Aiming for TOTAL CONTROL With SERETIDE

PRESCRIBING INFORMATION

QUALITATIVE AND QUANTITATIVE COMPOSITION: Each single actuation of ***Seretide*** provides: Salmeterol xinafoate equivalent to 25 micrograms of salmeterol and 50, 125 or 250 micrograms of fluticasone propionate.

PHARMACEUTICAL FORM: Inhalation aerosol.

CLINICAL PARTICULARS: 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 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): ***Seretide*** is indicated for the regular treatment of chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema.

Dosage and Administration: ***Seretide*** Evohaler is for inhalation only. Patients should be made aware that ***Seretide*** Evohaler 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 the 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. If a patient is inadequately controlled on inhaled corticosteroid therapy alone, substitution with *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 *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:- Two inhalations of 25 micrograms salmeterol and 50 micrograms fluticasone propionate twice daily. or Two inhalations of 25 micrograms salmeterol and 125 micrograms fluticasone propionate twice daily. or Two inhalations of 25 micrograms salmeterol and 250 micrograms fluticasone propionate twice daily.

Adults 18 years and older: Doubling the dose of all strengths of *SERETIDE* in adults for up to 14 days has comparable safety and tolerability to regular twice daily dosing and may be considered when patients require additional short term (up to 14 days) inhaled corticosteroid therapy as outlined in asthma treatment guidelines.

Children 4 years and older: Two inhalations of 25 micrograms salmeterol and 50 micrograms fluticasone propionate twice daily. There are no data available for use of ***Seretide*** in children aged under 4 years.

Chronic Obstructive Pulmonary Disease (COPD): For adult patients the recommended dose is two inhalations 25/125 micrograms to 25/250 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: ***Seretide*** is contraindicated in patients with a history of hypersensitivity to any of the ingredients.

Warnings and Precautions: The management of ROAD should normally follow a stepwise programme and patient response should be monitored clinically and by lung function tests. ***Seretide*** Evohaler 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 administration of antibiotics if an exacerbation is associated with infection. 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. 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. 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 Adverse Reactions) and this should be considered when prescribing to patients with a history of diabetes mellitus. A drug interaction study in healthy subjects has shown that ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can greatly increase fluticasone propionate plasma concentrations, resulting in markedly reduced serum cortisol concentrations. During post-marketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing's syndrome and adrenal suppression. Therefore, concomitant use of fluticasone propionate and ritonavir should be avoided, unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side-effects.

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 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.

Pregnancy and Lactation: Administration of drugs 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 drug or in combination, revealed the foetal effects expected at excessive systemic exposure levels of a potent beta2-adrenoreceptor agonist and glucocorticosteroid. 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.

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 drugs does not indicate any effect.

Adverse Reactions: 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. Salmeterol/fluticasone propionate Evohaler 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 beta2-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 reports of arthralgia and hypersensitivity reactions, including rash, oedema and angioedema. There have been reports of oropharyngeal irritation. There have been rare 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. 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. Both hoarseness and incidence of candidiasis may be relieved by gargling with water after use of salmeterol/fluticasone propionate Evohaler. Symptomatic candidiasis can be treated with topical anti-fungal therapy whilst still continuing with salmeterol/fluticasone propionate Evohaler. 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 *Warnings and Precautions).* There have 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).

Salmeterol/fluticasone propionate clinical trials: The following undesirable effects were commonly reported: Hoarseness/dysphonia, throat irritation, headache, candidiasis of mouth and throat and palpitations.

Salmeterol/fluticasone propionate post-marketing: 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 signs and symptoms of salmeterol overdose are tremor, headache and tachycardia. The preferred antidotes are cardioselective beta-blocking agents, which should be used with caution in patients with a history of bronchospasm. If ***Seretide*** therapy has to be withdrawn due to overdose of the beta agonist component of the drug, provision of appropriate replacement corticosteroid therapy should be considered. Acute inhalation of fluticasone propionate doses in excess of those approved may lead to temporary suppression of the hypothalamic-pituitary-adrenal axis. This does not usually require emergency action as normal adrenal function typically recovers within a few days. If higher than approved doses of ***Seretide*** are continued over prolonged periods, significant adrenocortical suppression is possible. There have been very rare reports of acute adrenal crisis, mainly occurring in children exposed to higher than approved doses over prolonged periods (several months or years); 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 *Dosage and Administration).*

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. 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 *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 *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 *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 ***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 ***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 and health status and reducing the risk of COPD exacerbations, in both current and ex-smokers.

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 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 hour) 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 steroios, 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. Even though plasma levels of ***Seretide*** are very low, potential interactions with other substrates and inhibitors of CYP 3A4 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 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.

Fluticasone propionate: The absolute bioavailability of inhaled fluticasone propionate in healthy subjects varies between approximately 10 to 30% of the nominal dose depending on the inhalation device used. 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 (1150 ml/min), a large volume of distribution at steady-state (approximately 300 l) 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.

PHARMACEUTICAL PARTICULARS: **Shelf Life:** 2 years.

Special Precautions for Storage: ***Seretide*** Evohaler should not be stored above 30°C. Protect from frost and direct sunlight. As with most inhaled medications in pressurised canisters, the therapeutic effect of this medication may decrease when the canister is cold. The canister should not be punctured, broken or burnt even when apparently empty.

Nature and Contents of Container: ***Seretide*** Evohaler comprises a suspension of salmeterol and fluticasone propionate in the non-CFC propellant HFA 134a. The suspension is contained in an aluminium alloy can sealed with a metering valve. The canisters are fitted into plastic actuators incorporating an atomising orifice and fitted with dustcaps. ***Seretide*** Evohaler has been formulated in three strengths and one pack size, delivering 120 actuations per inhaler.

Instructions for Use/Handling: Testing your inhaler: Before using for the first time or if your inhaler has not been used for a week or more remove the mouthpiece cover by gently squeezing the sides of the cover, shake the inhaler well, and release one puff into the air to make sure that it works.

Using your inhaler:
1. Remove the mouthpiece cover by gently squeezing the sides of the cover and check the mouthpiece inside and outside to see that it is clean.
2. Shake the inhaler well.
3. Hold the inhaler upright between fingers and thumb with your thumb on the base, below the mouthpiece.
4. Breathe out as far as is comfortable and then place the mouthpiece in your mouth between your teeth and close your lips around it, but do not bite it.
5. Just after starting to breathe in through your mouth, press down on the top of the inhaler to release salmeterol and fluticasone propionate, while still breathing in steadily and deeply.
6. While holding your breath, take the inhaler from your mouth and take your finger from the top of the inhaler. Continue holding your breath for as long as is comfortable.
7. To take the second puff keep the inhaler upright and wait about half a minute before repeating steps 2 to 6.
The mouthpiece cover is replaced by firmly pushing and snapping the cap into position.

IMPORTANT: Do not rush stages 4,5 and 6. It is important that you start to breathe in as slowly as possible just before operating your inhaler. Practise in front of a mirror for the first few times. If you see "mist" coming from the top of your inhaler or the sides of your mouth you should start again from stage 2. If your doctor has given you different instructions for using your inhaler, please follow them carefully. Tell your doctor if you have any difficulties.

Children: Young children may need help and an adult may need to operate the inhaler for them. Encourage the child to breathe out and operate the inhaler just after the child starts to breathe in. Practice the technique together. Older children or people with weak hands should hold the inhaler with both hands. Put the two forefingers on top of the inhaler and both thumbs on the base below the mouthpiece.

Cleaning: Your inhaler should be cleaned at least once a week.
1. Remove the mouth piece cover.
2. Do not remove the canister from the plastic casing.
3. Wipe the inside and outside of the mouthpiece and the plastic casing with a dry cloth, tissue or cottonbud.
4. Replace the mouthpiece cover.
DO NOT PUT THE METAL CANISTER INTO WATER.
Not all presentations are available in every country.
Version number: GDS17I1PIOS Date of issue: 10 September 2004.