For the use of Registered Medical Practitioner or a Hospital or a Laboratory only

Seroflo Inhaler (CFC FREE)

(Salmeterol & Fluticasone Propionate Inhaler)

Composition:

Seroflo-50 Inhaler (CFC FREE)

Each actuation delivers:
Salmeterol (as Salmeterol Xinafoate) Ph. Eur.....…25 mcg
Fluticasone Propionate BP …….....50 mcg
Suspended in Propellant 134a…….q.s.

Seroflo-125 Inhaler (CFC FREE)

Each actuation delivers:
Salmeterol (as Salmeterol Xinafoate) Ph. Eur.....…25 mcg
Fluticasone Propionate BP …….....125 mcg
Suspended in Propellant 134a…….q.s.

Seroflo-250 Inhaler (CFC FREE)

Each actuation delivers:
Salmeterol (as Salmeterol Xinafoate) Ph. Eur.....…25 mcg
Fluticasone Propionate BP …….....250 mcg
Suspended in Propellant 134a…….q.s.

Description
A one piece filled metal container fitted with a valve with plastic stem and printed with product name, batch number, and container no. On visual examination there is no sign of physical damage such as dents, bulged containers bent valve stem and uneven crimping.

Pharmacology

Pharmacodynamics

Pharmacotherapeutic Group: Adrenergics in combination with corticosteroids or other drugs, excl. Anticholinergics.

ATC Code: R03AK06

Mechanism of action and pharmacodynamic effects

Seroflo Inhaler (CFC Free) 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) β2 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 β2 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.

Pharmacokinetics

When salmeterol and fluticasone propionate were administered in combination by the inhaled route, the pharmacokinetics of each component were similar to those observed when the drugs were administered separately. For pharmacokinetic purposes therefore 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 a lesser degree of systemic exposure to inhaled fluticasone propionate has been observed.

Systemic absorption occurs mainly through the lungs and is initially rapid then prolonged. The remainder of the inhaled dose may be swallowed but contributes minimally to systemic exposure due to the low aqueous solubility and pre-systemic metabolism, resulting in oral availability of less than 1%. There is a linear increase in systemic exposure with increasing inhaled dose.

The disposition of fluticasone propionate is characterized by high plasma clearance (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 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 as faeces as metabolites and unchanged drug.

Indications

Reversible Obstructive Airways Disease (ROAD)

Seroflo Inhaler (CFC Free) is indicated in the regular treatment of reversible obstructive airways disease (ROAD), including asthma in children and adults, where use of a combination bronchodilator and inhaled corticosteroid) is appropriate.

This may include:
Patients on effective maintenance doses of long -acting beta-agonists and inhaled corticosteroids.
Patients who are symptomatic on current inhaled corticosteroid therapy.

Patients on regular bronchodilator therapy who require inhaled corticosteroids.

Chronic Obstructive Pulmonary Disease (COPD)

Seroflo Inhaler (CFC Free) is indicated for the regular treatment of chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema.

Dosage and Method of Administration

Seroflo Inhaler (CFC Free) is for inhalation only.

Patients should be made aware that Seroflo Inhaler (CFC Free) must be used regularly for optimum benefit, even when asymptomatic.

Patients should be regularly reassessed by a doctor, so that the strength of Seroflo Inhaler (CFC Free) they are receiving remains optimal and is only changed on medical advice.

Reversible Obstructive Airways Disease (ROAD)

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 salmeterol and fluticasone propionate titration to the lowest effective dose could include salmeterol and fluticasone propionate given once daily.

Patients should be given the strength of Seroflo Inhaler (CFC Free) 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 salmeterol and fluticasone propionate 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 salmeterol and fluticasone propionate may permit a reduction in corticosteroid dose while maintaining asthma control.

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 salmeterol and fluticasone propionate 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.

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

Mode of administration
Oral Inhalation

Contraindications
Salmeterol/fluticasone propionate is contraindicated in patients with hypersensitivity to any of the active substances or to the excipient.

Warnings and Precautions

Salmeterol/fluticasone propionate inhaler 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 salmeterol/fluticasone propionate 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 salmeterol/fluticasone propionate. Patients should be asked to continue

treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation on salmeterol/fluticasone propionate.

Increased requirements for use of reliever medication (short-acting bronchodilators), or decreased response to reliever medication indicate deterioration of asthma control and patients should be reviewed by a physician.

Sudden and progressive deterioration in control of asthma is potentially life-threatening and the patient should 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 salmeterol/fluticasone propionate. Regular review of patients as treatment is stepped down is important. The lowest effective dose of salmeterol/fluticasone propionate should be used (see Dosage and Method of Administration).

Treatment with salmeterol/fluticasone propionate should not be stopped abruptly due to risk of exacerbation. Therapy should be down-titrated under physician supervision.

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

Rarely, salmeterol/fluticasone propionate may cause cardiac arrhythmias e.g. supraventricular tachycardia, extrasystoles and atrial fibrillation, and a mild transient reduction in serum potassium at high therapeutic doses. Salmeterol/fluticasone propionate 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.

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

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. Salmeterol/fluticasone propionate inhaler 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 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 1000 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.

Systemic absorption of salmeterol and fluticasone propionate is largely through the lungs. As the use of a spacer device with a metered dose inhaler may increase drug delivery to the lungs it should be noted that this could potentially lead to an increase in the risk of systemic adverse effects. Single dose pharmacokinetic data have demonstrated that the systemic exposure to salmeterol and fluticasone propionate may change when the different spacer devices are used.

The benefits of inhaled fluticasone propionate therapy should minimize 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 Drug interactions).

There was an increased reporting of lower respiratory tract infections (particularly pneumonia and bronchitis) in a 3-year study in patients with Chronic Obstructive Pulmonary Disease (COPD) receiving salmeterol /fluticasone propionate as a fixed-dose combination administered via the dry powder inhaler compared with placebo (see Undesirable Effects). In a 3 year COPD study, older patients, patients with a lower

body mass index (<25kg/m^2) and patients with very severe disease (FEV_1<30% predicted) were at greatest risk of developing pneumonia regardless of treatment. Physicians should remain vigilant for the possible development of pneumonia and other lower respiratory tract infections in patients with COPD as the clinical features of such infections and exacerbation frequently overlap. If a patient with severe COPD has experienced pneumonia the treatment with salmeterol/fluticasone propionate should be re-evaluated.

Data from a large clinical trial (the Salmeterol Multi-Center Asthma Research Trial, SMART) suggested African-American patients were at increased risk of serious respiratory-related events or deaths when using salmeterol compared with placebo. It is not known if this was due to pharmacogenetic or other factors. Patients of black African or Afro-Caribbean ancestry should therefore be asked to continue treatment but to seek medical advice if asthma symptoms remained uncontrolled or worsen whilst using salmeterol/fluticasone propionate.

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 Drug interactions).

Paediatric population

Children and adolescents <16years taking high doses of fluticasone propionate (typically ≥ 1000 micrograms/day) may be at particular risk of systemic effects. 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.

Effect on Ability to Drive and Use Machines

Salmeterol and fluticasone inhaler has no or negligible influence on the ability to drive and use machines.

Drug Interactions
Both non-selective and selective beta-blockers should be avoided in patients with asthma, unless there are compelling reasons for their use.

Concomitant use of other beta-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 P450 3A4 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 P450 3A4 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 potent CYP3A inhibitors, such as itraconazole, is also expected to increase the systemic fluticasone propionate exposure and the risk of systemic side-effects. Caution is recommended and long-term treatment with such drugs should if possible be avoided.

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 Cmax 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 Warnings and Precautions).

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 CYP 3A4 inhibitors
Co-administration of erythromycin (500mg 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 Cmax and 1.2-fold AUC). Co-administration with erythromycin was not associated with any serious adverse effects.

Fertility, Pregnancy and lactation

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

Pregnancy
A moderate amount of data on pregnant women (between 300-1000 pregnancy outcomes) indicates no malformative or feto/neonatal toxicity of salmeterol and fluticasone propionate. Animal studies have shown reproductive toxicity after administration of beta-2-adrenoreceptor agonists and glucocorticosteroids.
Administration of salmeterol/fluticasone propionate to pregnant women should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus.

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

Lactation
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 breast-feeding or to discontinue salmeterol/fluticasone propionate therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Undesirable Effects

As Seroflo Inhaler (CFC Free) 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 (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000) 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	Common[1,3]
	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 disorder	Cataract	Uncommon
	Glaucoma	Rare[4]
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 Traumatic fractures Arthralgia Myalgia	Common Common[1,3] Common Common

1. Reported commonly in placebo
2. Reported very commonly in placebo
3. Reported over 3 years in a COPD study
4. See Warnings and Precautions

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. Salmeterol and fluticasone propionate inhaler 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 Salmeterol and fluticasone propionate inhaler.

Paediatric population

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

Overdoses

There are no data available from clinical trials on overdose with Salmeterol / fluticasone propionate; however data on overdose with both drugs are given below:

The signs and symptoms of salmeterol overdose are tremor, headache and tachycardia. The preferred antidotes are cardioselective beta-blocking agents, which should be used with caution in patients with a history of bronchospasm. If salmeterol/fluticasone propionate therapy has to be withdrawn due to overdose of the beta agonist component of the drug, provision of appropriate replacement steroid therapy should be considered. Additionally, hypokalaemia can occur and 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: Refer to section *Warnings and Precautions*: risk of adrenal suppression.

Monitoring of adrenal reserve may be necessary. In cases of fluticasone propionate overdose salmeterol/fluticasone propionate therapy may still be continued at a suitable dosage for symptom control.

Storage and Handling Instructions Store below 30°C. Do not freeze.

Shelf- Life: 24 months

Pack Size: Carton containing Canister of 120 metered doses.

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