficient experience of the use of salmeterol xinafoate and fluticasone propionate in human pregnancy and lactation.

Reproductive toxicity studies in animals, either with single agent or in combination, revealed the foetal effects expected at excessive systemic exposure levels of a potent β_2 -adrenoreceptor agonist and glucocorticosteroid.

Extensive clinical experience with medicines in these classes has revealed no evidence that the effects are relevant at therapeutic doses. Neither salmeterol xinafoate or fluticasone propionate have shown any potential for genetic toxicity.

Salmeterol and fluticasone propionate concentrations in plasma after inhaled therapeutic doses are very low and therefore concentrations in human breast milk are likely to be correspondingly low. This is supported by studies in lactating animals, in which low concentrations were measured in milk. There are no data available for human breast milk.

Effects on Ability to Drive and Use Machines

There have been no specific studies of the effect of SERETIDE on the above activities, but the pharmacology of both agents does not indicate any effect.

Interaction with Other Medicinal Products and Other Forms of Interaction

Both non-selective and selective β -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) and this may cause a prolongation of the QTc interval. (see Special Warnings and Precautions for Use, and Pharmacokinetic Properties).

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.

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 and short-acting inhaled bronchodilator. SERETIDE Accuhaler should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.

Adverse events which have been associated with salmeterol or fluticasone propionate are given below.

Salmeterol:-

The pharmacological side effects of β_2 -agonist treatment, such as tremor, subjective palpitations and headache, have been reported, but tend to be transient and reduce with regular therapy.

Cardiac arrhythmias (including atrial fibrillation, supraventricular tachycardia and extrasystoles) may occur, usually in susceptible patients.

There have been very rare reports of arthralgia.

Hypersensitivity reactions, including anaphylactic reactions such as oedema and angioedema, bronchospasm and anaphylactic shock have been reported very rarely. There have also been uncommon reports of rash.

There have been reports of oropharyngeal irritation.

There have been common reports of muscle cramps.

There have been very rare reports of hyperglycaemia.

Fluticasone propionate:-

Hoarseness and candidiasis (thrush) of the mouth and throat can occur in some patients. The incidence of candidiasis may be reduced by gargling with water after the use of SERETIDE Accuhaler.

Symptomatic candidiasis can be treated with topical anti-fungal therapy whilst still continuing with SERETIDE Accuhaler.

There have been uncommon reports of cutaneous hypersensitivity reactions. There have also been rare reports of hypersensitivity reactions manifesting as angioedema (mainly facial and oropharyngeal oedema), respiratory symptoms (dyspnoea and/or bronchospasm) and very rarely, anaphylactic reactions.

Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma (see Special Warnings and Special Precautions for Use). There have also been very rare reports of Hyperglycaemia.

There have been very rare reports of anxiety, sleep disorders and behavioural changes, including hyperactivity and irritability (predominantly in children).

SERETIDE Accuhaler clinical trials:

The following undesirable effects were commonly reported:

Hoarseness/dysphonia, throat irritation, headache, candidiasis of mouth and throat and palpitations. Pneumonia (in COPD patients).

There have been uncommon reports of contusions.

Salmeterol/fluticasone propionate postmarketing:-

There have been uncommon reports of cutaneous hypersensitivity reactions. There have also been rare reports of hypersensitivity reactions manifesting as angioedema (mainly facial and oropharyngeal oedema), respiratory symptoms (dyspnoea and/or bronchospasm) and very rarely, anaphylactic reactions.

There have been very rare reports of anxiety, sleep disorders and behavioural changes, including hyperactivity and irritability (predominantly in children).

There have also been very rare reports of hyperglycaemia.

Overdose

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

The expected symptoms and signs of salmeterol overdosage are those typical of excessive beta₂-adrenergic stimulation, including tremor, headache, tachycardia, increases in systolic blood pressure and hypokalaemia. The preferred antidotes are cardioselective β- 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 β agonist component of the drug, provision of appropriate replacement corticosteroid therapy should be considered.

Acute inhalation of fluticasone propionate doses in excess of those approved may lead to temporary suppression of 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); observed features have included hypoglycaemia associated with decreased consciousness and/or convulsions. 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.

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 approved dose at which effective control of disease is maintained (see Posology.)

Pharmacological Properties

Pharmacodynamic Properties

Salmeterol/fluticasone propionate clinical trials.

Symptomatic COPD patients who demonstrated less than 10% reversibility to a short acting Beta₂-agonist:-

Placebo-controlled clinical trials, over 6 and 12 months, have shown that regular use of SERETIDE 50/500 micrograms rapidly and significantly improves lung function, significantly reduced breathlessness and the use of relief medication. Over a 12-month period the risk of COPD exacerbations and the need for additional courses of oral corticosteroids was significantly reduced. There were also significant improvements in health status.

SERETIDE 50/500 micrograms was effective in improving lung function, health status and reducing the risk of COPD exacerbations, in both current and ex-smokers.

Symptomatic COPD patients without restriction to 10% reversibility to a short acting *Beta*₂-agonist:-

Placebo-controlled clinical trials, over 6 months, have shown that regular use of both SERETIDE 50/250 and 50/500 micrograms rapidly and significantly improves lung function, significantly reduced breathlessness and the use of relief medication. There were also significant improvements in health status.

TORCH study (Towards a Revolution in COPD Health):

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

	Placebo N=1524	Salmeterol 50 N=1521	Fluticasone propionate 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)	N/A	0.879 (0.73, 1.06)	1.060 (0.89, 1.27)	0.825 (0.68, 1.00)
P value		0.180	0.525	0.052 ¹
Hazard ratio Seretide 50/500 vs components (CIs)	N/A	0.932 (0.77, 1.13)	0.774 (0.64, 0.93)	N/A
P value		0.481	0.007	

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

There was a trend towards improved survival in subjects treated with Seretide compared with placebo over 3 years however this did not achieve the statistical significance level $p < 0.05$. The percentage of patients who died

within 3 years due to COPD-related causes was 6.0% for placebo, 6.1% for salmeterol, 6.9% for FP and 4.7% for Seretide.

Seretide reduced the rate of moderate to severe COPD exacerbations by 25% ($p < 0.001$) compared with placebo. Seretide reduced the exacerbation rate by 12% compared with salmeterol ($p = 0.002$) and 9% compared with fluticasone propionate ($p = 0.024$).

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 3 years for Seretide compared with placebo was -3.1 units ($p < 0.001$), compared with salmeterol was -2.2 units ($p < 0.001$) and compared with fluticasone propionate was -1.2 units ($p = 0.017$). The odds of Seretide subjects achieving a clinically significant improvement in health status (ie. ≥ 4 point reduction in SGRQ) was 86% greater compared to placebo ($p < 0.001$), 40% greater compared to salmeterol ($p < 0.001$) and 24% greater compared to fluticasone propionate ($p = 0.006$).

Over the 3 year treatment period, FEV₁ values were higher in subjects treated with Seretide than those treated with placebo (average difference over 3 years 92 mL, $p < 0.001$). Seretide was also more effective than salmeterol or fluticasone propionate in improving FEV₁ (average difference 50 mL, $p < 0.001$ for salmeterol and 44 mL, $p < 0.001$ for fluticasone propionate).

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 fluticasone propionate and 19.6% for Seretide (Hazard ratio for Seretide vs placebo: 1.64, $p < 0.001$). 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 fluticasone propionate and 8 for Seretide. There was no significant difference in probability of bone fracture between treatments. The incidence of adverse events of eye disorders, bone disorders, and HPA axis disorders was low and there was no difference observed between treatments. There was no evidence of an increase in cardiac adverse events in the treatment groups receiving salmeterol.

The all-cause mortality findings from TORCH were further supported by data from another study, INSPIRE, which was a 2 year randomised (n=1323), double blind study comparing the effects of Seretide 50/500mcg twice daily with tiotropium 18mcg once daily in COPD patients with post bronchodilator FEV₁ $< 50\%$ predicted normal. All-cause mortality was a safety end point in this study. The results showed that for time to death on-treatment, there was a 52% reduction in the risk of dying at anytime on therapy over the 2 year study period for Seretide compared to tiotropium ($p = 0.012$).

Mechanism of action:-

SERETIDE contains salmeterol and fluticasone propionate which have differing modes of action. Salmeterol protects against symptoms, fluticasone propionate improves lung function and prevents exacerbations of the condition. SERETIDE can offer a more convenient regime for patients on concurrent β -agonist and inhaled corticosteroid therapy. The respective mechanisms of action of both agents are discussed below:

Salmeterol:-

Salmeterol is a selective long-acting (12 hour) β_2 -adrenoceptor agonist with a long side chain which binds to the exo-site of the receptor.

These pharmacological properties of salmeterol offer more effective protection against histamine-induced bronchoconstriction and produce a longer duration of bronchodilation, lasting for at least 12 hours, than recommended doses of conventional short-acting β_2 -agonists.

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

In man salmeterol inhibits the early and late phase response to inhaled allergen; the latter persisting for over 30 hours after a single dose when the bronchodilator effect is no longer evident. Single dosing with salmeterol attenuates bronchial hyper-responsiveness. These properties indicate that salmeterol has additional non-bronchodilator activity but the full clinical significance is not yet clear. This mechanism is different from the anti-inflammatory effect of corticosteroids.

Fluticasone propionate:-

Fluticasone propionate given by inhalation at recommended doses has a potent 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.

Daily output of adrenocortical hormones usually remain within the normal range during chronic treatment with inhaled fluticasone propionate, even at the highest recommended doses in children and adults. After transfer from other inhaled steroids, the daily output gradually improves despite past and present intermittent use of oral steroids, thus demonstrating return of normal adrenal function on inhaled fluticasone propionate. The adrenal reserve also remains normal during chronic treatment, as measured by a normal increment on a stimulation test. However, any residual impairment of adrenal reserve from previous treatment may persist for a considerable time and should be borne in mind (see "Special Warnings and Special Precautions for Use").

Pharmacokinetic Properties

There is no evidence in animal or human subjects that the administration of salmeterol and fluticasone propionate 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 CYP3A4 cannot be excluded.

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 200pg/mL or less) achieved after inhaled dosing. After regular dosing with salmeterol xinafoate, hydroxynaphthoic acid can be detected in the systemic circulation, reaching steady state concentrations of approximately 100ng/mL. These concentrations are up to 1000 fold lower than steady state levels observed in toxicity studies. No detrimental effects have been seen following long-term regular dosing (more than 12 months) in patients with airway obstruction.

In a placebo-controlled, crossover drug interaction study in 15 healthy subjects, co-administration of salmeterol (50 mcg 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. In the remaining 12 subjects, co-administration of salmeterol and ketoconazole did not result in a clinically significant effect on heart rate, blood potassium or QTc duration. (see Special Warnings and Precautions for Use, and Interactions).

Fluticasone propionate:-

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. In healthy adult subjects the absolute bioavailability has been estimated for fluticasone propionate Accuhaler (7.8%), fluticasone propionate Inhaler (10.9%), Seretide Inhaler (5.3%) and Seretide Accuhaler (5.5%) respectively. In patients with ROAD 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 (1150mL/min), a large volume of distribution at steady-state (approximately 300L) and a terminal half-life of approximately 8 hours. Plasma protein binding is moderately high (91%). Fluticasone propionate is cleared very rapidly from the systemic circulation, principally by metabolism to an inactive carboxylic acid metabolite, by the cytochrome P450 enzyme CYP3A4. The renal clearance of fluticasone propionate is negligible (<0.2%) and less than 5% as the metabolite. Care should be taken when co-administering known CYP3A4 inhibitors, as there is potential for increased systemic exposure to fluticasone propionate.

Special Patient Populations

Salmeterol-fluticasone propionate

Population pharmacokinetic analysis was performed utilising data for asthmatic subjects (nine clinical studies for fluticasone propionate and five studies for salmeterol) and showed the following:

- Higher fluticasone propionate exposure seen following administration of Seretide (100/50 μ g) compared to fluticasone propionate alone (100 μ g) in adolescents and adults (ratio 1.52 [90% CI 1.08, 2.13]) and children (ratio 1.20 [90% CI 1.06, 1.37]).
- Higher fluticasone propionate exposure observed in children taking Seretide (100/50 μ g) compared to adolescents and adults (ratio 1.63 [90% CI 1.35, 1.96]).
- The clinical relevance of these findings are not known, however, no differences in HPA axis effects were observed in clinical studies of up to 12 weeks duration comparing Seretide (100/50 μ g) and fluticasone propionate (100 μ g) in both adolescents and adults and in children.
- Fluticasone propionate exposure was similar at the higher Seretide 500/50 μ g dose compared to the equivalent fluticasone propionate dose alone.
- Higher salmeterol exposure was observed in children taking Seretide (100/50 μ g) compared to adolescents and adults (ratio 1.23 [90% CI 1.10, 1.38]).
- The clinical relevance of these findings are not known, however there were no differences observed in cardiovascular effects or reports of tremor between adults, adolescents and children in clinical studies of up to 12 weeks duration.

Preclinical Safety Data

Salmeterol xinafoate and fluticasone propionate 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 β_2 -adrenoreceptor agonist and glucocorticosteroid.

In long term studies, salmeterol xinafoate induced benign tumours of smooth muscle in the mesovarium of rats and the uterus of mice. Rodents are sensitive to the formation of these pharmacologically- induced tumours. Salmeterol is not considered to represent a significant oncogenic hazard to man.

Co-administration of salmeterol and fluticasone propionate resulted in some cardiovascular interactions at high doses. In rats, mild atrial myocarditis and focal coronary arteritis were transient effects that resolved with regular dosing. In dogs, heart rate increases were greater after co-administration than after salmeterol alone. No clinically relevant serious adverse cardiac effects have been observed in studies in man.

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

Pharmaceutical particulars

List of Excipients

Lactose (which contains milk protein)

Incompatibilities

None reported

Shelf Life

18 months.

Special Precautions for Storage

Do not store above 30°C.

Store in a dry place.

Nature and Contents of Container

The Accuhaler releases a powder which 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 indicator on the Accuhaler indicates the number of doses left.

For detailed instructions for use refer to the Patient Information Leaflet.

Medicines classification

Prescription Only Medicine

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