

1. NAME OF THE MEDICINAL PRODUCT

Salflumix Easyhaler 50 microgram/250 microgram/dose, inhalation powder
Salflumix Easyhaler 50 microgram/500 microgram/dose, inhalation powder

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Salflumix Easyhaler 50 microgram/250 microgram: Each delivered dose (the dose that leaves the mouthpiece) contains salmeterol xinafoate corresponding to 48 micrograms of salmeterol and 238 micrograms fluticasone propionate.

This corresponds to a metered dose of salmeterol xinafoate corresponding to 50 micrograms of salmeterol and 250 micrograms fluticasone propionate.

Salflumix Easyhaler 50 microgram/500 microgram: Each delivered dose (the dose that leaves the mouthpiece) contains salmeterol xinafoate corresponding to 48 micrograms of salmeterol and 476 micrograms fluticasone propionate.

This corresponds to a metered dose of salmeterol xinafoate corresponding to 50 micrograms of salmeterol and 500 micrograms fluticasone propionate.

Excipient with known effect: Lactose monohydrate 17 mg per delivered dose

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Inhalation powder in a device metered inhaler (Easyhaler)
White powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Asthma

Salflumix Easyhaler is indicated in the regular treatment of asthma in adults and adolescents 12 years and over where use of a combination product (long-acting β_2 agonist and inhaled corticosteroid) is appropriate.

Chronic Obstructive Pulmonary Disease (COPD)

Salflumix Easyhaler is indicated for the symptomatic treatment of patients with COPD, and a history of repeated exacerbations, who have significant symptoms despite regular bronchodilator therapy.

4.2 Posology and method of administration

Posology

Patients should be made aware that Salflumix Easyhaler must be used daily for optimum benefit, even when asymptomatic.

Patients should be regularly reassessed by a doctor, so that the strength of Salflumix Easyhaler 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.** For dosages which cannot be achieved with Salflumix Easyhaler (i.e. 50 micrograms salmeterol and 100 micrograms fluticasone propionate) other fixed-dose combination products containing these two active ingredients are available.

Patients should be given the strength of Salflumix Easyhaler containing the appropriate fluticasone propionate dosage for the severity of their disease. If an individual patient should require dosages outside the recommended regimen, appropriate doses of β_2 agonist and/or corticosteroid should be prescribed.

If a patient is inadequately controlled on inhaled corticosteroid therapy alone, substitution with Salflumix Easyhaler at a therapeutically equivalent corticosteroid dose may result in an improvement in asthma control.

Recommended Doses:

Asthma

Adults and adolescents 12 years and older:

One inhalation of 50 micrograms salmeterol and 250 micrograms fluticasone propionate twice daily.

or

One inhalation of 50 micrograms salmeterol and 500 micrograms fluticasone propionate twice daily.

Salflumix Easyhaler is not intended for the initial management of mild asthma. Salmeterol/fluticasone propionate 50 microgram/100 micrograms strength is not appropriate in adults and children with severe asthma; it is recommended to establish the appropriate dosage of inhaled corticosteroid before any fixed-combination can be used in patients with severe asthma.

Paediatric population

Salflumix Easyhaler should not be used in children younger than 12 years.

COPD

Adults:

One inhalation of 50 micrograms salmeterol and 500 micrograms fluticasone propionate twice daily.

Special patient groups:

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

Method of administration

Inhalation use.

Instructions for correct use of Salflumix Easyhaler:

The inhaler is inspiratory flow-driven, which means that when the patient inhales through the mouthpiece, the substance will follow the inspired air into the airways.

Note: It is important to instruct the patient

- To carefully read the instructions for use in the patient information leaflet which is packed together with each Salflumix Easyhaler
- To hold the inhaler upright, gripping it between finger and thumb
- To vigorously shake the inhaler up and down 3 to 5 times before actuation
- To actuate (click) the inhaler before inhalation
- To breathe in forcefully and deeply through the mouthpiece to ensure that an optimal dose is delivered to the lungs
- To hold breath after inhaling for at least 5 seconds
- Never to breathe out through the mouthpiece as this will result in a reduction in the delivered dose. Should this happen the patient is instructed to tap the mouthpiece onto a table top or the palm of a hand to empty the powder, and then to repeat the dosing procedure.
- Never to actuate the device more than once without inhalation of the powder. Should this happen the patient is instructed to tap the mouthpiece onto a table top or the palm of a hand to empty the powder, and then to repeat the dosing procedure.
- To always replace the dust cap (and, if in use, close the protective cover) after use to prevent accidental actuation of the device (which could result in either overdosing or under dosing the patient when subsequently used)
- To rinse the mouth out with water and/or brush teeth after inhaling the maintenance dose to minimise the risk of oropharyngeal thrush.
- Water should never be used for cleaning the inhaler because the powder is sensitive to moisture
- To replace Salflumix Easyhaler when the counter reaches zero even though powder could still be observed within the inhaler.

4.3 Contraindications

Hypersensitivity to the active substances or to the excipient listed in section 6.1 (lactose, which contains small amounts of milk protein).

4.4 Special warnings and precautions for use

Deterioration of disease

Salflumix Easyhaler should not be used to treat acute asthma symptoms for which a fast and short-acting bronchodilator is required. Patients should be advised to have their inhaler to be used for relief in an acute asthma attack available at all times.

Patients should not be initiated on Salflumix Easyhaler 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 Salflumix Easyhaler. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation on Salflumix Easyhaler.

Increased requirements for use of reliever medication (short-acting bronchodilators), or decreased response to reliever medication indicate 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 undergo urgent medical assessment. Consideration should be given to increasing corticosteroid therapy.

Once asthma symptoms are controlled, consideration may be given to gradually reducing the dose of Salflumix Easyhaler. Regular review of patients as treatment is stepped down is important. The lowest effective dose of Salflumix Easyhaler should be used (see section 4.2).

For patients with COPD experiencing exacerbations, treatment with systemic corticosteroids is typically indicated, therefore patients should be instructed to seek medical attention if symptoms deteriorate with Salflumix Easyhaler.

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

As with all inhaled medication containing corticosteroids, Salflumix Easyhaler should be administered with caution in patients with active or quiescent pulmonary tuberculosis and fungal, viral or other infections of the airway. Appropriate treatment should be promptly instituted, if indicated.

Cardiovascular effects

Rarely, Salflumix Easyhaler may cause cardiac arrhythmias e.g. supraventricular tachycardia, extrasystoles and atrial fibrillation, and a mild transient reduction in serum potassium at high therapeutic doses. Salflumix Easyhaler should be used with caution in patients with severe cardiovascular disorders or heart rhythm abnormalities and in patients with diabetes mellitus, thyrotoxicosis, uncorrected hypokalaemia or patients predisposed to low levels of serum potassium.

Hyperglycaemia

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.

Paradoxical bronchospasm

As with other inhalation therapy paradoxical bronchospasm may occur with an immediate increase in wheezing and shortness of breath after dosing. Paradoxical bronchospasm responds to a rapid-acting bronchodilator and

should be treated straightaway. Salflumix Easyhaler should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.

The pharmacological side effects of β_2 agonist treatment, such as tremor, palpitations and headache, have been reported, but tend to be transient and reduce with regular therapy.

Systemic corticosteroid effects

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. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, decrease in bone mineral density, cataract and glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children) (see Paediatric population sub-heading below for information on the systemic effects of inhaled corticosteroids in children and adolescents). **It is important, therefore, that the patient is reviewed regularly and the dose of inhaled corticosteroid is reduced to the lowest dose at which effective control of asthma is maintained.**

Prolonged treatment of patients with high doses of inhaled corticosteroids may result in adrenal suppression and acute adrenal crisis. Very rare cases of adrenal suppression and acute adrenal crisis have also been described with doses of fluticasone propionate between 500 and less than 1,000 micrograms. Situations, which could potentially trigger acute adrenal crisis include trauma, surgery, infection or any rapid reduction in dosage. Presenting symptoms are typically vague and may include anorexia, abdominal pain, weight loss, tiredness, headache, nausea, vomiting, hypotension, decreased level of consciousness, hypoglycaemia, and seizures. Additional systemic corticosteroid cover should be considered during periods of stress or elective surgery.

The benefits of inhaled fluticasone propionate therapy should minimise the need for oral steroids, but patients transferring from oral steroids may remain at risk of impaired adrenal reserve for a considerable time. Therefore these patients should be treated with special care and adrenocortical function regularly monitored. Patients who have required high dose emergency corticosteroid therapy in the past may also be at risk. This possibility of residual impairment should always be borne in mind in emergency and elective situations likely to produce stress, and appropriate corticosteroid treatment must be considered. The extent of the adrenal impairment may require specialist advice before elective procedures.

Ritonavir can greatly increase the concentration of fluticasone propionate in plasma. Therefore, concomitant use should be avoided, unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects. There is also an increased risk of systemic side effects when combining fluticasone propionate with other potent CYP3A inhibitors (see section 4.5).

Visual disturbance

Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Pneumonia in patients with COPD

An increase in the incidence of pneumonia, including pneumonia requiring hospitalisation, has been observed in patients with COPD receiving inhaled corticosteroids. There is some evidence of an increased risk of pneumonia with increasing steroid dose but this has not been demonstrated conclusively across all studies.

There is no conclusive clinical evidence for intra-class differences in the magnitude of the pneumonia risk among inhaled corticosteroid products.

Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations.

Risk factors for pneumonia in patients with COPD include current smoking, older age, low body mass index (BMI) and severe COPD.

Interactions with potent CYP3A4 inhibitors

Concomitant use of systemic ketoconazole significantly increases systemic exposure to salmeterol. This may lead to an increase in the incidence of systemic effects (e.g. prolongation in the QTc interval and palpitations). 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 section 4.5).

Paediatric population

Children and adolescents <16 years taking high doses of fluticasone propionate (typically ≥ 1000 micrograms/day) may be at particular risk. Systemic effects may occur, particularly at high doses prescribed for long periods. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, acute adrenal crisis and growth retardation in children and adolescents and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression. Consideration should be given to referring the child or adolescent to a paediatric respiratory specialist.

It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroid is regularly monitored. **The dose of inhaled corticosteroid should be reduced to the lowest dose at which effective control of asthma is maintained.**

Excipients

Salflumix Easyhaler contains lactose up to 17.1 mg /dose as an excipient. This amount does not normally cause problems in lactose intolerant people. The excipient lactose contains small amounts of milk proteins, which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

β adrenergic blockers may weaken or antagonise the effect of salmeterol. Both non-selective and selective β blockers should be avoided unless there are compelling reasons for their use. Potentially serious hypokalaemia may result from β_2 agonist therapy. Particular caution is advised in acute severe asthma as this effect may be potentiated by concomitant treatment with xanthine derivatives, steroids and diuretics.

Concomitant use of other β adrenergic containing drugs can have a potentially additive effect.

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 CYP3A4 in the gut and liver. Hence, clinically significant drug interactions mediated by fluticasone propionate are unlikely.

In an interaction study in healthy subjects with intranasal fluticasone propionate, ritonavir (a highly potent cytochrome CYP3A4 inhibitor) 100 mg b.i.d. increased the fluticasone propionate plasma concentrations several hundred fold, resulting in markedly reduced serum cortisol concentrations. Information about this interaction is lacking for inhaled fluticasone propionate, but a marked increase in fluticasone propionate plasma levels is expected. Cases of Cushing's syndrome and adrenal suppression have been reported. The combination should be avoided unless the benefit outweighs the increased risk of systemic glucocorticoid side effects.

In a small study in healthy volunteers, the slightly less potent CYP3A inhibitor ketoconazole increased the exposure of fluticasone propionate after a single inhalation by 150%. This resulted in a greater reduction of plasma cortisol as compared with fluticasone propionate alone. Co-treatment with other CYP3A inhibitors, including itraconazole and cobicistat-containing products, and moderate CYP3A inhibitors, such as erythromycin, is also expected to increase the systemic fluticasone propionate exposure and the risk of systemic side-effects. Combinations should be avoided unless the benefit outweighs the potential increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid side-effects.

Salmeterol

Potent CYP3A4 inhibitors

Co-administration of ketoconazole (400 mg orally once daily) and salmeterol (50 micrograms inhaled twice daily) in 15 healthy subjects for 7 days resulted in a significant increase in plasma salmeterol exposure (1.4-fold C_{max} and 15-fold AUC). This may lead to an increase in the incidence of other systemic effects of salmeterol treatment (e.g. prolongation of QTc interval and palpitations) compared with salmeterol or ketoconazole treatment alone (see section 4.4).

Clinically significant effects were not seen on blood pressure, heart rate, blood glucose and blood potassium levels. Co-administration with ketoconazole did not increase the elimination half-life of salmeterol or increase salmeterol accumulation with repeat dosing.

The concomitant administration of ketoconazole should be avoided, unless the benefits outweigh the potentially increased risk of systemic side effects of salmeterol treatment. There is likely to be a similar risk of interaction with other potent CYP3A4 inhibitors (e.g. itraconazole, telithromycin, ritonavir).

Moderate CYP3A4 inhibitors

Co-administration of erythromycin (500 mg orally three times a day) and salmeterol (50 micrograms inhaled twice daily) in 15 healthy subjects for 6 days resulted in a small but non-statistically significant increase in salmeterol exposure (1.4-fold C_{max} and 1.2-fold AUC). Co-administration with erythromycin was not associated with any serious adverse effects.

4.6 Fertility, pregnancy and lactation

Pregnancy

A large amount of data on pregnant women (more than 1,000 pregnancy outcomes) indicates no malformative or fetoneonatal toxicity related to salmeterol and fluticasone propionate. Animal studies have shown reproductive toxicity after administration of β_2 adrenoreceptor agonists and glucocorticosteroids (see section 5.3).

Administration of Salflumix Easyhaler to pregnant women should only be considered if the expected benefit to the mother is greater than any possible risk to the fetus.

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

Breastfeeding

It is unknown whether salmeterol and fluticasone propionate/metabolites are excreted in human milk.

Studies have shown that salmeterol and fluticasone propionate, and their metabolites, are excreted into the milk of lactating rats.

A risk to breastfed newborns/infants cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue Salflumix Easyhaler therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility

There are no data in humans. However, animal studies showed no effects of salmeterol or fluticasone propionate on fertility.

4.7 Effects on ability to drive and use machines

There have been no specific studies of the effect of Salflumix on the above activities, but the pharmacology of both drugs does not indicate any effect.

4.8 Undesirable effects

As Salflumix Easyhaler contains salmeterol and fluticasone propionate, the type and severity of adverse reactions associated with each of the compounds may be expected. There is no incidence of additional adverse events following concurrent administration of the two compounds.

Adverse events which have been associated with salmeterol/fluticasone propionate are given below, listed by system organ class and frequency. Frequencies are defined as: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$) and not known (cannot be estimated from the available data). Frequencies were derived from clinical trial data. The incidence in placebo was not taken into account.

System Organ Class	Adverse Event	Frequency
Infections & Infestations	Candidiasis of the mouth and throat	Common
	Pneumonia (in COPD patients)	Common ^{1,3,5}
	Bronchitis	Common ^{1,3}
	Oesophageal candidiasis	Rare
Immune System Disorders	Hypersensitivity reactions with the following manifestations:	
	Cutaneous hypersensitivity reactions	Uncommon
	Angioedema (mainly facial and oropharyngeal oedema)	Rare
	Respiratory symptoms (dyspnoea)	Uncommon
	Respiratory symptoms (bronchospasm)	Rare
	Anaphylactic reactions including anaphylactic shock	Rare
Endocrine Disorders	Cushing's syndrome, Cushingoid features, Adrenal suppression, Growth retardation in children and adolescents, Decreased bone mineral density	Rare ⁴
Metabolism & Nutrition Disorders	Hypokalaemia	Common ³
	Hyperglycaemia	Uncommon ⁴
Psychiatric Disorders	Anxiety	Uncommon
	Sleep disorders	Uncommon
	Behavioural changes, including psychomotor hyperactivity and irritability (predominantly in children)	Rare
	Depression, aggression (predominantly in children)	Not known
Nervous System Disorders	Headache	Very Common ¹
	Tremor	Uncommon
Eye Disorders	Cataract	Uncommon
	Glaucoma	Rare ⁴

System Organ Class	Adverse Event	Frequency
	Vision, blurred (see also section 4.4)	Not known
Cardiac Disorders	Palpitations	Uncommon
	Tachycardia	Uncommon
	Cardiac arrhythmias (including supraventricular tachycardia and extrasystoles)	Rare
	Atrial fibrillation	Uncommon
	Angina pectoris	Uncommon
Respiratory, Thoracic & Mediastinal Disorders	Nasopharyngitis	Very Common ^{2,3}
	Throat irritation	Common
	Hoarseness/dysphonia	Common
	Sinusitis	Common ^{1,3}
	Paradoxical bronchospasm	Rare ⁴
Skin and subcutaneous tissue disorders	Contusions	Common ^{1,3}
Musculoskeletal & Connective Tissue Disorders	Muscle cramps	Common
	Traumatic fractures	Common ^{1,3}
	Arthralgia	Common
	Myalgia	Common

1. Reported commonly in placebo
2. Reported very commonly in placebo
3. Reported over 3 years in a COPD study
4. See section 4.4
5. See section 5.1.

Description of selected adverse reactions

The pharmacological side effects of β_2 agonist treatment, such as tremor, palpitations and headache, have been reported, but tend to be transient and reduce with regular therapy.

As with other inhalation therapy paradoxical bronchospasm may occur with an immediate increase in wheezing and shortness of breath after dosing. Paradoxical bronchospasm responds to a rapid-acting bronchodilator and

should be treated straightaway. Salflumix Easyhaler should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.

Due to the fluticasone propionate component, hoarseness and candidiasis (thrush) of the mouth and throat and, rarely, of the oesophagus can occur in some patients. Both hoarseness and incidence of mouth and throat candidiasis may be relieved by rinsing the mouth with water and/or brushing the teeth after using the product. Symptomatic mouth and throat candidiasis can be treated with topical anti-fungal therapy whilst still continuing with the Salflumix Easyhaler.

Paediatric population

Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression and growth retardation in children and adolescents (see section 4.4). Children may also experience anxiety, sleep disorders and behavioural changes, including hyperactivity and irritability.

4.9 Overdose

There are no data available from clinical trials on overdose with Salflumix Easyhaler, however data on overdose with both drugs are given below:

The signs and symptoms of salmeterol overdose are dizziness, increases in systolic blood pressure, tremor, headache and tachycardia. If Salflumix Easyhaler therapy has to be withdrawn due to overdose of the β agonist component of the drug, provision of appropriate replacement steroid therapy should be considered. Additionally, hypokalaemia can occur and therefore serum potassium levels should be monitored. Potassium replacement should be considered.

Acute: Acute inhalation of fluticasone propionate doses in excess of those recommended may lead to temporary suppression of adrenal function. This does not need emergency action as adrenal function is recovered in a few days, as verified by plasma cortisol measurements.

Chronic overdose of inhaled fluticasone propionate: Adrenal reserve should be monitored and treatment with a systemic corticosteroid may be necessary. When stabilised, treatment should be continued with an inhaled corticosteroid at the recommended dose. Refer to section 4.4: risk of adrenal suppression.

In cases of both acute and chronic fluticasone propionate overdose Salflumix Easyhaler therapy should be continued at a suitable dosage for symptom control.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Drugs for obstructive airway diseases, adrenergics in combination with corticosteroids or other drugs, excl. anticholinergics.

ATC Code: R03AK06

Mechanism of action and pharmacodynamic effects

Salflumix Easyhaler contains salmeterol and fluticasone propionate which have differing modes of action. The respective mechanisms of action of both drugs are discussed below.

Salmeterol

Salmeterol is a selective long-acting (12 hour) β_2 adrenoceptor agonist with a long side chain which binds to the exo-site of the receptor.

Salmeterol produces a longer duration of bronchodilation, lasting for at least 12 hours, than recommended doses of conventional short-acting β_2 agonists.

Fluticasone propionate

Fluticasone propionate given by inhalation at recommended doses has a glucocorticoid anti-inflammatory action within the lungs, resulting in reduced symptoms and exacerbations of asthma, with less adverse effects than when corticosteroids are administered systemically.

Clinical efficacy and safety

Asthma clinical trials

The 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, and only 47% of subjects reported ICS use at baseline.

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)	

Paediatric population

Salflumix Easyhaler is not recommended for use in children aged less than 12 years. The safety and efficacy of Salflumix Easyhaler in this young population have not been established.

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

Within the asthma cohort of 5,362 first trimester ICS-exposed pregnancies, 131 diagnosed MCMs were identified; 1,612 (30%) were exposed to FP or salmeterol-FP 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 salmeterol-FP. 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).

Twelve month study

A large twelve-month study (Gaining Optimal Asthma Control, GOAL) in 3,416 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.

COPD clinical trials

TORCH was a 3-year study to assess the effect of treatment with salmeterol/FP 50/500 micrograms bd, salmeterol 50 micrograms bd, FP 500 micrograms bd or placebo on all-cause mortality in patients with COPD. COPD patients 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 salmeterol/FP vs Placebo.

	Placebo N = 1,524	Salmeterol 50 N = 1,521	FP 500 N = 1,534	Salmeterol/FP 50/500 N = 1,533
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 salmeterol/FP 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. Non significant P value after adjustment 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 salmeterol/FP 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 FP and 4.7% for salmeterol/FP.

The mean number of moderate to severe exacerbations per year was significantly reduced with salmeterol/FP as compared with treatment with salmeterol, FP and placebo (mean rate in the salmeterol/FP group 0.85 compared with 0.97 in the salmeterol group, 0.93 in the FP group and 1.13 in the placebo). This translates to a reduction in the rate of moderate to severe exacerbations of 25% (95% CI: 19% to 31%; $p < 0.001$) compared with placebo, 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 salmeterol/FP 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 ($p = 0.017$). A 4-unit decrease is considered clinically relevant.

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 salmeterol/FP (Hazard ratio for salmeterol/FP 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 salmeterol/FP. There was no significant difference in probability of bone fracture (5.1% placebo, 5.1% salmeterol, 5.4% FP and 6.3% salmeterol/FP; Hazard ratio for salmeterol/FP vs placebo: 1.22, 95% CI: 0.87 to 1.72, $p = 0.248$).

Placebo-controlled clinical trials, over 6 and 12 months, have shown that regular use of salmeterol/FP 50/500 micrograms improves lung function and reduces breathlessness and the use of relief medication.

5.2 Pharmacokinetic properties

For pharmacokinetic purposes each component can be considered separately.

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 picogram/mL or less) achieved after inhaled dosing.

Fluticasone propionate

The absolute bioavailability of a single dose of inhaled fluticasone propionate in healthy subjects varies between approximately 5 to 11% of the nominal dose depending on the inhalation device used. 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 presystemic 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 (1,150 mL/min), a large volume of distribution at steady-state (approximately 300 L) and a terminal half-life of approximately 8 hours.

Plasma protein binding is 91%.

Fluticasone propionate is cleared very rapidly from the systemic circulation. The main pathway is metabolism to an inactive carboxylic acid metabolite, by the cytochrome P450 enzyme CYP3A4. Other unidentified metabolites are also found in the faeces.

The renal clearance of fluticasone propionate is negligible. Less than 5% of the dose is excreted in urine, mainly as metabolites. The main part of the dose is excreted in faeces as metabolites and unchanged drug.

Paediatric population

Salflumix Easyhaler is not recommended for use in children aged less than 12 years. The safety and efficacy of Salflumix Easyhaler in this young population have not been established.

5.3 Preclinical safety data

The only safety concerns for human use derived from animal studies of salmeterol and fluticasone propionate given separately were effects associated with exaggerated pharmacological actions.

In animal reproduction studies, glucocorticosteroids have been shown to induce malformations (cleft palate, skeletal malformations). However, these animal experimental results do not seem to be relevant for man given recommended doses. Animal studies with salmeterol have shown embryofetal toxicity only at high exposure levels. Following co-administration, increased incidences of transposed umbilical artery and incomplete ossification of occipital bone were found in rats at doses associated with known glucocorticoid-induced

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate (which contains milk proteins)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

As packaged for sale: 2 years.

After first opening the foil bag: 1 month [50/250 strength], 2 months [50/500 strength].

6.4 Special precautions for storage

Do not store above 30°C.

After opening: Store below 30°C. Store the inhaler in its protective cover. Protect from moisture.

6.5 Nature and contents of container

The multidose powder inhaler consists of seven plastic parts and a stainless steel spring. The plastic materials of the inhaler are: polybutylene terephthalate, low density polyethylene, polycarbonate, styrene butadiene, polypropylene. The inhaler is sealed in a foil bag and packed with or without a protective cover (polypropylene and thermoplastic elastomer) in a cardboard box.

Packages:

Each inhaler contains 60 doses. The multidose powder inhaler is sealed in a foil bag and packed with or without a protective cover in a cardboard box.

6.6 Special precautions for disposal and other handling

No special requirements.

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