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

Salmeterol and Fluticasone Propionate Powder for Inhalation

new

Seroflo-S

Multi-haler ™

COMPOSITION:

Seroflo-S 250 multihaler

Each dose contains:
Salmeterol ..... 50 mcg
(As Salmeterol Xinafoate Ph.Eur)
Fluticasone propionate BP ..... 250 mcg
Excipient ..... q.s.

Seroflo-S 500 multihaler

Each dose contains:
Salmeterol ..... 50 mcg
(As Salmeterol Xinafoate Ph.Eur)
Fluticasone propionate BP ..... 500 mcg
Excipient ..... q.s.

DOSAGE FORM:

Dry Powder for inhalation

DESCRIPTION

SEROFLO-S MULTIHALER 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 beta2-adrenoceptor agonist with duration of action of at least 12 hours.

PHARMACOLOGY

Pharmacodynamics

Since **SEROFLO-S MULTIHALER** contain both fluticasone propionate and salmeterol, the mechanism of action described below for the individual components apply to **SEROFLO-S MULTIHALER**. 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 with these results.

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.

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, especially from mast cells.

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.

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 25/250; 2 inhalations of salmeterol/fluticasone dry powder rotacaps 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 rotacaps for fluticasone propionate inhalation aerosol and 42% of the value from the individual rotacaps for salmeterol inhalation aerosol. Peak plasma concentrations from salmeterol/fluticasone for fluticasone propionate (86 versus 120 pg/mL) and salmeterol (170 versus 510 pg/mL) were significantly lower compared to individual rotacaps.

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 rotacapss (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 rotacaps and dry powder rotacaps, 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 rotacaps, 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 rotacaps, 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 rotacaps 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 rotacaps [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 rotacaps [70 pg•h/mL (95% CI 19, 254)].

INDICATIONS

SEROFLO-S MULTIHALER 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 chronic obstructive pulmonary disease (COPD).

DOSAGE AND ADMINISTRATION

Adults and adolescents 12 years and over

Asthma:

SEROFLO-S 250/500 MULTI-HALER: One inhalation twice daily

Chronic Obstructive Pulmonary Disease (COPD):

SEROFLO-S 250/500 MULTI-HALER: One inhalation twice daily

CONTRAINDICATIONS

SEROFLO-S MULTIHALER 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 MULTIHALER** must be used daily for optimum benefit, even when asymptomatic.

SEROFLO-S MULTIHALER 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 MULTIHALER** should be administered with caution in patients with pulmonary tuberculosis.

SEROFLO-S MULTIHALER 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 MULTIHALER** 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 CYP3A4 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 **SEROFLO-S** have not been conducted to examine differences in patients with renal impairment.

Hepatic Impairment

Pharmacokinetic studies using **SEROFLO-S** 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 MULTIHALER** 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 MULTIHALER** 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.

UNDESIRABLE EFFECTS

As **SEROFLO-S MULTIHALER** 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; 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; unspecified oropharyngeal plaques; dryness of nose; weight gain; allergic eye disorders; eye oedema and swelling; gastrointestinal discomfort and pain; 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 angio-oedema and bronchospasm, have been reported.

OVERDOSAGE

The signs and symptoms of **SEROFLO-S MULTIHALER** 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 a higher than recommended dosage is continued over prolonged periods, some degree of adrenal suppression may result. Monitoring of adrenal reserve may be necessary.

STORAGE:

Store below 30°C. Protect from heat and moisture.

PACKAGING INFORMATION

SEROFLO-S 250 MULTI-HALER
inhalation device containing 30 doses.

SEROFLO-S 500 MULTI-HALER
inhalation device containing 30 doses.

Last updated: December 2007

Cipla

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Patient Information Leaflet

Before using your

new

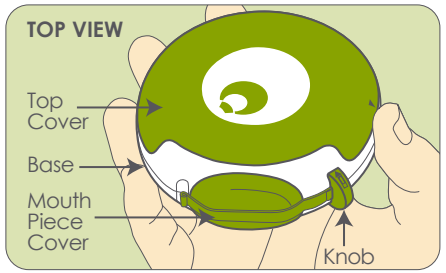
Seroflo-S

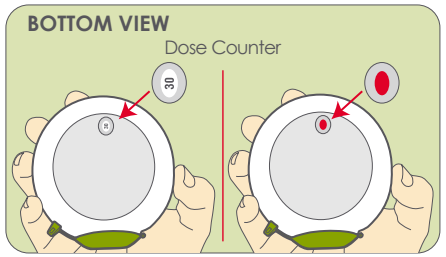
Multi-haler ™

read this leaflet carefully and follow the instructions

What is Seroflo-S Multi-haler ?

Seroflo-S Multi-haler is a dry powder inhaler device containing medicine prescribed by your doctor.





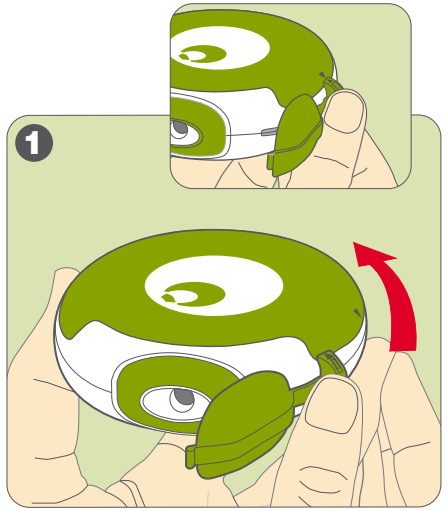
Each **Seroflo-S Multi-haler** contains 30 doses.

The dose counter on the bottom (base) of the **Multi-haler** indicates you how many doses are left. Dose indicater will display **30** in a new device. Each time you use the **Multi-haler**, the dose counter number will decrease.

When there are no doses left you will see a **Red** circle in the window.

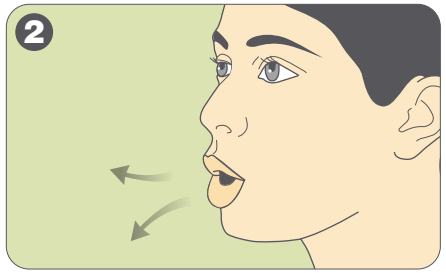
How to use your Seroflo-S Multi-haler?

First remove the **Multi-haler** from the pouch. Now to take your dose from the **Seroflo-S Multi-haler,** follow these simple steps



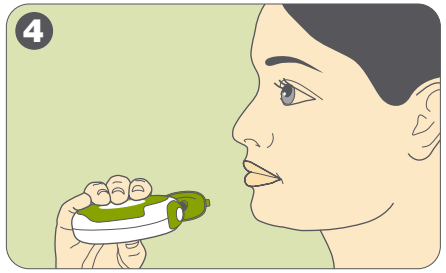
Hold the **Multi-haler** by the base as shown in the picture above. Open the mouthpiece cover. Put your thumb on the knob and slide it **till the arrow on the knob meets the arrow on the top cover.** While you are doing this you will hear a click sound which is normal.

The **Multi-haler** is now ready for use.

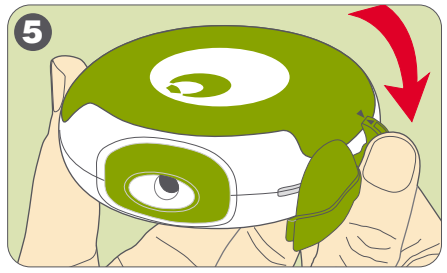


Before taking a dose, breathe out fully. Never breathe out into the **Multi-haler** mouthpiece.

Place the mouthpiece between your lips and breathe in through your mouth deeply.



Remove the **Multi-haler** from your mouth and hold your breath for about 10 seconds or as long as you are comfortable. Then breathe out slowly.



Slide the knob backwards (as shown in fig.) & then close the mouthpiece cover after use. For the next dose repeat steps 1 to 3.

For Children

Parents must assist those children who need help in using the **Multi-haler** correctly.

Remember

- Never breathe out into the **Multi-haler.**
- Never attempt to take the **Multi-haler** apart
- Always use the **Multi-haler** in a level, horizontal position
- Every time you open & slide the mouthpiece cover a dose is ready to be inhaled. Sliding back & closing the mouthpiece cover, without inhaling or playing with the mouthpiece cover will lead to wastage of the doses.
- After inhalation, rinse the mouth with water without swallowing
- The **Multi-haler** should NEVER be washed. It should always be kept dry
- The **Multi-haler** requires no refilling. Discard the **Multi-haler** when the dose counter shows the red circle (after 30 doses)
- Keep out of reach of children.

Keeping and storing your Multi-Haler

- The outside of the mouthpiece may be wiped with a dry cloth or tissue.

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