NEW ZEALAND DATA SHEET

1. PRODUCT NAME

SERETIDE ACCUHALER, 50 mcg/100 mcg, inhalation powder

SERETIDE ACCUHALER, 50 mcg/250 mcg, inhalation powder

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each delivered dose contains salmeterol xinafoate 50 mcg and fluticasone propionate (100 mcg or 250 mcg).

Excipients with known effect:

SERETIDE ACCUHALER also contains the excipient lactose monohydrate (which contains milk protein) (see Section 4.3 Contraindications).

For full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Inhalation powder.

Moulded plastic device containing a foil strip with regularly placed blisters.

4. CLINCAL PARTICULARS

4.1 Therapeutic indications

Asthma

SERETIDE is indicated for the regular treatment of asthma (Reversible Obstructive Airways Disease) in adults, adolescents and children aged 4 years and over, where use of a combination product (bronchodilator and inhaled corticosteroid) is appropriate.

This may include:

- Patients on effective maintenance doses of both long-acting beta-agonists and inhaled corticosteroids using separate products.
- Patients who are not adequately controlled on current inhaled corticosteroid therapy.
- Patients who are not adequately controlled on “as needed” short-acting beta-agonists, as an alternative to initiation of maintenance therapy with moderate or high doses of inhaled corticosteroid alone.

SERETIDE should not typically be used for the initial management of asthma, unless symptoms are severely uncontrolled, nor in patients whose asthma can be managed by occasional use of short-acting beta$_2$ agonists.

SERETIDE should not be used in the treatment of acute asthmatic symptoms.

Chronic Obstructive Pulmonary Disease (COPD)

SERETIDE is indicated for the symptomatic treatment of adult patients with moderate to severe COPD (pre-bronchodilator FEV_1<60% predicted normal), who have significant symptoms despite bronchodilator therapy.

4.2 Dose and method of administration

Dose

SERETIDE ACCUHALER is for inhalation only.

Patients should be made aware that SERETIDE ACCUHALER must be used regularly for optimum benefit, even when asymptomatic. Patients must be warned not to stop therapy or reduce it without medical advice, even if they feel better on SERETIDE.

Patients should be regularly reassessed by a doctor, so that the strength of SERETIDE they are receiving remains optimal and is only changed on medical advice.

The dose should be titrated to the lowest dose at which effective control of symptoms is maintained. Where the control of symptoms is maintained with the lowest strength of the SERETIDE ACCUHALER (50 mcg/100 mcg) given twice daily, the next step could include a test of inhaled corticosteroid alone. As an alternative, patients requiring a long-acting $beta_{-2}$ agonist could be titrated to SERETIDE given once daily if, in the opinion of the prescriber, it would be adequate to maintain disease control. In the event of once daily dosing when the patient has a history of nocturnal symptoms, the dose should be given at night; and when the patient has a history of mainly day-time symptoms, the dose should be given in the morning.

Regular review of patients as treatment is stepped down is important.

Asthma

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

Patients should be instructed not to take additional doses to treat symptoms but to take a short-acting inhaled $beta_{-2}$ agonist.

Adults and adolescents 12 years and older:

One inhalation (50 mcg salmeterol and 100 mcg fluticasone propionate) twice daily.

or

One inhalation (50 mcg salmeterol and 250 mcg fluticasone propionate) twice daily.

Paediatric population

Children 4 years and older:

One inhalation (50 mcg salmeterol and 100 mcg fluticasone propionate) twice daily.

Children under 4 years of age:

There are insufficient clinical data at present to recommend use of SERETIDE in children aged under 4 years.

Chronic Obstructive Pulmonary Disease (COPD)

Adults:

One inhalation (50 mcg salmeterol and 250 mcg fluticasone propionate) twice daily.

Special populations

There is no need to adjust the dose in elderly patients or in those with renal or hepatic impairment.

Method of administration

For instructions on the use and handling of this medicine, please see Section 6.6 Special precautions for disposal and other handling.

4.3 Contraindications

SERETIDE is contraindicated in patients with a history of hypersensitivity to salmeterol xinafoate, fluticasone propionate or any of the excipients listed in Section 6.1 List of excipients.

SERETIDE ACCUHALER is contraindicated in patients with severe milk-protein allergy.

4.4 Special warnings and precautions for use

Use in asthma patients

SERETIDE should not be initiated in patients during an exacerbation, or if they have unstable or acutely deteriorating asthma.

SERETIDE ACCUHALER 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.

Asthma-related adverse events

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 of SERETIDE.

Deterioration of asthma control

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

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.

Patients should be advised to seek medical attention if sudden deterioration of their asthma occurs, if they find that short-acting relief bronchodilator treatment becomes less effective or if they need more inhalations than usual.

Paradoxical Bronchospasm

As with other inhalation therapy paradoxical bronchospasm may occur with an immediate increase in wheezing after dosing. This should be treated immediately with a fast and short-acting inhaled bronchodilator. SERETIDE ACCUHALER should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary (see Section 4.8 Undesirable effects).

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 Undesirable effects).

Use in COPD patients

There was an increased reporting of pneumonia in studies of patients with COPD receiving SERETIDE (see Section 4.8 Undesirable effects). Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of pneumonia and exacerbation frequently overlap.

Discontinuation

Once asthma symptoms are controlled, consideration may be given to gradually reducing the dose of SERETIDE. Regular review of patients as treatment is stepped down is important.

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.

Corticosteroids

SERETIDE contains an inhaled corticosteroid (fluticasone propionate).

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 Overdose). Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation and (very rarely) behavioural disturbances in children and adolescents, decrease in bone mineral density, cataract, glaucoma and central serous chorioretinopathy. Therefore, it is important, that the patient is reviewed regularly and 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 Overdose).

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 are encouraged to carry a steroid warning card indicating the possible need for additional therapy in times of stress.

It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroid is regularly monitored.

In rare cases inhaled therapy may unmask underlying eosinophilic conditions (e.g. Churg Strauss syndrome). These cases have usually been associated with reduction or withdrawal of oral corticosteroid therapy. A direct causal relationship has not been established.

Patients with other medical conditions

Pulmonary tuberculosis

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

Thyrotoxicosis

SERETIDE should be administered with caution in patients with thyrotoxicosis.

Cardiovascular disease

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. Rarely, SERETIDE may cause cardiac arrhythmias e.g. supraventricular tachycardia, extrasystoles and atrial fibrillation. Therefore, SERETIDE should be used with caution in patients with pre-existing cardiovascular disorders.

Lower serum potassium

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.

Diabetes mellitus

There have been very rare reports of increases in blood glucose levels (see Section 4.8 Undesirable effects) and this should be considered when prescribing to patients with a history of diabetes mellitus.

Other

SERETIDE ACCUHALER contains lactose up to 12.5 milligrams per dose. This amount does not normally cause problems in lactose intolerant people.

Drug interaction potential

Ritonavir

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 Interaction with other medicines and other forms of interaction).

CYP3A4 inhibitors

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 Section 4.5 Interaction with other medicines and other forms of interaction and Section 5.2 Pharmacokinetic properties).

4.5 Interaction with other medicines and other forms of interaction

Salmeterol

Beta-blockers

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

CYP3A4 inhibitors

Co-administration of ketoconazole and salmeterol resulted in a significant increase in plasma salmeterol exposure (1.4-fold C_{max} and 15-fold AUC). This may lead to prolongation of the QTc interval. Due to the potential increased risk of cardiovascular adverse events, the concomitant use of salmeterol with strong CYP3A43 inhibitors (e.g. ketoconazole, atazanavir, ritonavir, clarithromycin, indinavir, intraconazole, nefazodone, nelfinavir and saquinavir) is not recommended (see Section 4.4 Special warnings and precautions for use and Section 5.2 Pharmacokinetic properties).

Fluticasone propionate

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.

Ritonavir

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.

CYP3A4 inhibitors

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data in pregnant women. Administration during pregnancy should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus.

An observational retrospective epidemiological cohort study utilising electronic health records from the United Kingdom was conducted to evaluate the risk of major congenital malformations (MCMs) following first trimester exposure to inhaled fluticasone propionate alone and salmeterol-fluticasone propionate relative to non-fluticasone propionate containing inhaled corticosteroids. No placebo comparator was included in this study.

Within the asthma cohort of 5362 first trimester inhaled corticosteroids-exposed pregnancies, 131 diagnosed MCMs were identified; 1612 (30%) were exposed to fluticasone propionate or salmeterol-fluticasone propionate 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 fluticasone propionate exposed vs non-fluticasone propionate inhaled corticosteroid 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 fluticasone propionate alone versus salmeterol-fluticasone propionate. Absolute risks of MCM across the asthma severity strata ranged from 2.0 to 2.9 per 100 fluticasone propionate-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).

Results from the retrospective epidemiological study did not find an increased risk of MCMs following exposure to fluticasone propionate when compared to other inhaled corticosteroids, during the first trimester of pregnancy.

Reproductive toxicity studies in animals, either with single agent 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 medicines in these classes has revealed no evidence that the effects are relevant at therapeutic doses.

Breast-feeding

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

There is insufficient experience of the use of salmeterol xinafoate and fluticasone propionate in human 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 concentrations were measured in milk. There are no data available for human breast milk.

Fertility

There are no data on human fertility. Animal studies indicate no effects of fluticasone propionate or salmeterol xinofoate on male or female fertility.

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 agents does not indicate any effect.

4.8 Undesirable effects

Summary of 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	(>1/1000 to <1/100)
Rare	(>1/10,000 to <1/1000)
Very rare	(<1/10,000) including isolated reports

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 Special warnings and precautions for use):

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 Special warnings and precautions for use)

Uncommon: Tremor (see Section 4.4 Special warnings and precautions for use)

Cardiac disorders

Uncommon: Palpitations (see Section 4.4 Special warnings and precautions for use), 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 Section 4.4 Special warnings and precautions for use):

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 Special warnings and precautions for use)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via: https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

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 Dose and method of administration).

The available information on overdose with SERETIDE, salmeterol and/or fluticasone propionate is given below:

Symptoms and signs

The expected symptoms and signs of salmeterol over-dosage are those typical of excessive beta$_{-2}$ adrenergic stimulation, including tremor, headache, tachycardia, increases in systolic blood pressure and hypokalaemia and raised blood glucose levels.

Acute inhalation of fluticasone propionate doses in excess of those approved may lead to temporary suppression of 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.

Treatment

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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Andrenergics in combination with corticosteroids or other drugs, excl. Anticholinergics.

ATC code: R03AK06.

Mechanism of action

SERETIDE contains salmeterol and fluticasone propionate which have differing modes of action. Salmeterol provides symptomatic relief while fluticasone propionate improves lung function and prevents exacerbations of the condition. SERETIDE can offer a more convenient regime for patients on concurrent long-acting beta-agonist and inhaled corticosteroid therapy. The respective mechanisms of action of both agents are discussed below:

Salmeterol

Salmeterol is a selective long-acting (12 hour) beta$_{-2}$-adrenoceptor agonist with a long side chain which binds to the exo-site of the receptor.

These pharmacological properties of salmeterol offer a slower onset of action, but more effective protection against histamine-induced bronchoconstriction and produce a longer duration of bronchodilation, lasting for approximately 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. 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 Special warnings and precautions for use).

Clinical efficacy and safety

Asthma

Safety and efficacy of salmeterol-fluticasone propionate versus fluticasone propionate alone in asthma:

Two multi-centre 26-week studies were conducted to compare the safety and efficacy of salmeterol-fluticasone propionate versus fluticasone propionate 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-fluticasone propionate) was non-inferior to ICS (fluticasone propionate) 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-fluticasone propionate) was superior to ICS therapy alone (fluticasone propionate) 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 randomised 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-fluticasone propionate (n = 5,834)	Fluticasone propionate alone (n = 5,845)	Salmeterol-fluticasone propionate (n = 3,107)	Fluticasone propionate 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-fluticasone propionate /fluticasone propionate 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-fluticasone propionate relative to fluticasone propionate was seen in both studies, however only AUSTRI met statistical significance:

	AUSTRI		**VESTRI**	
	Salmeterol-fluticasone propionate (n = 5,834)	Fluticasone propionate alone (n = 5,845)	Salmeterol-fluticasone propionate (n = 3,107)	Fluticasone propionate alone (n = 3,101)
Number of subjects with an asthma exacerbation	480 (8%)	597 (10%)	265 (9%)	309 (10%)
Salmeterol-fluticasone propionate /fluticasone propionate 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 salmeterol-fluticasone propionate 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 salmeterol-fluticasone propionate achieved #'Well-controlled' asthma compared with 59% of patients treated with inhaled corticosteroid alone.
- 41% of patients treated with salmeterol-fluticasone propionate achieved ##'Total control' of asthma compared with 28% of patients treated with inhaled corticosteroid alone.

These effects were observed earlier with salmeterol-fluticasone propionate 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 salmeterol-fluticasone propionate 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 salmeterol-fluticasone propionate 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 salmeterol-fluticasone propionate 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 salmeterol-fluticasone propionate 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 salmeterol-fluticasone propionate, in these endpoints, are maintained over at least 12 months.

COPD

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

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.

TORCH study (Towards a Revolution in COPD Health):

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

	Placebo N=1524	Salmeterol 50 N=1521	Fluticasone propionate 500 N=1534	Seretide 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 Seretide 50/500 vs	N/A	0.932 (0.77, 1.13)	0.774 (0.64, 0.93)	N/A

components (CIs) P value		0.481	0.007	

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

There was a trend towards improved survival in subjects treated with SERETIDE compared with placebo over 3 years however this did not achieve the statistical significance level $p \leq 0.05$. 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 fluticasone propionate and 4.7% for SERETIDE.

SERETIDE reduced the rate of moderate to severe COPD exacerbations by 25% ($p<0.001$) compared with placebo. SERETIDE reduced the exacerbation rate by 12% compared with salmeterol ($p=0.002$) and 9% compared with fluticasone propionate ($p=0.024$).

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 3 years for SERETIDE compared with placebo was -3.1 units ($p<0.001$), compared with salmeterol was -2.2 units ($p<0.001$) and compared with fluticasone propionate was -1.2 units ($p=0.017$). The odds of SERETIDE subjects achieving a clinically significant improvement in health status (ie. ≥ 4 point reduction in SGRQ) was 86% greater compared to placebo ($p<0.001$), 40% greater compared to salmeterol ($p<0.001$) and 24% greater compared to fluticasone propionate ($p=0.006$).

Over the 3 year treatment period, FEV_1 values were higher in subjects treated with SERETIDE than those treated with placebo (average difference over 3 years 92 mL, $p<0.001$). SERETIDE was also more effective than salmeterol or fluticasone propionate in improving FEV_1 (average difference 50 mL, $p<0.001$ for salmeterol and 44 mL, $p<0.001$ for fluticasone propionate).

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 fluticasone propionate and 19.6% for SERETIDE (Hazard ratio for SERETIDE vs placebo: 1.64, $p<0.001$). 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 fluticasone propionate and 8 for SERETIDE. There was no significant difference in probability of bone fracture between treatments. 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.

The all-cause mortality findings from TORCH were further supported by data from another study, INSPIRE, which was a 2 year randomised (n=1323), double blind study comparing the effects of SERETIDE 50/500 mcg twice daily with tiotropium 18 mcg once daily in COPD patients with post bronchodilator FEV_1 <50% predicted normal. All-cause mortality was a safety end point in this study. The results showed that for time to death on-treatment, there was a 52% reduction in the risk of dying at anytime on therapy over the 2 year study period for SERETIDE compared to tiotropium ($p=0.012$).

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.

Even though plasma levels of SERETIDE are very low, potential interactions with other substrates and inhibitors of CYP3A4 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 200pg/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 100ng/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.

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 Section 4.4 Special warnings and precautions for use and Section 4.5 Interaction with other medicines and other forms of interaction).

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 (7.8%), fluticasone propionate Inhaler (10.9%), SERETIDE Inhaler (5.3%) and SERETIDE ACCUHALER (5.5%) respectively. In patients with ROAD or COPD a lesser degree of systemic exposure to inhaled fluticasone propionate has been observed. Systemic absorption occurs mainly through the lungs and is initially rapid then prolonged. The remainder of the inhaled dose may be swallowed but contributes minimally to systemic exposure due to the low aqueous solubility and pre-systemic metabolism, resulting in oral availability of less than 1%. There is a linear increase in systemic exposure with increasing inhaled dose. The disposition of fluticasone propionate is characterised by high plasma clearance (1150mL/min), a large volume of distribution at steady-state (approximately 300L) 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

Population pharmacokinetic analysis was performed utilising data for asthmatic subjects (nine clinical studies for fluticasone propionate and five studies for salmeterol) and showed the following:

- Higher fluticasone propionate exposure seen following administration of SERETIDE (50 mcg/100 mcg) compared to fluticasone propionate alone (100μg) 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 fluticasone propionate exposure observed in children taking SERETIDE (100 mcg/50 mcg) 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 (100 mcg/50 mcg) and fluticasone propionate (100 mcg) in both adolescents and adults and in children.
- Fluticasone propionate exposure was similar at the higher SERETIDE 500 mcg/50 mcg dose compared to the equivalent fluticasone propionate dose alone.
- Higher salmeterol exposure was observed in children taking SERETIDE (100 mcg/50 mcg) 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 $beta_2$-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) (see Section 4.3 Contraindications).

6.2 Incompatibilities

None reported

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 30°C

Store in a dry place

6.5 Nature and contents of container

SERETIDE ACCUHALER 50 mcg/100 mcg

Moulded plastic device containing a foil strip with 60 regularly placed blisters each containing 50 mcg of salmeterol xinafoate and 100 mcg of fluticasone propionate.

SERETIDE ACCUHALER 50 mcg/250 mcg

Moulded plastic device containing a foil strip with 60 regularly placed blisters each containing 50 mcg of salmeterol xinafoate and 250 mcg of fluticasone propionate.

6.6 Special precautions for disposal and other handling

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 ACCUHALER indicates the number of doses left.

For detailed instructions for use refer to the Patient Information Leaflet.

7. MEDICINE SCHEDULE

Prescription Only Medicine

8. SPONSOR

GlaxoSmithKline NZ Limited
Private Bag 106600
Downtown
Auckland
New Zealand

Phone: (09) 367 2900

Facsimile: (09) 367 2910

9. DATE OF FIRST APPROVAL

26 August 2000

10. DATE OF REVISION OF THE TEXT

17 August 2022

Summary table of changes

Section changed	Summary of new information
1, 2, 4.2, 6.5	Removed reference to Seretide Accuhaler 50µg/500µg presentation.

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