



Salmeterol + Fluticasone propionate

Seretide[®] Diskus[®] Dry Powder for Inhalation

PRODUCT DESCRIPTION

Salmeterol + Fluticasone propionate Dry Powder for Inhalation 50/100mcg (*Seretide[®] 100 Diskus[®]*) is a moulded plastic device containing a foil strip with 60 regularly placed blisters each containing 50 micrograms of salmeterol as salmeterol xinafoate and 100 micrograms of fluticasone propionate.

Salmeterol + Fluticasone propionate Dry Powder for Inhalation 50/250mcg (*Seretide[®] 250 Diskus[®]*) is a moulded plastic device containing a foil strip with 60 regularly placed blisters each containing 50 micrograms of salmeterol as salmeterol xinafoate and 250 micrograms of fluticasone propionate.

Salmeterol + Fluticasone propionate Dry Powder for Inhalation 50/500mcg (*Seretide[®] 500 Diskus[®]*) is a moulded plastic device containing a foil strip with 28 or 60 regularly placed blisters each containing 50 micrograms of salmeterol as salmeterol xinafoate and 500 micrograms of fluticasone propionate.

List of excipients

Lactose (which contains milk protein)

PHARMACOLOGIC PROPERTIES

Pharmacodynamics

Salmeterol (*Serevent[®]*) clinical trials

Asthma

The Salmeterol Multi-center Asthma Research Trial (SMART) was a large US study that compared the safety of Salmeterol (*Serevent[®]*) or placebo added to usual therapy. There were no significant differences in the primary endpoint of the combined number of respiratory-related deaths and respiratory-related life-threatening experiences. The study showed a significant increase in asthma-related deaths in patients receiving Salmeterol (*Serevent[®]*) (13 deaths out of 13,176 patients treated for 28 weeks on Salmeterol (*Serevent[®]*) versus 3 deaths out of 13,179 patients on placebo). The study was not designed to assess the impact of concurrent inhaled corticosteroid use. However, post-hoc analyses showed there was no significant difference between treatment groups for asthma-related deaths for those patients using inhaled steroids at baseline (4/6127 on Salmeterol (*Serevent[®]*) versus 3/6138 on placebo). The numbers of asthma-related deaths in the groups not using inhaled steroids were 9/7049 on Salmeterol (*Serevent[®]*) versus 0/7041 on placebo. Further, a meta-analysis of 42 clinical studies involving 8,030 patients on Salmeterol + Fluticasone propionate (*Seretide[®]*) and 7,925 patients on Fluticasone propionate (*Flixotide[®]*) did not show a statistical difference between Salmeterol + Fluticasone propionate (*Seretide[®]*) and Fluticasone propionate (*Flixotide[®]*) for serious respiratory-related events or asthma-related hospitalisations.

Salmeterol + Fluticasone propionate (*Seretide[®]*) clinical trials

Asthma

A large twelve-month study (Gaining Optimal Asthma Control, GOAL) in 3416 asthma patients compared the efficacy and safety of Salmeterol + Fluticasone propionate (*Seretide[®]*) versus inhaled corticosteroid alone in achieving pre-defined levels of asthma control. Treatment was stepped-up every 12 weeks until ^{###}'Total control' was achieved or the highest dose of study drug was reached. Control needed to be sustained for at least 7 out of the last 8 weeks of treatment. The study showed that:

- 71% of patients treated with Salmeterol + Fluticasone propionate (*Seretide[®]*) achieved [#]'Well-controlled' asthma compared with 59% of patients treated with inhaled corticosteroid alone.
- 41% of patients treated with Salmeterol + Fluticasone propionate (*Seretide[®]*) achieved ^{###}'Total control' of asthma compared with 28% of patients treated with inhaled corticosteroid alone.

These effects were observed earlier with Salmeterol + Fluticasone propionate (*Seretide[®]*) compared with inhaled corticosteroid alone and at a lower inhaled corticosteroid dose.

The GOAL study also showed that:

- The rate of exacerbations was 29% lower with Salmeterol + Fluticasone propionate (*Seretide[®]*) compared to inhaled corticosteroid treatment alone.
- Attaining 'Well controlled' and 'Totally controlled' asthma improved Quality of Life (QoL). 61% of patients reported minimal or no impairment on QoL, as measured by an asthma specific quality of life questionnaire, after treatment with Salmeterol + Fluticasone propionate (*Seretide[®]*) compared to 8% at baseline.

[#]Well controlled asthma; less than or equal to 2 days with symptom score greater than 1 (symptom score 1 defined as 'symptoms for one short period during the day'), SABA use on less than or equal to 2 days and less than or equal to 4 occasions/week, greater than or equal to 80% predicted morning peak expiratory flow, 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 morning peak expiratory flow, no night-time awakenings, no exacerbations and no side effects enforcing a change in therapy.

Two further studies have shown improvements in lung function, percentage of symptom free days and reduction in rescue medication use, at 60% lower inhaled corticosteroid dose with Salmeterol + Fluticasone propionate (*Seretide[®]*) compared to treatment with inhaled corticosteroid alone, whilst the control of the underlying airway inflammation, measured by bronchial biopsy and bronchoalveolar lavage, was maintained.

Additional studies have shown that treatment with Salmeterol + Fluticasone propionate (*Seretide*[®]) significantly improves asthma symptoms, lung function and reduces the use of rescue medication compared to treatment with the individual components alone and placebo. Results from GOAL show that the improvements seen with Salmeterol + Fluticasone propionate (*Seretide*[®]), in these endpoints, are maintained over at least 12 months.

COPD

Symptomatic COPD patients without restriction to 10% reversibility to a short acting beta₂-agonist:-

Placebo-controlled clinical trials, over 6 months, have shown that regular use of both Salmeterol + Fluticasone propionate (*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.

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 Salmeterol + Fluticasone propionate (*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.

Salmeterol + Fluticasone propionate (*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.

TORCH study (Towards a Revolution in COPD Health):

TORCH was a 3-year study to assess the effect of treatment with Salmeterol + Fluticasone propionate Dry Powder for Inhalation (*Seretide*[®] *Diskus*[®]) Diskus 50/500 micrograms twice daily, salmeterol Diskus 50 micrograms twice daily, FP Diskus 500 micrograms 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 Salmeterol + Fluticasone propionate Dry Powder for Inhalation (*Seretide*[®] *Diskus*[®]) vs placebo.

	Placebo N = 1524	Salmeterol 50 N = 1521	FP 500 N = 1534	Salmeterol + Fluticasone propionate Dry Powder for Inhalation (<i>Seretide</i> [®] <i>Diskus</i> [®]) 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) 0.0521
Hazard Ratio Salmeterol + Fluticasone propionate Dry Powder for Inhalation (<i>Seretide</i> [®] <i>Diskus</i> [®]) 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. P value adjusted for 2 interim analyses on the primary efficacy comparison from a log-rank analysis stratified by smoking status

Salmeterol + Fluticasone propionate Dry Powder for Inhalation (*Seretide*[®] *Diskus*[®]) reduced the risk of dying at any time during the 3 years by 17.5% compared to placebo (Hazard Ratio 0.825 (95% CI 0.68, 1.00, p=0.052; all adjusted for interim analyses). There was a 12% reduction in the risk of dying at any time within 3 years from any cause for salmeterol compared with placebo (p=0.180) and a 6% increase for FP compared with placebo (p=0.525).

A supporting analysis using Cox's Proportional Hazards model gave a hazard ratio of 0.811 (95% CI 0.670, 0.982, p=0.031) for Salmeterol + Fluticasone propionate Dry Powder for Inhalation (*Seretide*[®] *Diskus*[®]) vs placebo which represented a 19% reduction in the risk of dying at any time within 3 years. The model adjusted for important factors (smoking status, age, sex, region, baseline FEV1 and Body Mass Index). There was no evidence that treatment effects varied for these factors.

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 Salmeterol + Fluticasone propionate Dry Powder for Inhalation (*Seretide*[®] *Diskus*[®]).

Salmeterol + Fluticasone propionate Dry Powder for Inhalation (*Seretide*[®] *Diskus*[®]) reduced the rate of moderate to severe exacerbations by 25% (95% CI: 19% to 31%; p<0.001) compared with placebo. Salmeterol + Fluticasone propionate Dry Powder for Inhalation (*Seretide*[®] *Diskus*[®]) reduced the exacerbation rate by 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 Salmeterol + Fluticasone propionate Dry Powder for Inhalation (*Seretide[®] Diskus[®]*) 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 ($p = 0.017$).

Over the 3 year treatment period, FEV1 values were higher in subjects treated with Salmeterol + Fluticasone propionate Dry Powder for Inhalation (*Seretide[®] Diskus[®]*) than for those treated with placebo (average difference over 3 years 92mL, 95% CI: 75 to 108 mL; $p < 0.001$). Salmeterol + Fluticasone propionate Dry Powder for Inhalation (*Seretide[®] Diskus[®]*) was also more effective than salmeterol or FP in improving FEV1 (average difference 50 mL, $p < 0.001$ for salmeterol and 44mL, $p < 0.001$ for FP).

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 Salmeterol + Fluticasone propionate Dry Powder for Inhalation (*Seretide[®] Diskus[®]*) (Hazard ratio for Salmeterol + Fluticasone propionate Dry Powder for Inhalation (*Seretide[®] Diskus[®]*) 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 Salmeterol + Fluticasone propionate Dry Powder for Inhalation (*Seretide[®] Diskus[®]*). There was no significant difference in probability of bone fracture (5.1% placebo, 5.1% salmeterol, 5.4% FP and 6.3% Salmeterol + Fluticasone propionate Dry Powder for Inhalation (*Seretide[®] Diskus[®]*); Hazard ratio for Salmeterol + Fluticasone propionate Dry Powder for Inhalation (*Seretide[®] Diskus[®]*) vs placebo: 1.22, 95% CI: 0.87 to 1.72, $p = 0.248$). 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.

Fluticasone propionate containing medications in asthma during pregnancy

An observational retrospective epidemiological cohort study utilising electronic health records from the United Kingdom was conducted to evaluate the risk of MCMs following first trimester exposure to inhaled FP alone and Salmeterol + Fluticasone propionate (*Seretide[®]*) relative to non-FP containing ICS. No placebo comparator was included in this study.

Within the asthma cohort of 5362 first trimester ICS-exposed pregnancies, 131 diagnosed MCMs were identified; 1612 (30%) were exposed to FP or Salmeterol + Fluticasone propionate (*Seretide[®]*) 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 FP exposed vs non-FP ICS 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 FP alone versus Salmeterol + Fluticasone propionate (*Seretide[®]*). Absolute risks of MCM across the asthma severity strata ranged from 2.0 to 2.9 per 100 FP-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).

Mechanism of action:

Salmeterol + Fluticasone propionate (*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. Salmeterol + Fluticasone propionate (*Seretide[®]*) can offer a more convenient regime for patients on concurrent beta-agonist and inhaled corticosteroid therapy. The respective mechanisms of action of both drugs are discussed below:

Salmeterol:

Salmeterol is a selective long-acting (12 hours) beta₂-adrenoceptor agonist with a long side chain which binds to the exo-site of the receptor.

These pharmacological properties of salmeterol offer more effective protection against histamine-induced bronchoconstriction and produce a longer duration of bronchodilation, lasting for at least 12 hours, than recommended doses of conventional short-acting beta₂-agonists.

In 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 Warnings and Precautions)

Pharmacokinetics

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.

In a placebo-controlled, crossover drug interaction study in 15 healthy subjects, coadministration of Salmeterol (*Serevent[®]*) (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 (*Serevent[®]*) and ketoconazole co-administration due to QTc prolongation or palpitations with sinus tachycardia. In the remaining

12 subjects, co-administration of Salmeterol (*Serevent*[®]) and ketoconazole did not result in a clinically significant effect on heart rate, blood potassium or QTc duration. (see *Warnings and Precautions, and Interactions*)

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 picograms/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 100 nanograms/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.

An *in vitro* study showed that salmeterol is extensively metabolised to α -hydroxysalmeterol (aliphatic oxidation) by cytochrome P450 3A4 (CYP3A4). A repeat dose study with salmeterol and erythromycin in healthy volunteers showed no clinically significant changes in pharmacodynamic effects at 500 mg three times daily doses of erythromycin. However, a salmeterol-ketoconazole interaction study resulted in a significant increase in plasma salmeterol exposure. (see *Warnings and Precautions, 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 Diskus (7.8%), fluticasone propionate Diskhaler (9.0%), fluticasone propionate Evohaler (10.9%), salmeterol-fluticasone propionate Evohaler (5.3%) and salmeterol-fluticasone propionate Diskus (5.5%) respectively. 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 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 Dry Powder for Inhalation (*Seretide*[®] *Diskus*[®])

Diskus:

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

- Higher FP exposure seen following administration of Salmeterol + Fluticasone propionate Dry Powder for Inhalation (*Seretide*[®] *Diskus*[®]) (50/100 micrograms) compared to FP alone (100 micrograms) 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 FP exposure observed in children taking Salmeterol + Fluticasone propionate Dry Powder for Inhalation (*Seretide*[®] *Diskus*[®]) (50/100 micrograms) 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 Salmeterol + Fluticasone propionate Dry Powder for Inhalation (*Seretide*[®] *Diskus*[®]) (50/100 micrograms) and FP (100 micrograms) in both adolescents and adults and in children.
- FP exposure was similar at the higher Salmeterol + Fluticasone propionate Dry Powder for Inhalation (*Seretide*[®] *Diskus*[®]) 50/500 microgram dose compared to the equivalent FP dose alone.
- Higher salmeterol exposure was observed in children taking Salmeterol + Fluticasone propionate Dry Powder for Inhalation (*Seretide*[®] *Diskus*[®]) (50/100 micrograms) 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.

Pre-clinical 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 beta₂-adrenoreceptor agonist and glucocorticosteroid. Neither salmeterol xinafoate or fluticasone propionate have shown any potential for genetic toxicity.

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.

INDICATIONS

Asthma (Reversible Obstructive Airways Disease)

Salmeterol + Fluticasone propionate (*Seretide*[®]) is indicated in the regular treatment of asthma (Reversible Obstructive Airways Disease).

This may include:

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

Patients who are symptomatic on current inhaled corticosteroid therapy.

Patients on regular bronchodilator therapy who require inhaled corticosteroids.

Chronic Obstructive Pulmonary Disease (COPD)

Salmeterol + Fluticasone propionate (*Seretide*[®]) is indicated for the regular treatment of chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema.

DOSAGE AND ADMINISTRATION

Salmeterol + Fluticasone propionate (*Seretide*[®]) Diskus[®] is for inhalation only.

Patients should be made aware that Salmeterol + Fluticasone propionate (*Seretide*[®]) Diskus[®] must be used regularly for optimum benefit, even when asymptomatic.

Patients should be regularly reassessed by a doctor, so that the strength of Salmeterol + Fluticasone propionate (*Seretide*[®]) they are receiving remains optimal and is only changed on medical advice.

Asthma (Reversible Obstructive Airways Disease)

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 twice daily Salmeterol + Fluticasone propionate (*Seretide*[®]), titration to the lowest effective dose could include Salmeterol + Fluticasone propionate (*Seretide*[®]) given once daily.

Patients should be given the strength of Salmeterol + Fluticasone propionate (*Seretide*[®]) containing the appropriate fluticasone propionate dosage for the severity of their disease.

If a patient is inadequately controlled on inhaled corticosteroid therapy alone, substitution with Salmeterol + Fluticasone propionate (*Seretide*[®]) at a therapeutically equivalent corticosteroid dose may result in an improvement in asthma control. For patients whose asthma control is acceptable on inhaled corticosteroid therapy alone, substitution with Salmeterol + Fluticasone propionate (*Seretide*[®]) may permit a reduction in corticosteroid dose while maintaining asthma control. For further information, please refer to the 'Pharmacodynamics' section.

Recommended Doses:

Adults and adolescents 12 years and older:

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

or

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

or

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

Children 4 years and older:

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

There are no data available for use of Salmeterol + Fluticasone propionate (*Seretide*[®]) in children aged under 4 years.

Chronic Obstructive Pulmonary Disease (COPD)

For adult patients the recommended dose is one inhalation 50/250 micrograms to 50/500 micrograms salmeterol/fluticasone propionate twice daily.

Special patient groups:

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

CONTRAINDICATIONS

Salmeterol + Fluticasone propionate (*Seretide*[®]) is contraindicated in patients with a history of hypersensitivity to any of the ingredients (see *List of Excipients*).

WARNINGS AND PRECAUTIONS

Salmeterol + Fluticasone propionate (*Seretide*[®]) Diskus[®] 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 Salmeterol + Fluticasone propionate (*Seretide*[®]) has failed to give adequate control of asthma, the patient should be reviewed by a physician.

Treatment with Salmeterol + Fluticasone propionate (*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 Salmeterol + Fluticasone propionate Dry Powder for Inhalation (*Seretide*[®] Diskus[®]) (see Adverse Reactions). 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, Salmeterol + Fluticasone propionate (*Seretide*[®]) should be administered with caution in patients with active or quiescent pulmonary tuberculosis.

Salmeterol + Fluticasone propionate (*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, Salmeterol + Fluticasone propionate (*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, Salmeterol + Fluticasone propionate (*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 asthma 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.

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 *Adverse Reactions*) 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 *Interactions*).

Data from a large US study (SMART) comparing the safety of Salmeterol (*Serevent*[®]) (a component of Salmeterol + Fluticasone propionate (*Seretide*[®])) or placebo added to usual therapy showed a significant increase in asthma-related deaths in patients receiving Salmeterol (*Serevent*[®]). Data from this study suggested that African-American patients may be at greater risk of serious respiratory-related events or deaths when using Salmeterol (*Serevent*[®]) 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. (see *Clinical Studies*)

It was observed in a drug interaction study that concomitant use of systemic ketoconazole increases exposure to Salmeterol (*Serevent*[®]). 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 (*Serevent*[®]). (see *Interactions, 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 and short-acting inhaled bronchodilator. Salmeterol-FP Accuhaler/Diskus or Evohaler should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary. (see *Adverse Reactions*)

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

Effects on Ability to Drive and Use Machines

There have been no specific studies of the effect of Salmeterol + Fluticasone propionate (*Seretide*[®]) on the above activities, but the pharmacology of both drugs does not indicate any effect.

DRUG INTERACTIONS

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 (*Serevent*[®]) 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 *Warnings and Precautions, and Pharmacokinetics*)

PREGNANCY AND LACTATION

There are no data on human fertility. Animal studies indicate no effects of fluticasone propionate or salmeterol xinafoate on male or female fertility.

There are limited data in pregnant women. Administration of drugs during pregnancy should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus or child.

Results from a retrospective epidemiological study did not find an increased risk of major congenital malformations (MCMs) following exposure to fluticasone propionate when compared to other inhaled corticosteroids, during the first trimester of pregnancy (see *Pharmacodynamics*).

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 beta₂-adrenoreceptor agonist and glucocorticosteroid. Extensive clinical experience with drugs in these classes has revealed no evidence that the effects are relevant at therapeutic doses. 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 drug concentrations were measured in milk. 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.

ADVERSE EFFECTS

All of the adverse reactions associated with the individual components, salmeterol xinafoate and fluticasone propionate, are listed below. There are no additional adverse reactions attributed to the combination product when compared to the adverse event profiles of the individual components.

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common ($\geq 1/10$), common ($\geq 1/100$ to $<1/10$), uncommon ($\geq 1/1000$ to $<1/100$), rare ($\geq 1/10,000$ to $<1/1000$) and very rare ($<1/10,000$). The majority of frequencies were determined from pooled clinical trial data from 23 asthma and 7 COPD studies. Not all events were reported in clinical trials. For these events, the frequency was calculated based on spontaneous data.

Clinical Trial Data

Infections and infestations

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

Rare: Oesophageal candidiasis

Immune system disorders

Hypersensitivity Reactions:

Uncommon: Cutaneous hypersensitivity reactions, dyspnoea.

Rare: Anaphylactic reactions

Endocrine disorders

Possible systemic effects include (see *Warnings and 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 *Warnings and Precautions*).

Uncommon: Tremor. (see *Warnings and Precautions*).

Cardiac disorders

Uncommon: Palpitations (**see Warnings and Precautions**), tachycardia, atrial fibrillation.

Rare: Cardiac arrhythmias including supraventricular tachycardia and extrasystoles.

Respiratory, thoracic and mediastinal disorders

Common: Hoarseness/dysphonia.

Uncommon: 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:

Rare: Angioedema (mainly facial and oropharyngeal oedema) and bronchospasm.

Endocrine disorders

Possible systemic effects include (see *Warnings and Precautions*):

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

Respiratory, thoracic and mediastinal disorders

Rare: Paradoxical bronchospasm (see *Warnings and Precautions*)

OVERDOSAGE AND TREATMENT

The available information on overdose with Salmeterol + Fluticasone propionate (*Seretide*[®]), salmeterol and/or fluticasone propionate is given below:

The expected symptoms and signs of salmeterol overdose are those typical of excessive beta₂-adrenergic stimulation, including tremor, headache, tachycardia, increases in systolic blood pressure and hypokalaemia. 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 as necessary.

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 Salmeterol + Fluticasone propionate (*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 Salmeterol + Fluticasone propionate (*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 Dosage and Administration).

STORAGE CONDITIONS

Store at temperatures not exceeding 30°C. Store in a dry place.

The Diskus[®] is sealed in a foil overwrap which should only be opened when it is to be used for the first time. Once opened the foil overwrap should be discarded.

INSTRUCTIONS FOR USE/HANDLING

The Diskus[®] is sealed in a foil overwrap. The overwrap provides moisture protection and should only be opened when you are ready to use it for the first time. Once opened the foil overwrap should be discarded.

The Diskus[®] releases a powder which is inhaled into the lungs.

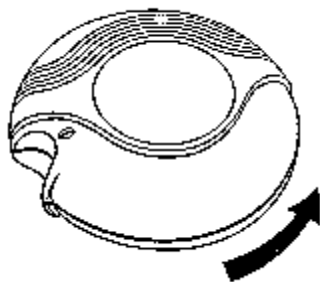
The device is opened and primed by sliding the lever. The mouthpiece is then placed in the mouth and the lips closed around it. The dose can then be inhaled and the device closed.

A dose indicator on the Diskus[®] indicates the number of doses left.

Instructions for use of your Salmeterol + Fluticasone propionate (*Seretide*[®]) Diskus[®]

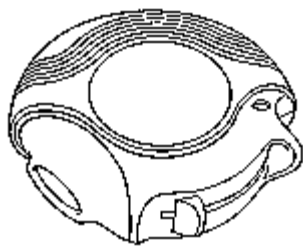
CLOSED

When you take your Diskus[®] out of its box and remove the foil overwrap, it will be in the closed position.



OPENED

A new Diskus[®] contains 28 or 60 doses individually protected doses of your medicine, in powder form. The dose indicator tells you how many doses are left.



Each dose is accurately measured and hygienically protected. It requires no maintenance - and no refilling.

The dose indicator on top of your Diskus[®] tells you how many doses are left. Numbers 5 to 0 will appear in RED, to warn you when there are only a few doses left.

The Diskus[®] is easy to use. When you need a dose, just follow the five simple steps illustrated:-

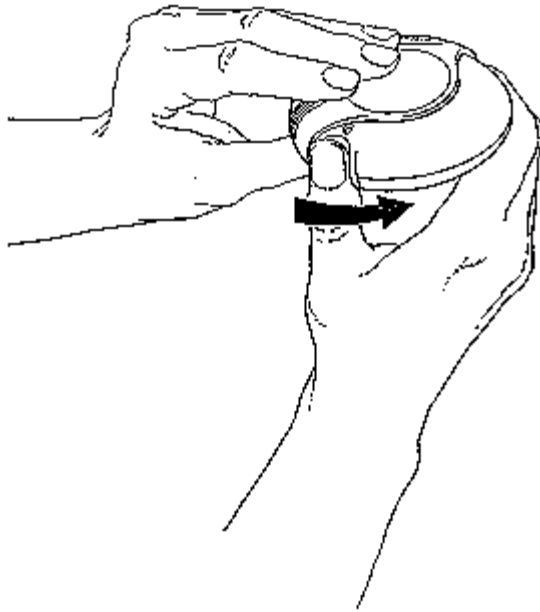
1. Open.
2. Slide.
3. Inhale.
4. Close.
5. Rinse.

How your Diskus[®] works

Sliding the lever of your Diskus[®] opens a small hole in the mouthpiece and unwraps a dose, ready for you to inhale it. When you close the Diskus[®], the lever automatically moves back to its original position, ready for your next dose when you need it. The outer case protects your Diskus[®] when it is not in use.

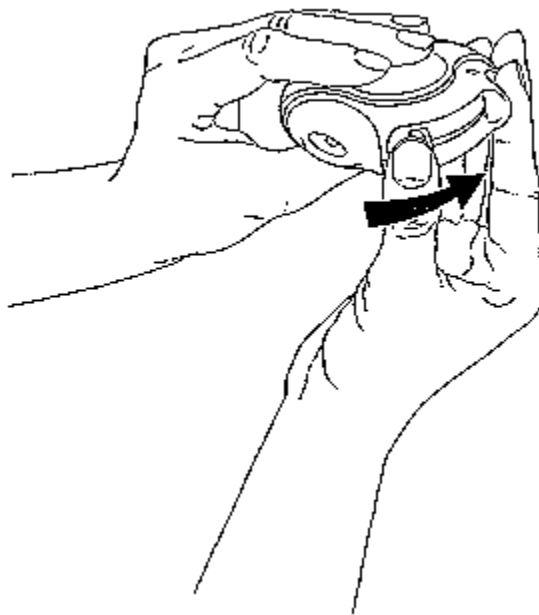
1. Open - How to use the Diskus[®].

To open your Diskus[®], hold the outer case in one hand and put the thumb of your other hand on the thumbgrip. Push your thumb away from you as far as it will go.



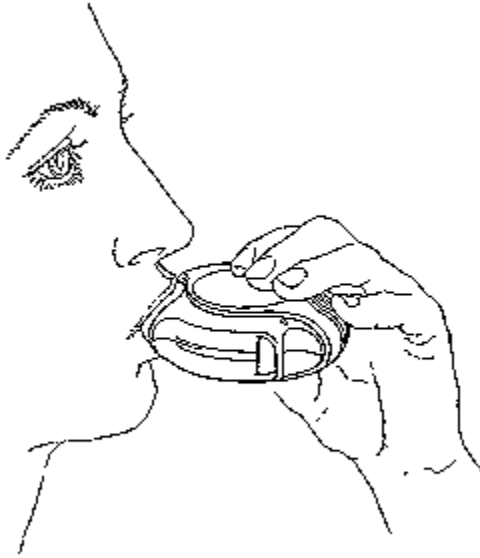
2. Slide.

Hold your Diskus[®] with the mouthpiece towards you. Slide the lever away from you, as far as it will go - until it clicks. Your Diskus[®] is now ready to use. Every time the lever is pushed back, a dose is made available for inhaling. This is shown by the dose counter. Do not play with the lever as this releases doses which will be wasted.



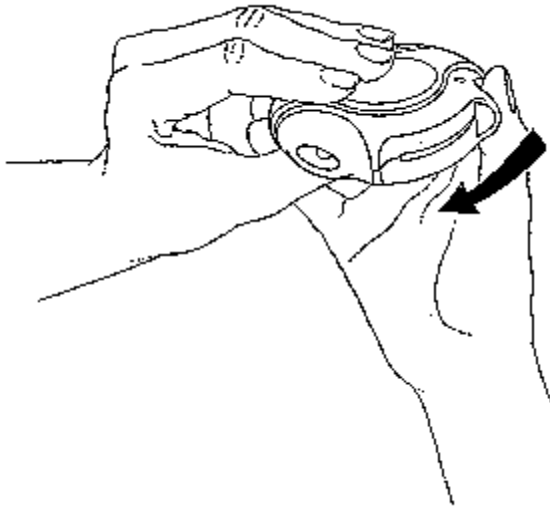
3. Inhale

- Before you start to inhale the dose, read through this section carefully.
- Hold the Diskus[®] away from your mouth. Breathe out as far as is comfortable. Remember - never breathe into your Diskus[®].
- Put the mouthpiece to your lips. Breathe in steadily and deeply - through the Diskus[®], not through your nose.
- Remove the Diskus[®] from your mouth.
- Hold your breath for about 10 seconds, or for as long as is comfortable.
- Breathe out slowly.



4. Close

To close your Diskus[®], put your thumb in the thumbgrip, and slide the thumbgrip back towards you, as far as it will go. When you close the Diskus[®], it clicks shut. The lever automatically returns to its original position and is reset. Your Diskus[®] is now ready for you to use again.



5. Rinse

Afterwards, rinse your mouth with water and spit it out.

If you have been instructed to take two inhalations you must close the Diskus[®] and repeat stages 1 to 4.

REMEMBER

Keep your Diskus[®] dry.

Keep it closed when not in use.

Never breathe into your Diskus[®].

Only slide the lever when you are ready to take a dose.

Do not exceed the stated dose.

AVAILABILITY

Salmeterol + Fluticasone propionate Dry Powder for Inhalation 50/100mcg (*Seretide[®] 100 Diskus[®]*): Blister pack fitted in a discus plastic device enclosed in foil laminate overwrap 60 doses

Salmeterol + Fluticasone propionate Dry Powder for Inhalation 50/250mcg (*Seretide[®] 250 Diskus[®]*): Blister pack fitted in a discus plastic device enclosed in foil laminate overwrap 60 doses

Salmeterol + Fluticasone propionate Dry Powder for Inhalation 50/50mcg (*Seretide[®] 500 Diskus[®]*): Blister pack fitted in a discus plastic device enclosed in foil laminate overwrap 60 doses

CAUTION

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

Keep out of reach of children.

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