Cipla

Salmeterol & Fluticasone Propionate Inhaler

Seroflo-S inhaler

with

dose indicator

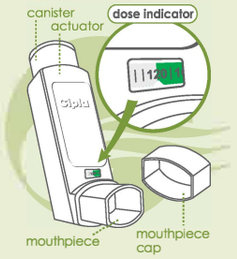
patient information leaflet

please read this leaflet completely before use

CFC-FREE

ABOUT YOUR SEROFLO-S INHALER

PARTS OF THE INHALER



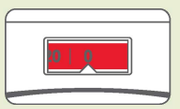
Your **SEROFLO-S** inhaler now comes with a dose indicator. It shows the number of puffs in the inhaler. As you use the inhaler, the dose indicator will countdown and indicate the number of puffs remaining.

HOW TO KNOW THAT YOUR SEROFLO-S INHALER IS GETTING OVER

When there are 40 puffs remaining, the colour on the dose indicator will change from green to red.

This indicates that fewer doses are remaining in the inhaler. You should now consider getting a new inhaler or ask your doctor if you need another one.

When the dose indicator displays '0', this means that there is no more medicine left in the inhaler & you need to discard the inhaler. Your inhaler may not feel empty & it may continue to operate, but you will not get the right amount of medicine, if you keep using it beyond '0'.



BEFORE USING YOUR SEROFLO-S INHALER

1 Remove the cap from the mouthpiece & make sure that the mouthpiece is clean.

2 Hold the inhaler away from your face. Shake it well & release two puffs into the air.

3 The dose indicator will show the number '120', indicating the number of puffs in the inhaler. Now your **SEROFLO-S** inhaler is ready for use.

IF you have not used your inhaler for a week or more, shake well and release one puff into the air.

USING YOUR SEROFLO-S INHALER

1 Sit or stand upright. Remove the mouthpiece cap & shake the inhaler well. Hold it upright as shown, with your thumb at the base below the mouthpiece. Place either one or two fingers on top of the canister.

2 **Breathe out fully,** through your mouth.

3 Place the mouthpiece of the inhaler in your mouth between your teeth & close your lips around it (do not bite it). **Start breathing in slowly through your mouth. Press down the canister firmly & fully to release one spray while continuing to breathe in slowly & deeply.**

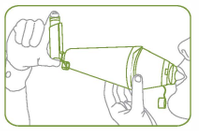
4 Remove the inhaler from your mouth & hold your breath for 10 seconds, or for as long as is comfortable. Breathe out normally.

5 If another puff is required, wait for at least 1 minute. Shake inhaler well & repeat steps 2 to 4. After use, replace the mouthpiece cap firmly & snap it into position.

6 After taking each dose, rinse your mouth with water & spit it out.

IMPORTANT:
Do not rush steps 2, 3 & 4. It is important that you start to breathe in slowly before releasing a puff.
To ensure correct use of the inhaler, use it in front of a mirror for the first few times. If you see 'mist' coming out from the top of the inhaler or the sides of your mouth, start again from step 1. This escaping mist indicates incorrect technique.

In case of difficulty in using the inhaler correctly, you may use it along with a spacer device.



FOR CHILDREN:
Parents must assist those children who need help in using the **SEROFLO-S** inhaler correctly with/without a spacer.

CLEANING YOUR SEROFLO-S INHALER

It is important to keep your inhaler clean. Clean your inhaler atleast once a week.

1 Take the mouthpiece cap off. **DO NOT take the metal canister out of the actuator.**

2 Wipe the inside & the outside of the mouthpiece with a clean, dry cloth.

3 Replace the mouthpiece cap.

4 DO NOT wash or soak any part of the inhaler in water.

STORING YOUR SEROFLO-S INHALER

Store below 30°C and
Protect from direct sunlight
Do not freeze.

Keep the inhaler in an upright position, with the mouthpiece down.

DO NOT

- × *Spray the inhaler in your eyes.*
- × *Exceed the recommended dose.*
- × *Change/tamper with the numbers on the dose indicator.*
- × *Puncture or burn the inhaler even when empty as it is pressurized.*

Keep the inhaler out of the reach of children.

KH43 A

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

Salmeterol & Fluticasone Propionate Inhaler

Seroflo-S inhaler

COMPOSITION

SEROFLO-S 50 Inhaler
Each actuation delivers:
Salmeterol (as Salmeterol Xinafoate Ph.Eur) .....25 mcg
Fluticasone Propionate BP.....50 mcg
Suspended in Propellant HFA - 134a ....q.s.
Also contains Absolute alcohol Ph. Eur.

SEROFLO-S 125 Inhaler
Each actuation delivers:
Salmeterol (as Salmeterol Xinafoate Ph.Eur) .....25 mcg
Fluticasone Propionate BP.....125 mcg
Suspended in Propellant HFA - 134a ....q.s.
Also contains Absolute alcohol Ph. Eur.

SEROFLO-S 250 Inhaler
Each actuation delivers:
Salmeterol (as Salmeterol Xinafoate Ph.Eur) .....25 mcg
Fluticasone Propionate BP.....250 mcg
Suspended in Propellant HFA - 134a ....q.s.
Also contains Absolute alcohol Ph. Eur.

DOSAGEFORM
Inhalation Aerosol

DESCRIPTION

SEROFLO-S Inhaler is a combination of fluticasone propionate, a synthetic corticosteroid, and salmeterol, a selective, long-acting $beta_2$-agonist.
Fluticasone propionate is a synthetic, trifluorinated glucocorticoid with potent anti-inflammatory activity. Salmeterol is a selective, long-acting $beta_2$-adrenoceptor agonist with duration of action of at least 12 hours.

PHARMACOLOGY

Pharmacodynamics

Since **SEROFLO-S Inhaler** contains both fluticasone propionate and salmeterol, the mechanism of action described below for the individual components apply to **SEROFLO-S Inhaler**. These drugs represent two classes of medications (a synthetic corticosteroid and a selective, long-acting $beta_2$- adrenergic receptor agonist) that have different effects on the clinical, physiologic, and inflammatory indices of asthma.

Fluticasone Propionate

Fluticasone propionate is a synthetic, trifluorinated corticosteroid with potent anti-inflammatory activity. *In vitro* assays using cytosol preparations from human lungs have established fluticasone propionate as a human glucocorticoid receptor agonist with an affinity eighteen times greater than dexamethasone, almost twice that of beclomethasone -17-monopropionate (BMP), the active metabolite of beclomethasone dipropionate, and over three times that of budesonide. Data from the McKenzie vasoconstrictor assay in humans are consistent withthese results.

The precise mechanisms of fluticasone propionate action in asthma are unknown. Inflammation is an important component in the pathogenesis of asthma. Corticosteroids have been shown to inhibit multiple cell types (e.g., mast cells, eosinophils, basophils, lymphocytes, macrophages, and neutrophils) and mediator production or secretion (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in the asthmatic response. These anti-inflammatory actions of corticosteroids contribute to their efficacy in asthma.

Salmeterol

Salmeterol is a long-acting $beta_2$-adrenergic agonist. *In vitro* studies and *in vivo* pharmacologic studies demonstrate that salmeterol is selective for $beta_2$-adrenoceptors compared with isoproterenol, which has approximately equal agonist activity on $beta_1$- and $beta_2$-adrenoceptors. *In vitro* studies show salmeterol to be at least fifty times more selective for $beta_2$-adrenoceptors than salbutamol. Although $beta_2$-adrenoceptors are the predominant adrenergic receptors in bronchial smooth muscle and $beta_1$-adrenoceptors are the predominant receptors in the heart, there are also $beta_2$-adrenoceptors in the human heart, comprising 10–50% of the total beta-adrenoceptors. The precise function of these receptors has not been established, but their presence raises the possibility that even selective $beta_2$-agonists may have cardiac effects.

Mechanism of Action

The pharmacologic effects of $beta_2$-adrenoceptor agonist drugs, including salmeterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyses the conversion of adenosine triphosphate (ATP) to cyclic-3', 5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especiallyfrommast cells.

Salmeterol contains a long side chain, which binds to the exo-site of the receptor. These pharmacological properties of salmeterol offer more effective protection against histamine-induced bronchoconstriction and produce a longer duration of bronchodilation, lasting for at least 12 hours, than recommended doses of conventional short-acting $beta_2$ agonists. In humans, 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.

In vitro tests show that salmeterol is a potent and long-lasting inhibitor of the release of mast cell mediators, such as histamine, leukotrienes, and prostaglandin D_2, from human lungs. Salmeterol inhibits histamine-induced plasma protein extravasation and inhibits platelet activating factor-induced eosinophil accumulation in the lungs of guinea pigs when administered by the inhaled route. In humans, single doses of salmeterol administered via inhalation aerosol attenuate allergen-induced bronchial hyper- responsiveness. Salmeterol has been studied in the treatment of conditions associated with chronic obstructive pulmonary disease (COPD) and has been shown to improve symptoms, pulmonary function, and quality of life.

Pharmacokinetics

Three single-dose, placebo-controlled, crossover studies were conducted in healthy subjects:
(1) A study using 4 inhalations of salmeterol/ fluticasone 25/250, salmeterol inhalation aerosol 25 mcg, or fluticasone propionate inhalation aerosol 250 mcg
(2) A study using 8 inhalations of salmeterol/ fluticasone 25/50, salmeterol/fluticasone 25/125, or salmeterol/fluticasone 25/250
(3) A study using 4 inhalations of salmeterol/ fluticasone 25/25b; 2 inhalations of salmeterol/ fluticasone dry powder inhaler 50/500;
4 inhalations of fluticasone propionate inhalation aerosol 250 mcg; or 1,010 mcg of fluticasone propionate given intravenously. Peak plasma concentrations of fluticasone propionate were achieved in 0.33–1.5 hours and those of salmeterol were achieved in 5–10 minutes.

Peak plasma concentrations of fluticasone propionate (n = 20 subjects) following 8 inhalations of salmeterol/fluticasone 25/50, salmeterol/fluticasone 25/125, and salmeterol/ fluticasone 25/250 averaged 41, 108, and 173 pg/mL, respectively. Peak plasma salmeterol concentrations ranged from 220–470 pg/mL.

Systemic exposure (n = 20 subjects) from 4 inhalations of salmeterol/fluticasone 25/250 was 53% of the value from the individual inhaler for fluticasone propionate inhalation aerosol and 42% of the value from the individual inhaler for salmeterol inhalation aerosol. Peak plasma concentrations from salmeterol/fluticasone for fluticasone propionate (86 versus 120 pg/mL) and salmeterol (170versus 510 pg/mL) were significantly lower compared to individual inhalers.

In 15 healthy subjects, systemic exposure to fluticasone propionate from 4 inhalations of salmeterol/ fluticasone 25/250 and 2 inhalations of salmeterol/fluticasone 50/500 were similar between the two inhalers (i.e., 799 versus 832 pg•h/mL), but approximately half the systemic exposure from 4 inhalations of fluticasone propionate inhalation aerosol 250 mcg (1,543 pg•h/mL). Similar results were observed for peak fluticasone propionate plasma concentrations (186 and 182 pg/mL from salmeterol/fluticasone inhaler and dry powder inhaler, respectively, and 307 pg/mL from the fluticasone propionate inhalation aerosol). Systemic exposure to salmeterol was higher (317 versus 169 pg•h/mL) and peak salmeterol concentrations were lower (196 versus 223 pg/mL) following salmeterol/ fluticasone inhalation aerosol compared to salmeterol/fluticasone dry powder inhaler, although pharmacodynamic results were comparable.

Absolute bioavailability of fluticasone propionate from salmeterol/fluticasone was 5.3%. Terminal half-life estimates of fluticasone propionate for salmeterol/fluticasone inhalation aerosol, salmeterol/fluticasone dry powder inhaler, and fluticasone propionate inhalation aerosol were similar and averaged 5.9 hours. No terminal half-life estimates were calculated for salmeterol.

A double-blind, crossover study was conducted in 13 adult patients with asthma to evaluate the steady-state pharmacokinetics of fluticasone propionate and salmeterol following administration of 2 inhalations of salmeterol/ fluticasone inhalation aerosol 25/125 twice daily, or 1 inhalation of salmeterol/fluticasone dry powder inhaler 50/250 twice daily for 4 weeks. Systemic exposure (AUC) to fluticasone propionate was similar for salmeterol/fluticasone inhalation aerosol [274 pg•h/mL (95% CI 150, 502)] and salmeterol/fluticasone dry powder inhaler [338 pg•h/mL (95% CI 197, 581)]. Systemic exposure to salmeterol was also similar for salmeterol/fluticasone inhalation aerosol [53 pg•h/mL (95% CI: 17, 164)] and salmeterol/ fluticasone dry powder inhaler [70 pg•h/mL (95% CI 19, 254)].

INDICATIONS

SEROFLO-S Inhaler is indicated in the regular treatment of asthma, where use of a combination (long-acting $beta_2$-agonist and inhaled corticosteroid) has been found to be appropriate, and in patients with severe COPD.

DOSAGE AND AOMINISTRATION

Asthma
Adults and Adolescents (12 years and older)
SEROFLO-S 50: Two inhalations twice daily
SEROFLO-S 125: Two inhalations twice daily
SEROFLO-S 250: Two inhalations twice daily

Children (4 years and older)
SEROFLO-S 50: Two inhalations twice daily

Not recommended for children below 4 years of age.

COPD
SEROFLO-S 125: Two inhalations twice daily
SEROFLO-S 250: Two inhalations twice daily

CONTRAINDICATIONS

SEROFLO-S Inhaler is contraindicated in patients with a history of hypersensitivity to any of the component of the drug product.

WARNINGS AND PRECAUTIONS

Patients should be made aware that **SEROFLO-S Inhaler** must be used daily for optimum benefit, even when asymptomatic.

SEROFLO-S Inhaler should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of asthma.

SEROFLO-S Inhaler should not be used for transferring patients from systemic corticosteroid therapy.

SEROFLO-S Inhaler should not be used in conjuction with an inhaled LABA.

SEROFLO-S 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 relief medication available at all times.

As with all inhaled medication containing corticosteroids, **SEROFLO-S Inhaler** should be administered with caution in patients with pulmonary tuberculosis.

SEROFLO-S Inhaler should be administered with caution in patients with severe cardiovascular disorders, including heart rhythm abnormalities, diabetes mellitus, untreated hypokalaemia, or thyrotoxicosis.

Potentially serious hypokalaemia may result from systemic $beta_2$-agonist therapy. But following inhalation at therapeutic doses, plasma levels of salmeterol are very low.

Paradoxical bronchospasm may occur. In such a case, **SEROFLO-S Inhaler** should be discontinued immediately, the patient assessed and alternative therapy instituted, if necessary.

Systemic effects are much less likely to occur with inhaled corticosteroids than with oral corticosteroids. Possible systemic effects include adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract, and glaucoma. It is important, therefore, that the dose is titrated to the lowest dose at which effective control is maintained.

Drug Interactions

Even though plasma levels of salmeterol and fluticasone are very low, potential interactions with other substrates or inhibitors of CYP 3A4 cannot be excluded.

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.

Renal Impairment

Pharmacokinetic studies using salmeterol/ fluticasone have not been conducted to examine differences in patients with renal impairment.

Hepatic Impairment

Pharmacokinetic studies using salmeterol/ fluticasone have not been conducted to examine differences in patients with hepatic impairment. However, since both fluticasone propionate and salmeterol are predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of fluticasone propionate and salmeterol in plasma. Therefore, patients with hepatic impairment should be closely monitored.

Pregnancy

Use of **SEROFLO-S Inhaler** in pregnancy should be considered only if the expected benefit to the expectant mother is greater than any possible risk to the foetus.

Lactation

Use of **SEROFLO-S Inhaler** in women who are breastfeeding should only be considered if the expected benefit to the nursing mother is greater than any possible risk to the infant. Caution should be exercised when Seroflo-S Inhaler is administered to a nursing women

UNDESIRABLE EFFECTS

As **SEROFLO-S Inhaler** contains salmeterol and fluticasone propionate, the type and severity of side effects associated with each of the compounds may be expected. There is no incidence of additional side effects following concurrent administration of the two compounds.

Adverse events that occurred in the groups receiving salmeterol/fluticasone in trials, with an incidence of 1–3% and at a greater incidence than with placebo were:
Tachycardia; arrhythmias; myocardial infarction; palpitation; post-operative complications; wounds and lacerations; soft tissue injuries; poisoning and toxicity; pressure-induced disorder; ear, nose, and throat infection; ear signs and symptoms; rhinorrhoea/postnasal drip; epistaxis; nasal congestion/blockage; laryngitis; nasopharyngitis, sinusitis unspecified oropharyngeal plaques; dryness of nose; weight gain; allergic eye disorders; eye oedema and swelling; gastrointestinal discomfort and pain; Hoarseness; dysphonia; dizziness; anxiety; behavioural changes(predominantly in children); cushing's syndrome; cushingoid features; hypokalemia; hyperglycaemia; headache; dental discomfort and pain; candidiasis mouth/throat; hyposalivation; gastrointestinal infections; disorders of the hard tissue of teeth; haemorrhoids; gastrointestinal gaseous symptoms; abdominal discomfort and pain; constipation; oral abnormalities; arthralgia and articular rheumatism; muscle cramps and spasms; musculoskeletal inflammation; bone and skeletal pain; sleep disorders; migraines; allergies
and allergic reactions; viral infections; bacterial infections; candidiasis unspecified site; congestion; inflammation; bacterial reproductive
infections.

Lower respiratory signs and symptoms,
lower respiratory infections, lower respiratory haemorrhage, eczema, dermatitis, and dermatosis, and urinary infections can occur.
Rare cases of immediate and delayed hypersensitivity reactions, including rash and other rare events of anglo-oedema and bronchospasm, have been reported.

OVERDOSAGE

The signs and symptoms of
SEROFLO-S Inhaler 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. Additionally, hypokalaemia can occur and potassium replacement should be considered. If a higher than recommended dosage is continued over prolonged periods, some degree of adrenal suppression may result. Monitoring of adrenal reserve may be necessary.

INCOMPATIBILITY
None known

SHELF-LIFE : See on pack

STORAGE AND HANDLING INSTRUCTIONS
Store below 30°C and
Protect from direct sunlight
Do not freeze.

PACKAGING INFORMATION
SEROFLO-S 50, SEROFLO-S 125 and **SEROFLO-S 250 Inhalers with dose indicator** are available in canisters containing 120 metered doses.

Last updated: June 2012

Cipla

KH43 A