SERETIDE™ DISKUS™

Salmeterol/fluticasone propionate

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dose of Seretide provides:
Salmeterol xinafoate equivalent to 50 micrograms of salmeterol and 100, 250 or 500 micrograms of fluticasone propionate.
(See List of Excipients)

PHARMACEUTICAL FORM

Inhalation powder, pre-dispensed.

CLINICAL PARTICULARS

Therapeutic Indications

Asthma

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

- patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short acting beta-2-agonist
  or
- patients already adequately controlled on both inhaled corticosteroid and long-acting beta-2-agonist.

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

Chronic Obstructive Pulmonary Disease

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

Posology and Method of Administration

SERETIDE Diskus is for inhalation only.
Patients should be made aware that 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 Seretide they are receiving remains optimal and is only changed on medical advice. The dose should be titrated to the lowest dose at which effective control of symptoms is maintained. Where the control of symptoms is maintained with the lowest strength of the combination given twice daily then the next step could include a test of inhaled corticosteroid alone. As an alternative, patients requiring long acting beta-2-agonist could be titrated to Seretide given once daily if, in the opinion of the prescriber, it would be adequate to maintain disease control. In the event of once daily dosing when the patient has a history of nocturnal symptoms the dose should be given at night and when the patient has a history of mainly day-time symptoms the dose should be given in the morning.
Patients should be given the strength of Seretide containing the appropriate fluticasone propionate dosage for the severity of their disease. Prescribers should be aware that, in patients with asthma, fluticasone propionate is as effective as other inhaled steroids at approximately half the microgram daily dose. For example, 100mcg of fluticasone propionate is approximately equivalent to 200mcg of beclomethasone dipropionate (CFC containing) or budesonide. If an individual patient should require dosages outside the recommended regimen, appropriate doses of beta-agonist and/or corticosteroid should be prescribed.
Recommended Doses:

Asthma

Adults and adolescents 12 years and older:
One inhalation of 50 micrograms salmeterol and 100 micrograms fluticasone propionate twice daily.
or One inhalation of 50 micrograms salmeterol and 250 micrograms fluticasone propionate twice daily.
or One inhalation of 50 micrograms salmeterol and 500 micrograms fluticasone propionate twice daily.
A short term trial of Seretide may be considered as initial maintenance therapy in adults or adolescents with moderate persistent asthma (defined as patients with daily symptoms, daily rescue use and moderate to severe airflow limitation) for whom rapid control of asthma is essential. In these cases, the recommended initial dose is one inhalation of 50 micrograms salmeterol and 100 micrograms fluticasone propionate twice daily. Once control of asthma is attained treatment should be reviewed and consideration given as to whether patients should be stepped down to an inhaled corticosteroid alone. Regular review of patients as treatment is stepped down is important.
A clear benefit has not been shown as compared to inhaled fluticasone propionate alone used as initial maintenance therapy when one or two of the criteria of severity are missing. In general inhaled corticosteroids remain the first line treatment for most patients. Seretide is not intended for the initial management of mild asthma. Seretide 50/100 micrograms strength is not appropriate in adults and children with severe asthma; it is recommended to establish the appropriate dosage of inhaled corticosteroid before any fixed combination can be used in patients with severe asthma.
Children 4 years and older:
One inhalation of 50 micrograms salmeterol and 100 micrograms fluticasone propionate twice daily. The maximum licensed dose of fluticasone propionate delivered by Seretide Diskus in children is 100mcg twice daily.
There are no data available for use of Seretide in children aged under 4 years.

COPD

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

Special patient groups:

There is no need to adjust the dose in elderly patients or in those with renal impairment. There are no data available for use of Seretide in patients with hepatic impairment.
Using the Diskus:
The device is opened and primed by sliding the lever. The mouthpiece is then placed in the mouth and the lips closed round it. The dose can then be inhaled and the device closed.

Contra-indications

Seretide is contraindicated in patients with hypersensitivity (allergy) to any of the active substances or to the excipient. (see List of Excipients)

Special Warnings and Special Precautions for Use

Seretide Diskus should not be used to treat acute asthma 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 undergo urgent medical assessment. 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.
Treatment with Seretide should not be stopped abruptly in patients with asthma due to risk of exacerbation. Therapy should be down-titrated under physician supervision. For patients with COPD cessation of therapy may also be associated with symptomatic decompensation and should be supervised by a physician.
There was an increased reporting of pneumonia in studies of patients with COPD receiving Seretide (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, 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.
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.
Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods.
These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, 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 Overdosage*).
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.
It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroid is regularly monitored.
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 (a component of salmeterol-FP) 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. Caution should be exercised when strong CYP3A4 inhibitors (e.g. ketoconazole) are co-administered with salmeterol.
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 Diskus should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.
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.

Interaction with other Medicinal Products and Other forms of Interaction

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

Pregnancy and Lactation

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

Undesirable 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 (≥ 1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥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).
Immune system disorders
Hypersensitivity Reactions:
Uncommon: Cutaneous hypersensitivity reactions, dyspnoea.
Rare: Anaphylactic reactions
Endocrine disorders
Possible systemic effects include:
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.
Uncommon: Tremor.
Cardiac disorders
Uncommon: Palpitations, 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:
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.

Overdose:
The expected symptoms and signs of salmeterol overdosage are those typical of excessive $beta_2$– adrenergic stimulation, including tremor, headache, tachycardia, increases in systolic blood pressure and hypokalaemia.
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.
There is no specific treatment for an overdose of Seretide. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

SERETIDE clinical trials

Asthma

A large twelve-month study (Gaining Optimal Asthma ControL, GOAL) in 3416 asthma patients compared the efficacy and safety of 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 SERETIDE achieved #'Well-controlled' asthma compared with 59% of patients treated with inhaled corticosteroid alone.
- 41% of patients treated with SERETIDE achieved ##'Total control' of asthma compared with 28% of patients treated with inhaled corticosteroid alone.

These effects were observed earlier with 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 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 SERETIDE compared to 8% at baseline.

#Well controlled asthma; occasional symptoms or SABA use or less than 80% predicted lung function plus no night-time awakenings, no exacerbations and no side effects enforcing a change in therapy.
##Total control of asthma; no symptoms, no SABA use greater than or equal to 80% predicted lung function, no night-time awakenings, no exacerbations and no side effects enforcing a change in therapy.

COPD

TORCH study (Towards a Revolution in COPD Health):

TORCH was a 3-year study to assess the effect of treatment with Seretide Diskus 50/500mcg bd, salmeterol Diskus 50mcg bd, fluticasone propionate (FP) Diskus 500mcg bd or placebo on all-cause mortality in patients with COPD.
Patients with moderate to severe COPD with a baseline (pre-bronchodilator) FEV_1 <60% of predicted normal were randomised to double-blind medication. During the study, patients were permitted usual COPD therapy with the exception of other inhaled corticosteroids, long-acting bronchodilators and long-term systemic corticosteroids. Survival status at 3 years was determined for all patients regardless of withdrawal from study medication. The primary endpoint was reduction in all cause mortality at 3 years for Seretide vs Placebo.

PHARMACEUTICAL PARTICULARS

List of Excipients

Lactose monohydrate (which contains milk proteins).

Special Precautions for Storage

Do not store above 30°C.
GDS Version Number: 31
Version Date: 25 April 2013

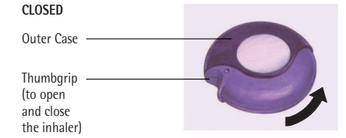
Manufactured by:

Glaxo Wellcome Production*, Evreux, France
* Member of the GlaxoSmithKline group of companies.
* Member of GlaxoSmithKline Group of Companies

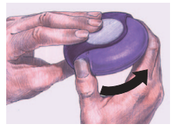
SERETIDE™ DISKUS™

HOW TO USE YOUR DISKUS INHALER

When you take your Diskus out of its box, your Diskus will be in the closed position.



The counter on the top of your Diskus tells you how many blisters are left. Numbers 5 to 0 will appear in **RED,** to warn you when there are only a few blisters left.



1 OPEN

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 until you hear a click.

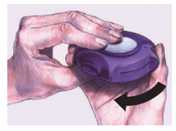
2 SLIDE

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 blister is opened and the powder made available for inhaling. This is shown by the counter. Do not play with the lever because this opens the blisters and wastes the medicine.

3 INHALE

BEFORE YOU START TO INHALE 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.
- Remove the Diskus from your mouth.
- Hold your breath for about 10 seconds, or 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. If you have been instructed to take two blisters you must close the Diskus and repeat steps 1 to 4.

CLEANING

Wipe the mouthpiece of the Diskus with a dry tissue to clean it.

THIS IS A MEDICAMENT	ان هذا الدواء
Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you. Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament. - The doctor and the pharmacist are the experts in medicines, their benefits and risks. - Do not by yourself interrupt the period of treatment prescribed. - Do not repeat the same prescription without consulting your doctor. - Keep all medicaments out of reach of children.	مستحضر يؤثر على صحتك واستهلاكه خلافاً للتعليمات يعرضك للخطر. اتبع بدقة وصفة الطبيب وطريقة الاستعمال المنصوص عليها وتعليمات الصيدلي الذي صرفها لك. - الطبيب والصيدلي هما الخبيران في الدواء وفي نفعه وضرره. - لا تقطع مدة العلاج المحددة لك من تلقاء نفسك. - لا تكرر صرف الدواء بدون استشارة الطبيب. - لا تترك الأدوية في متناول الأطفال.
Council of Arab Health Ministers, Union of Arab Pharmacists.	مجلس وزراء الصحة العرب واتحاد الصيادلة العرب

GlaxoSmithKline

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