SERETIDE DISKUS
Salmeterol xinafoate
Fluticasone propionate

1. NAME OF THE MEDICINAL PRODUCT
SERETIDE Diskus

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
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.

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.

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

3. PHARMACEUTICAL FORM
Inhalation powder.

4. CLINICAL PARTICULARS
4.1 Indications
Asthma (Reversible Obstructive Airways Disease)
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.

4.2 Dosage and 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.

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 *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:
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 *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.

4.3 Contraindications
SERETIDE is contraindicated in patients with a history of hypersensitivity to any of the ingredients (*see List of Excipients*).

4.4 Warnings and Precautions
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. *SERETIDE* Diskus is not intended for the initial management of asthma until the need for and approximate dosage of corticosteroids has been established.

Increasing use of short-acting bronchodilators to relieve symptoms indicates deterioration of control and patients should be reviewed by a physician.

Sudden and progressive deterioration in control of asthma is potentially life-threatening and the patient should be reviewed by a physician. Consideration should be given to increasing corticosteroid therapy. Also, where the current dosage of *SERETIDE* has failed to give adequate control of asthma, the patient should be reviewed by a physician.

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

There was an increased reporting of pneumonia in studies of patients with COPD receiving *SERETIDE* (*see 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 severe cardiovascular disorders, including heart rhythm abnormalities, diabetes mellitus, untreated-hypokalaemia or thyrotoxicosis.

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

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

Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods; these effects are much less likely to occur than with oral corticosteroids (*see Overdose*). Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract, glaucoma and central serous chorioretinopathy. 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*).

It was observed in a drug interaction study that concomitant use of systemic ketoconazole increases exposure to salmeterol. This may lead to prolongation in the QTc interval. Caution should be exercised when strong CYP3A4 inhibitors (e.g. ketoconazole) are co-administered with salmeterol (*see Interactions, and 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 Diskus or Inhaler 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*).

4.5 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.

Concomitant use of other beta-adrenergic containing drugs can have a potentially additive effect. MAO-inhibitors, tricyclic antidepressants, L-dopa, L-thyroxine, oxytocin and in some cases also antiarrhytmics can increase the cardiovascular side effects of β-sympathomimetics and thus also of *SERETIDE*. With xanthines there is a risk of hypokalaemia. Short-acting beta$_2$-agonists are effective when administered together with *SERETIDE* and should kept available as rescue medications.

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

4.6 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 beta$_2$-adrenoreceptor agonist and glucocorticosteroid.

Extensive clinical experience with drugs in these classes has revealed no evidence that the effects are relevant at therapeutic doses.

The lowest effective dose of fluticasone propionate needed to maintain adequate asthma control should be used in the treatment of pregnant women.

Both salmeterol and fluticasone propionate are excreted into breast milk in rats.

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 child.

4.7 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.

4.8 Adverse Reactions
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 (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) 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

Post-marketing 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*)

4.9 Overdose
The available information on overdose with *SERETIDE*, salmeterol and/or fluticasone propionate is given below:
The expected symptoms and signs of salmeterol overdosage are those typical of excessive beta$_2$-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, as verified by plasma cortisol measurements.

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*).

Additionally, hypokalaemia can occur, and potassium replacement should be considered.

Although the bioavailability of the active principles contained in *SERETIDE* is low, accidental consumption less than an hour before which could lead to severe intoxication gastric lavage and then (if necessary repeated) administration of charcoal should be carried out. In the case of severe intoxication monitoring and correction of the electrolyte and acid-base balance is required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics

Asthma

Salmeterol Multi-center Asthma Research Trial (SMART)

The Salmeterol Multi-center Asthma Research Trial (SMART) was a 28-week US study that evaluated the safety of salmeterol compared to placebo added to usual therapy in adult and adolescent subjects. Although 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 (13 deaths out of 13,176 patients treated with salmeterol versus 3 deaths out of 13,179 patients on placebo). The study was not designed to assess the impact of concurrent inhaled corticosteroid use.

Safety and efficacy of salmeterol-FP versus FP alone in asthma

Two multi-center 26-week studies were conducted to compare the safety and efficacy of salmeterol-FP versus FP alone, one in adult and adolescent subjects (AUSTRI trial), and the other in paediatric subjects 4-11 years of age (VESTRI trial). For both studies, enrolled subjects had moderate to severe persistent asthma with history of asthma-related hospitalisation or asthma exacerbation in the previous year. The primary objective of each study was to determine whether the addition of LABA to ICS therapy (salmeterol-FP) was non-inferior to ICS (FP) alone in terms of the risk of serious asthma related events (asthma-related hospitalisation, endotracheal intubation, and death). A secondary efficacy objective of these studies was to evaluate whether ICS/LABA (salmeterol-FP) was superior to ICS therapy alone (FP) in terms of severe asthma exacerbation (defined as deterioration of asthma requiring the use of systemic corticosteroids for at least 3 days or an in-patient hospitalisation or emergency department visit due to asthma that required systemic corticosteroids).

A total of 11,679 and 6,208 subjects were randomized and received treatment in the AUSTRI and VESTRI trials, respectively. For the primary safety endpoint, non-inferiority was achieved for both trials (*see Table below*).

Serious Asthma-Related Events in the 26-Week AUSTRI and VESTRI Trials

	AUSTRI		VESTRI	
	Salmeterol-FP (n = 5,834)	FP Alone (n = 5,845)	Salmeterol-FP (n = 3,107)	FP Alone (n = 3,101)
Composite endpoint (Asthma-related hospitalisation, endotracheal intubation, or death)	34 (0.6%)	33 (0.6%)	27 (0.9%)	21 (0.7%)
Salmeterol-FP/FP Hazard ratio (95% CI)	1.029 (0.638 - 1.662)[a]		1.285 (0.726 - 2.272)[b]	
Death	0	0	0	0
Asthma-related hospitalisation	34	33	27	21
Endotracheal intubation	0	2	0	0

[a] If the resulting upper 95% CI estimate for the relative risk was less than 2.0, then non-inferiority was concluded.

[b] If the resulting upper 95% CI estimate for the relative risk was less than 2.675, then non-inferiority was concluded.

For the secondary efficacy endpoint, reduction in time to first asthma exacerbation for salmeterol-FP relative to FP was seen in both studies, however only AUSTRI met statistical significance:

	AUSTRI		VESTRI	
	Salmeterol-FP (n = 5,834)	FP Alone (n = 5,845)	Salmeterol-FP (n = 3,107)	FP Alone (n = 3,101)
Number of subjects with an asthma exacerbation	480 (8%)	597 (10%)	265 (9%)	309 (10%)
Salmeterol-FP/FP Hazard ratio (95% CI)	0.787 (0.698, 0.888)		0.859 (0.729, 1.012)	

Twelve-month study
A large twelve-month study (Gaining Optimal Asthma ControL, GOAL) in 3,416 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; 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 *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 beta$_2$-agonist:
Placebo-controlled clinical trials, over 6 months, have shown that regular use of both *SERETIDE* 50/250 and 50/500 micrograms rapidly and significantly improves lung function, significantly reduced breathlessness and the use of relief medication. There were also significant improvements in health status.

Symptomatic COPD patients who demonstrated less than 10% reversibility to a short-acting beta$_2$-agonist:
Placebo-controlled clinical trials, over 6 and 12 months, have shown that regular use of *SERETIDE* improves lung function, reduced breathlessness and the use of relief medication. Over a 12-month period the risk of COPD exacerbations was reduced from 1.42 per year to 0.99 per year compared with placebo and the risk of exacerbations requiring oral corticosteroids was significantly reduced from 0.81 to 0.47 per year compared with placebo. There were also significant improvements in health status.

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 *SERETIDE* relative to non-FP containing ICS. No placebo comparator was included in this study.

Within the asthma cohort of 5,362 first trimester ICS-exposed pregnancies, 131 diagnosed MCMs were identified; 1,612 (30%) were exposed to FP or *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 *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:
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 hours) beta$_2$-adrenoceptor agonist with a long side chain which binds to the exo-site of the receptor.

These pharmacological properties of salmeterol offer more effective protection against histamine-induced bronchoconstriction and produce a longer duration of bronchodilation, lasting for at least 12 hours, than recommended doses of conventional short-acting beta$_2$-agonists.

In vitro tests have shown salmeterol is a potent and long-lasting inhibitor of the release, from human lung, of mast cell mediators such as histamine, leukotrienes and prostaglandin D$_2$.

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.

Fluticasone propionate:
Fluticasone propionate given by inhalation at recommended doses has a potent glucocorticoid antiinflammatory 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 remains 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*).

5.2 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, co-administration of salmeterol (50 mcg twice daily inhaled) and the CYP3A4 inhibitor ketoconazole (400 mg once daily orally) for 7 days resulted in a significant increase in plasma salmeterol exposure (1.4-fold C_{max} and 15-fold AUC). There was no increase in salmeterol accumulation with repeat dosing. Three subjects were withdrawn from salmeterol and ketoconazole co-administration due to QTc prolongation or palpitations with sinus tachycardia. In the remaining 12 subjects, co-administration of salmeterol and ketoconazole did not result in a clinically significant effect on heart rate, blood potassium or QTc duration (*see 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 1,000-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 Inhaler (10.9%), salmeterol-fluticasone propionate Inhaler (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 characterized by high plasma clearance (1,150 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. The main part of the dose is excreted in faeces as metabolites and unchanged drug. Other unidentified metabolites are also found in faeces. Care should be taken when co-administering known CYP3A4 inhibitors, as there is potential for increased systemic exposure to fluticasone propionate.

Special Patient Populations
***SERETIDE* 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 *SERETIDE* (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 *SERETIDE* (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 *SERETIDE* (50/100 micrograms) and FP (100 micrograms) in both adolescents and adults and in children.
- FP exposure was similar at the higher *SERETIDE* 50/500 microgram dose compared to the equivalent FP dose alone.
- Higher salmeterol exposure was observed in children taking *SERETIDE* (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.

5.3 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 beta$_2$-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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Lactose (which contains milk protein).

6.2 Incompatibilities

None reported.

6.3 Shelf Life

The expiry date is indicated on the packaging.

6.4 Special Precautions for Storage

Do not store above 30°C.

Store in a dry place.

If your Diskus is provided sealed in a foil overwrap, this should be discarded after the Diskus is used for the first time.

6.5 Nature and Contents of Container

As registered locally.

6.6 Instructions for Use/Handling

Your Diskus may be provided in a sealed foil overwrap which provides moisture protection. If so, the foil overwrap should only be opened when you are ready to use the Diskus for the first time. Once removed/opened the foil overwrap should be discarded.

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

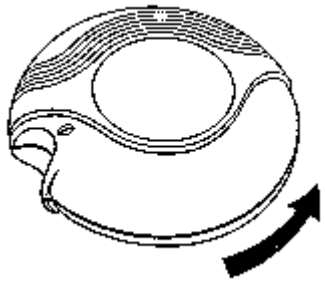
The device is opened and primed by sliding the lever. The mouthpiece is then placed in the mouth and the lips closed around it. The dose can then be inhaled, and the device closed.

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

Instructions for use of your *SERETIDE* Diskus

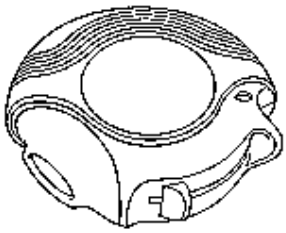
CLOSED

When you take your Diskus out of its box and remove any foil overwrap that may be present, the Diskus will be in the closed position.



OPENED

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



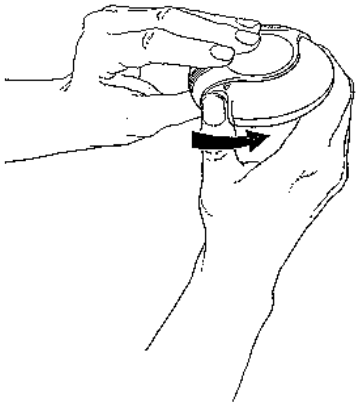
Each dose is accurately measured and hygienically protected. It requires no maintenance - and no refilling.

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.

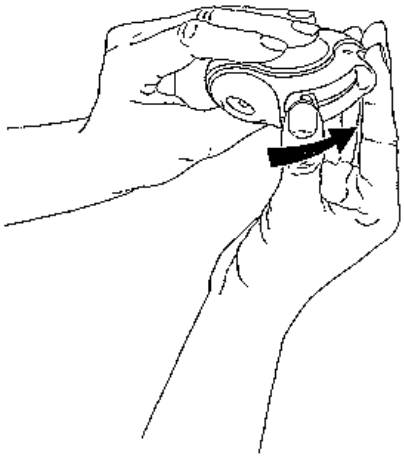
The Diskus is easy to use. When you need a dose, just follow the five simple steps illustrated:
1. Open.
2. Slide.
3. Inhale.
4. Close.
5. Rinse.

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 thumb grip. Push your thumb away from you as far as it will go.



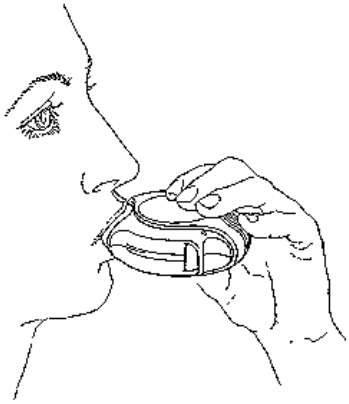
2. Slide
Hold your Diskus with the mouthpiece towards you. Slide the lever away from you, as far as it will go - until it clicks. Your Diskus is now ready to use. Every time the lever is pushed back, a dose is made available for inhaling. This is shown by the dose counter. Do not play with the lever 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 it's comfortable.
- Breathe out slowly.

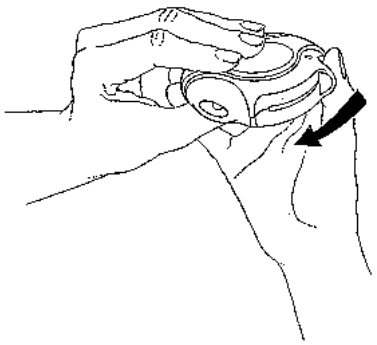
You may not be able to taste or feel the powder on your tongue, even if you have used the Diskus correctly.



4. Close

To close your Diskus, put your thumb in the thumb grip, and slide the thumb grip 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.

Keep out of reach of children.

Not all presentations are available in every country.

Package Quantities and Registration Number
SERETIDE Diskus 50/100 mcg, Reg. No. DKI1991500167A1
SERETIDE Diskus 50/250 mcg, Reg. No. DKI1991500167B1
SERETIDE Diskus 50/500 mcg, Reg. No. DKI1991500167C1

HARUS DENGAN RESEP DOKTER

Manufactured by
Glaxo Wellcome Production
Evreux, France

Imported by
PT Glaxo Wellcome Indonesia
Jakarta, Indonesia

PI based on ver GDS36/IPI21 (28 October 2019)

AWB_leaSERdis_Site Transfer to Evreux + GDS36 IPI21_circ3_8May2020
ERS_leSERdis_Site Transfer to Evreux_circ2_28Mar19

Disetujui oleh BPOM: 22 Desember 2020

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