

1. NAME OF THE MEDICINAL PRODUCT

SERETIDE 125/25MCG EVOHALER/MDI

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2. 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.

For the full list of excipients, see section 6.1.

None of the excipients used in this formulation has been identified or reported to cause side effects.

3. PHARMACEUTICAL FORM

Inhalation aerosol

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ASTHMA (Reversible Obstructive Airways Disease)

SERETIDE is indicated in the regular treatment of asthma (Reversible Obstructive Airways Disease).

This may include:

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

Patients who are symptomatic on current inhaled corticosteroid therapy.

Patients on regular bronchodilator therapy who require inhaled corticosteroids.

Chronic Obstructive Pulmonary Disease (COPD)

SERETIDE is indicated for the regular treatment of chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema and has been shown to reduce all-cause mortality.

4.2 Posology and method of administration

Posology

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.

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:-

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.

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. At a dose of 50/500 micrograms twice daily, *SERETIDE* Accuhaler/Diskus has been shown to reduce all-cause mortality (see *Clinical Studies*).

Special populations

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.

4.4 Special warnings and precautions for use

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 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 section 4.8). Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of pneumonia and exacerbation frequently overlap.

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

SERETIDE should be administered with caution in patients with thyrotoxicosis.

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

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

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 section 4.9). 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 section 4.9).

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 section 4.8*) 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 section 4.5*).

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. Caution should be exercised when strong CYP3A4 inhibitors (e.g. ketoconazole) are co-administered with *SEREVENT*. (*see section 4.5, and section 5.2*).

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 section 4.8*).

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 section 4.8*).

4.5 Interaction with other medicinal products and other forms of interaction

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

Under normal circumstances, low plasma concentrations of fluticasone propionate are achieved after inhaled dosing, due to extensive first pass metabolism and high systemic clearance mediated by cytochrome P450

3A4 in the gut and liver. Hence, clinically significant drug interactions mediated by fluticasone propionate are unlikely.

A drug interaction study in healthy subjects has shown that ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can greatly increase fluticasone propionate plasma concentrations, resulting in markedly reduced serum cortisol concentrations. During post-marketing use, there have been reports of clinically significant drug interactions in patients receiving intranasal or inhaled fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing's syndrome and adrenal suppression. Therefore, concomitant use of fluticasone propionate and ritonavir should be avoided, unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side-effects.

Studies have shown that other inhibitors of cytochrome P450 3A4 produce negligible (erythromycin) and minor (ketoconazole) increases in systemic exposure to fluticasone propionate without notable reductions in serum cortisol concentrations. Nevertheless, care is advised when co-administering potent cytochrome P450 3A4 inhibitors (e.g. ketoconazole) as there is potential for increased systemic exposure to fluticasone propionate.

Co-administration of ketoconazole and *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 section 4.4, and section 5.2)

4.6 Fertility, 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 section 5.1).

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 β_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.

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.

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 Undesirable effects

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

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

Clinical Trial Data

Infections and infestations

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

Rare: Oesophageal candidiasis

Immune system disorders

Hypersensitivity Reactions:

Uncommon: Cutaneous hypersensitivity reactions, dyspnoea.

Rare: Anaphylactic reactions

Endocrine disorders

Possible systemic effects include (*see section 4.4*):

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 section 4.4*).

Uncommon: Tremor. (*see section 4.4*).

Cardiac disorders

Uncommon: Palpitations (*see section 4.4*), 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 section 4.4*):

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 section 4.4*)

Healthcare professionals are requested to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) <https://pv.pharmacyboardkenya.org>.

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 beta₂-adrenergic stimulation, including tremor, headache, tachycardia, increases in systolic blood pressure and hypokalaemia. There is no specific treatment for an overdose of salmeterol and fluticasone propionate. If overdose occurs, the 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 section 4.2*).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code

Anatomical Therapeutic Chemical (ATC) code: R03AK06
Pharmacotherapeutic group: Adrenergics in combination with corticosteroids or other drugs, excl. anticholinergics.

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) ^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 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; 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 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.

TORCH study (TOwards a Revolution in COPD Health):

TORCH was a 3-year study to assess the effect of treatment with *SERETIDE* Accuhaler/Diskus 50/500 micrograms twice daily, salmeterol Accuhaler/Diskus 50 micrograms twice daily, FP Accuhaler/Diskus 500 micrograms twice daily or placebo on all-cause mortality in patients with COPD. Patients with moderate to severe COPD with a baseline (pre-bronchodilator) FEV₁ <60% of predicted normal were randomised to double-blind medication. During the study, patients were permitted usual COPD therapy with the exception of other inhaled corticosteroids, long-acting bronchodilators, and long-term systemic corticosteroids. Survival status at 3 years was determined for all patients regardless of withdrawal from study medication. The primary endpoint was reduction in all-cause mortality at 3 years for *SERETIDE* vs placebo.

	Placebo N = 1524	Salmeterol 50 N = 1521	FP 500 N = 1534	<i>SERETIDE</i> 50/500 N = 1533
All cause mortality at 3 years				
Number of deaths (%)	231 (15.2%)	205 (13.5%)	246 (16.0%)	193 (12.6%)
Hazard Ratio vs Placebo (CIs) p value	N/A	0.879 (0.73, 1.06) 0.180	1.060 (0.89, 1.27) 0.525	0.825 (0.68, 1.00) 0.052 ¹
Hazard Ratio <i>SERETIDE</i> 50/500 vs components (CIs) p value	N/A	0.932 (0.77, 1.13) 0.481	0.774 (0.64, 0.93) 0.007	N/A

1. P value adjusted for 2 interim analyses on the primary efficacy comparison from a log-rank analysis stratified by smoking status

SERETIDE reduced the risk of dying at any time during the 3 years by 17.5% compared to placebo (Hazard Ratio 0.825 (95% CI 0.68, 1.00, p=0.052; all adjusted for interim analyses). There was a 12% reduction in the risk of dying at any time within 3 years from any cause for salmeterol

compared with placebo ($p=0.180$) and a 6% increase for FP compared with placebo ($p=0.525$).

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

The percentage of patients who died within 3 years due to COPD-related causes was 6.0% for placebo, 6.1% for salmeterol, 6.9% for FP and 4.7% for *SERETIDE*.

SERETIDE reduced the rate of moderate to severe exacerbations by 25% (95% CI: 19% to 31%; $p<0.001$) compared with placebo. *SERETIDE* reduced the exacerbation rate by 12% compared with salmeterol (95% CI: 5% to 19%, $p=0.002$) and 9% compared with FP (95% CI: 1% to 16%, $p=0.024$). Salmeterol and FP significantly reduced exacerbation rates compared with placebo by 15% (95% CI: 7% to 22%; $p<0.001$) and 18% (95% CI: 11% to 24%; $p<0.001$) respectively.

Health Related Quality of Life, as measured by the St George's Respiratory Questionnaire (SGRQ) was improved by all active treatments in comparison with placebo. The average improvement over three years for *SERETIDE* compared with placebo was -3.1 units (95% CI: -4.1 to -2.1; $p<0.001$), compared with salmeterol was -2.2 units ($p<0.001$) and compared with FP was -1.2 units ($p=0.017$).

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

The estimated 3 year probability of having pneumonia reported as an adverse event was 12.3% for placebo, 13.3% for salmeterol, 18.3% for FP and 19.6% for *SERETIDE* (Hazard ratio for *SERETIDE* vs placebo: 1.64, 95% CI: 1.33 to 2.01, $p<0.001$). There was no increase in pneumonia related deaths; deaths while on treatment that were adjudicated as primarily due to pneumonia were 7 for placebo, 9 for salmeterol, 13 for FP and 8 for *SERETIDE*. There was no significant difference in probability of bone fracture (5.1% placebo, 5.1% salmeterol, 5.4% FP and 6.3% *SERETIDE*; Hazard ratio for *SERETIDE* vs placebo: 1.22, 95% CI: 0.87 to 1.72, $p=0.248$). The incidence of adverse events of eye disorders, bone disorders, and HPA axis disorders was low and there was no difference observed between treatments. There was no evidence of an

increase in cardiac adverse events in the treatment groups receiving salmeterol.

Fluticasone propionate containing medications in asthma during pregnancy

An observational retrospective epidemiological cohort study utilising electronic health records from the United Kingdom was conducted to evaluate the risk of MCMs following first trimester exposure to inhaled FP alone and *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. 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 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 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 section 4.4*).

5.2 Pharmacokinetic properties

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

In a placebo-controlled, crossover drug interaction study in 15 healthy subjects, coadministration of *SEREVENT* (50 mcg twice daily inhaled) and the CYP3A4 inhibitor ketoconazole (400 mg once daily orally) for 7 days resulted in a significant increase in plasma salmeterol exposure (1.4-fold C_{max} and 15-fold AUC). There was no increase in salmeterol accumulation with repeat dosing. Three subjects were withdrawn from *SEREVENT* and ketoconazole co-administration due to QTc prolongation or palpitations with sinus tachycardia. In the remaining 12 subjects, coadministration of *SEREVENT* and ketoconazole did not result in a clinically significant effect on heart rate, blood potassium or QTc duration. (*see section 4.4, and section 4.5*)

Salmeterol:-

Salmeterol acts locally in the lung therefore plasma levels are not an indication of therapeutic effects. In addition there are only limited data available on the pharmacokinetics of salmeterol because of the technical difficulty of assaying the drug in plasma due to the low plasma concentrations at therapeutic doses (approximately 200 picograms/mL or less) achieved after inhaled dosing. After regular dosing with salmeterol xinafoate, hydroxynaphthoic acid can be detected in the systemic circulation, reaching steady state concentrations of approximately 100 nanograms/mL. These concentrations are up to 1000 fold lower than steady state levels observed in toxicity studies. No detrimental effects have been seen following long-term regular dosing (more than 12 months) in patients with airway obstruction.

An *in vitro* study showed that salmeterol is extensively metabolised to α -hydroxysalmeterol (aliphatic oxidation) by cytochrome P450 3A4 (CYP3A4). A repeat dose study with salmeterol and erythromycin in healthy volunteers showed no clinically significant changes in pharmacodynamic effects at 500 mg three times daily doses of erythromycin. However, a salmeterol-ketoconazole interaction study resulted in a significant increase in plasma salmeterol exposure. (see section 4.5, and section 4.5)

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. In patients with asthma or COPD a lesser degree of systemic exposure to inhaled fluticasone propionate has been observed. Systemic absorption occurs mainly through the lungs and is initially rapid then prolonged. The remainder of the inhaled dose may be swallowed but contributes minimally to systemic exposure due to the low aqueous solubility and pre-systemic metabolism, resulting in oral availability of less than 1%. There is a linear increase in systemic exposure with increasing inhaled dose. The disposition of fluticasone propionate is characterised by high plasma clearance (1150 mL/min), a large volume of distribution at steady-state (approximately 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.

Special Patient Populations

SERETIDE

Accuhaler/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 Preclinical safety data

Salmeterol xinafoate and fluticasone propionate have been extensively evaluated in animal toxicity tests. Significant toxicities occurred only at doses in excess of those recommended for human use and were those expected for a potent beta₂-adrenoreceptor agonist and

glucocorticosteroid. Neither salmeterol xinafoate or fluticasone propionate have shown any potential for genetic toxicity.

In long term studies, salmeterol xinafoate induced benign tumours of smooth muscle in the mesovarium of rats and the uterus of mice.

Rodents are sensitive to the formation of these pharmacologically-induced tumours. Salmeterol is not considered to represent a significant oncogenic hazard to man.

Co-administration of salmeterol and fluticasone propionate resulted in some cardiovascular interactions at high doses. In rats, mild atrial myocarditis and focal coronary arteritis were transient effects that resolved with regular dosing. In dogs, heart rate increases were greater after co-administration than after salmeterol alone. No clinically relevant serious adverse cardiac effects have been observed in studies in man.

Co-administration did not modify other class-related toxicities in animals.

The non-CFC propellant, HFA134a, has been shown to have no toxic effect at very high vapour concentrations, far in excess of those likely to be experienced by patients, in a wide range of animal species exposed daily for periods of two years.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

HFA 134a.

6.2 Incompatibilities

None reported.

6.3 Shelf-life

The expiry date is indicated on the packaging.

6.4 Special precautions for storage

The storage conditions are detailed on the packaging

Replace the mouthpiece cover firmly and snap it into position.

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.

Pressurised container. Do not expose to temperatures higher than 50°C. The canister should not be punctured, broken or burnt even when apparently empty.

6.5 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.

6.6 Special precautions for disposal and other 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.

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.

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.

7. MARKETING AUTHORISATION HOLDER

Manufactured by:

Glaxo Wellcome Production

Zone Industrielle No. 2

23, rue Lavoisier

27000 Evreux

France

8. MARKETING AUTHORISATION NUMBER(S)

H2004/198/3501 - SERETIDE 50/25MCG EVOHALER/MDI

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10. DATE OF REVISION OF TEXT:

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To report any Adverse events, please contact: pm.safety@gsk.com