

# Seretide Evohaler

Salmeterol/fluticasone propionate

## 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

#### Asthma

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

- Patients not adequately controlled with inhaled corticosteroids and “as needed” inhaled short-acting-beta<sub>2</sub>-agonist

or

- Patients already adequately controlled on both inhaled corticosteroids and long-acting-beta<sub>2</sub>-agonist

Note: Seretide 25/50 mcg strength is not appropriate in adults with severe asthma.

### Dosage and Administration

Seretide Evohaler is for oral 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. The dose should be titrated to the lowest dose at which effective control of symptoms is maintained.

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

#### Recommended Doses:

## **Asthma**

Adults and adolescents 12 years and older:

- Two inhalations of 25 mcg salmeterol and 50 mcg fluticasone propionate twice daily.

or

- Two inhalations of 25 mcg salmeterol and 125 mcg fluticasone propionate twice daily.

or

- Two inhalations of 25 mcg salmeterol and 250 mcg fluticasone propionate twice daily.

Children 4 years and older:

- Two inhalations of 25 mcg salmeterol and 50 mcg fluticasone propionate twice daily.

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

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**

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.

Patients should not be initiated on Seretide during an exacerbation, or if they have significantly worsening or acutely deteriorating asthma.

Serious asthma-related adverse events and exacerbations may occur during treatment with Seretide. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation on Seretide.

Increasing use of short-acting bronchodilators to relieve asthma symptoms indicates deterioration of asthma 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.

As with all inhaled medication containing corticosteroids, Seretide should be administered with caution in patients with active or quiescent pulmonary tuberculosis.

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

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

Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods; these effects are much less likely to occur than with oral corticosteroids (see *Overdose*). Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract, 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 *Undesirable Effects*) and this should be considered when prescribing to patients with a history of diabetes mellitus.

During post-marketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing's syndrome and adrenal suppression. Therefore, concomitant use of fluticasone propionate and ritonavir should be avoided, unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side-effects (see *Interactions*).

It was observed in a drug interaction study that concomitant use of systemic ketoconazole increases exposure to SEREVENT. This may lead to prolongation in the QTc interval. Concomitant treatment with ketoconazole or other potent CYP3A4 inhibitors should therefore be avoided unless the benefits outweigh the potentially increased risk of systemic side effects of salmeterol treatment (see *Interactions* and *Pharmacokinetics*).

As with other inhalation therapy paradoxical bronchospasm may occur with an immediate increase in wheezing after dosing. This should be treated immediately with a fast and short-acting inhaled bronchodilator. Salmeterol-FP Accuhaler/Diskus or Evohaler should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary (see *Adverse Reactions*).

The pharmacological side-effects of beta<sub>2</sub>-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*).

## **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.

Caution should be exercised when other potent cytochrome P450 3A4 inhibitors are co-administered with fluticasone propionate. In a drug interaction study, co-administration of orally inhaled fluticasone propionate (1000 mcg) and ketoconazole (200 mg once daily) resulted in increased plasma fluticasone propionate exposure and reduced plasma cortisol AUC, but had no effect on urinary excretion of cortisol. In another

multiple-dose drug interaction study, co-administration of orally inhaled fluticasone propionate (500 mcg twice daily) and erythromycin (333 mg 3 times daily) did not affect fluticasone propionate pharmacokinetics.

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

## **Pregnancy and Lactation**

### **Fertility**

There are no data on human fertility. Animal studies indicate no effects of fluticasone propionate or salmeterol xinafoate on male or female fertility (see *Pharmacodynamic Properties*).

### **Pregnancy**

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<sub>2</sub>-adrenoreceptor agonist and glucocorticosteroid.

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

### **Lactation**

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

Administration during lactation should only be considered if the expected benefit to the mother is greater than any possible risk to the child.

## **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**

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

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

## **Clinical Trial Data**

### **Infections and infestations**

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

Rare: Oesophageal candidiasis.

### **Immune system disorders**

Hypersensitivity Reactions:

Uncommon: Cutaneous hypersensitivity reactions, dyspnoea.

Rare: Anaphylactic reactions.

### **Eye disorders**

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

Uncommon: Cataract.

Rare: Glaucoma.

### **Metabolism and nutrition disorders**

Uncommon: Hyperglycaemia.

### **Psychiatric disorders**

Uncommon: Anxiety, sleep disorders.

Rare: Behavioural changes, including hyperactivity and irritability (predominantly in children).

### **Nervous system disorders**

Very common: Headache (see *Warnings and Precautions*).

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

### **Cardiac disorders**

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

Rare: Cardiac arrhythmias, including supraventricular tachycardia and extrasystoles.

### **Respiratory, thoracic and mediastinal disorders**

Common: Hoarseness/dysphonia.

Uncommon: Throat irritation.

### **Skin and subcutaneous tissue disorders**

Uncommon: Contusions.

### **Musculoskeletal and connective tissue disorders**

Common: Muscle cramps, arthralgia.

### **Postmarketing Data**

#### **Immune system disorders**

Hypersensitivity reactions manifesting as:

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

#### **Endocrine disorders**

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

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

#### **Respiratory, thoracic and mediastinal disorders**

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

#### Fluticasone propionate

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.

## 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<sub>2</sub>-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 patients should be treated supportively with appropriate monitoring as necessary. Acute inhalation of fluticasone propionate doses in excess of those approved may lead to temporary suppression of the hypothalamic-pituitary-adrenal axis. This does not usually require emergency action as normal adrenal function typically recovers within a few days.

If higher than approved doses of 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

#### 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-centre 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) <sup>a</sup>		1.285 (0.726-2.272) <sup>b</sup>	
Death	0	0	0	0
Asthma-related hospitalisation	34	33	27	21
Endotracheal intubation	0	2	0	0

<sup>a</sup> If the resulting upper 95% CI estimate for the relative risk was less than 2.0, then non-inferiority was concluded.

<sup>b</sup> 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)	

### **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 5362 first trimester ICS-exposed pregnancies, 131 diagnosed MCMs were identified; 1612 (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. The adjusted odds ratio for MCMs diagnosed by 1 year was 0.9 (95% CI: 0.3-2.9) for FP alone and 1.3 for Seretide (95% CI: 0.5-3.2) as compared to any non-fluticasone propionate inhaled corticosteroid for women with moderate asthma. The adjusted odds ratio for MCMs diagnosed by 1 year was 1.3 (95% CI: 0.6-3.0) for FP alone and 1.1 for Seretide (95% CI: 0.6-2.0) as compared to any non-fluticasone propionate inhaled corticosteroid for women with severe asthma. 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 hour) beta<sub>2</sub>-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<sub>2</sub>-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<sub>2</sub>.

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

### Fluticasone propionate

Fluticasone propionate given by inhalation at recommended doses has a potent glucocorticoid anti-inflammatory action within the lungs, resulting in reduced symptoms and exacerbations of asthma, without the adverse effects observed when corticosteroids are administered systemically.

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

### **Pharmacokinetics**

There is no evidence in animal or human subjects that the administration of salmeterol and fluticasone propionate together by the inhaled route affects the pharmacokinetics of either component. For pharmacokinetic purposes therefore each component can be considered separately.

In a placebo-controlled, crossover drug interaction study in 15 healthy subjects, co-administration of SEREVENT (50 mcg twice daily inhaled) and the CYP3A4 inhibitor ketoconazole (400 mg once daily orally) for 7 days resulted in a significant increase in plasma salmeterol exposure (1.4-fold C<sub>max</sub> and 15-fold AUC). There was no increase in salmeterol accumulation with repeat dosing. Three subjects were withdrawn from SEREVENT and ketoconazole co-administration due to QTc prolongation or

palpitations with sinus tachycardia. In the remaining 12 subjects, co-administration of SEREVENT and ketoconazole did not result in a clinically significant effect on heart rate, blood potassium or QTc duration (see *Warnings and Precautions* and *Interactions*).

Even though plasma levels of fluticasone propionate and salmeterol 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 pg/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 ng/mL. These concentrations are up to 1000 fold lower than steady state levels observed in toxicity studies. No detrimental effects have been seen following long-term regular dosing (more than 12 months) in patients with airway obstruction.

An *in vitro* study showed that salmeterol is extensively metabolised to  $\alpha$ -hydroxysalmeterol (aliphatic oxidation) by cytochrome P450 3A4 (CYP3A4). 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 Accuhaler/Diskus (7.8%), fluticasone propionate Diskhaler (9.0%), fluticasone propionate Evohaler (10.9%), salmeterol-fluticasone propionate Evohaler (5.3%) and salmeterol-fluticasone propionate Accuhaler/Diskus (5.5%) respectively. 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.

## **Preclinical Data**

### Reproductive toxicology

Fluticasone propionate, administered subcutaneously at doses of up to 50 mcg/kg/day (up to 100 mcg/kg/day in males, prior to Day 36), did not affect the fertility or mating performance of the F0 and F1 generation rats, when given throughout the periods of gametogenesis, mating, gestation, parturition and lactation. No effects were identified on the fertility of male and female rats treated orally with salmeterol xinafoate during gametogenesis using a maximum dosage level of 2 mg/kg/day. An equivalent oral fertility study with salmeterol base that used a high dose level of 10 mg/kg/day was also without effect.

## **Special Precautions for Storage**

Replace the mouthpiece cover firmly and snap it into position,

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.

For presentations with a dose counter, the canister has a counter attached to it, which shows how many actuations of medicine are left. The number will show through a window in the back of the plastic actuator.

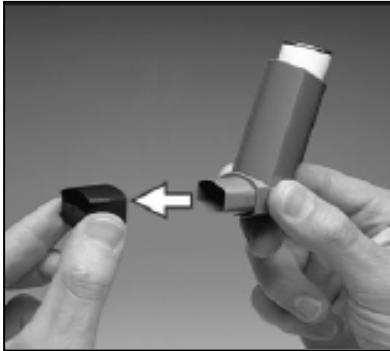
## **Instructions for Use/Handling**

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 two puffs into the air to make sure that it works.

For presentations with a dose counter, each time the inhaler is activated the number on the counter will count down by one. In certain circumstances dropping the inhaler may cause the counter to count on.

Using your inhaler:



1. Remove the mouthpiece cover by gently squeezing the sides of the cover.
2. Check inside and outside of the inhaler including the mouthpiece for the presence of loose objects.



3. Shake the inhaler well to ensure that any loose objects are removed and that the contents of the inhaler are evenly mixed.



4. Hold the inhaler upright between fingers and thumb with your thumb on the base, below the mouthpiece.



5. 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.



6. Just after starting to breathe in through your mouth, press firmly down on the top of the inhaler to release salmeterol and fluticasone propionate, while still breathing in steadily and deeply.



7. 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.



8. To take the second puff keep the inhaler upright and wait about half a minute before repeating steps 3 to 7.
9. Afterwards rinse your mouth with water and spit it out.
10. Replace the mouthpiece cover by firmly pushing and snapping the cap into position.

**IMPORTANT:**

Do not rush stages 5, 6 and 7. 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.

For presentations with a dose counter:

You should consider getting a replacement when the counter shows the number 020. When the counter reads 000 you must replace it. Any puffs left in the device may not be enough to give you a full dose.

Never try to alter the numbers on the counter or detach the counter from the metal canister. The counter cannot be reset and is permanently attached to the canister.

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.**

## **Product Registrant**

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**Version number: GDS35/IPI19 (SI)**

**Date of issue: 11 April 2018**

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