SEROFLO Autohaler (Salmeterol xinafoate + Fluticasone propionate)

Composition

SEROFLO 250 Autohaler
Each actuation delivers:
Salmeterol (as Salmeterol Xinafoate IP) .............. 25 mcg
Fluticasone Propionate IP ................................... 250 mcg
Suspended in propellant HFA 134a .................... q.s

Dosage Form

Breath actuated aerosol for inhalation

Description

SEROFLO Autohaler is a combination of fluticasone propionate, a synthetic corticosteroid, and salmeterol, a selective, long-acting beta₂-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 Autohaler contains both fluticasone propionate and salmeterol, the mechanism of action described below for the individual components apply to SEROFLO Autohaler. These drugs represent two classes of medications (a synthetic corticosteroid and a selective, long-acting beta₂-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-1-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 mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in inflammation. These anti-inflammatory actions of corticosteroids contribute to their efficacy in asthma.

Salmeterol
Salmeterol is a long-acting beta₂-adrenergic agonist. In vitro studies and in vivo pharmacologic studies demonstrate that salmeterol is selective for beta₂-adrenoceptors compared with isoproterenol, which has approximately equal agonist activity on beta₁- and beta₂-adrenoceptors. In vitro studies show salmeterol to be at least fifty times more selective for beta₂-adrenoceptors than salbutamol. Although beta₂-adrenoceptors are the predominant adrenergic receptors in bronchial smooth muscle and beta₁-adrenoceptors are the predominant receptors in the heart, there are also beta₂-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 beta₂-agonists may have cardiac effects.

The pharmacologic effects of beta₂-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. 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 beta₂-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 D₂, 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

#### Absorption

**Fluticasone Propionate**

Peak steady-state fluticasone propionate plasma concentrations in adult patients with asthma (N = 11) ranged from undetectable to 266 pg/mL after a 500-mcg twice-daily dose of fluticasone propionate inhalation powder. The mean fluticasone propionate plasma concentration was 110 pg/mL.

**Salmeterol Xinafoate**

Because of the small therapeutic dose, systemic levels of salmeterol are low or undetectable after inhalation of recommended doses (50 mcg of salmeterol inhalation powder twice daily).

Following chronic administration of an inhaled dose of 50 mcg of salmeterol inhalation powder twice daily, salmeterol was detected in plasma within 5 to 45 minutes in 7 patients with asthma; plasma concentrations were very low, with mean peak concentrations of 167 pg/mL at 20 minutes and no accumulation with repeated doses.

#### Distribution

**Fluticasone Propionate**

Following intravenous administration, the initial disposition phase for fluticasone propionate was rapid and consistent with its high lipid solubility and tissue binding. The volume of distribution averaged 4.2 L/kg. The percentage of fluticasone propionate bound to human plasma proteins averages 99%. Fluticasone propionate is
weakly and reversibly bound to erythrocytes and is not significantly bound to human transcortin.

**Salmeterol**
The percentage of salmeterol bound to human plasma proteins averages 96% in vitro over the concentration range of 8 to 7,722 ng of salmeterol base per milliliter, much higher concentrations than those achieved following therapeutic doses of salmeterol.

**Metabolism**

**Fluticasone Propionate**
The total clearance of fluticasone propionate is high (average, 1,093 mL/min), with renal clearance accounting for less than 0.02% of the total. The only circulating metabolite detected in man is the 17(beta)-carboxylic acid derivative of fluticasone propionate, which is formed through the CYP 3A4 pathway. This metabolite had less affinity (approximately 1/2,000) than the parent drug for the glucocorticoid receptor of human lung cytosol in vitro and negligible pharmacological activity in animal studies. Other metabolites detected in vitro using cultured human hepatoma cells have not been detected in man.

**Salmeterol**
Salmeterol base is extensively metabolized by hydroxylation, with subsequent elimination predominantly in the feces. No significant amount of unchanged salmeterol base was detected in either urine or feces.

An in vitro study using human liver microsomes showed that salmeterol is extensively metabolized to (alpha)-hydroxysalmeterol (aliphatic oxidation) by CYP 3A4. Ketoconazole, a strong inhibitor of CYP 3A4, essentially completely inhibited the formation of (alpha)-hydroxysalmeterol in vitro.

**Elimination**

**Fluticasone Propionate**
Following intravenous dosing, fluticasone propionate showed polyexponential kinetics and had a terminal elimination half-life of approximately 7.8 hours. Less than 5% of a radiolabeled oral dose was excreted in the urine as metabolites, with the remainder excreted in the feces as parent drug and metabolites. Terminal half-life estimate of fluticasone propionate is 5.6 hours.

**Salmeterol**
In 2 healthy adult subjects who received 1 mg of radiolabeled salmeterol (as salmeterol xinafoate) orally, approximately 25% and 60% of the radiolabeled salmeterol was eliminated in urine and feces, respectively, over a period of 7 days. The terminal elimination half-life was about 5.5 hours (1 volunteer only).

The xinafoate moiety has no apparent pharmacologic activity. The xinafoate moiety is highly protein bound (>99%) and has a long elimination half-life of 11 days. No terminal half-life estimates were calculated for salmeterol following administration of combination of inhaled salmeterol and fluticasone propionate (SFC).

**Indications**

SEROFLO Autohaler is indicated in the regular treatment of asthma, where use of a combination (long-acting beta2-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 Autohaler 250: Two inhalation twice daily.

**Chronic Obstructive Pulmonary Disease (COPD):**
**Contraindications**

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

The use of SEROFLO Autohaler is contraindicated in primary treatment of status asthmaticus or other acute episodes of asthma or COPD where intensive measures are required. SEROFLO Autohaler is also contraindicated in patients with severe hypersensitivity to milk proteins.

**Warnings And Precautions**

**General**

Patients should be made aware that SEROFLO Autohaler must be used daily for optimum benefit, even when asymptomatic. SEROFLO Autohaler should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of asthma. As with all inhaled medication containing corticosteroids, SEROFLO Autohaler should be administered with caution in patients with pulmonary tuberculosis. Patients should not be initiated on SEROFLO Autohaler 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 SEROFLO Autohaler. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation on SEROFLO Multi-haler. Treatment with SEROFLO Autohaler 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.

**Serious Asthma-Related Events – Hospitalizations, Intubations, Death**

Use of long-acting beta₂-adrenergic (LABA) as monotherapy (without ICS) for asthma is associated with an increased risk of asthma-related death. Available data from controlled clinical trials also suggest that use of LABA as monotherapy increases the risk of asthma-related hospitalization in pediatric and adolescent patients. These findings are considered a class effect of LABA monotherapy. When LABA are used in fixed-dose combination with ICS, data from large clinical trials do not show a significant increase in the risk of serious asthma-related events (hospitalizations, intubations, death) compared with ICS alone.

**Deterioration of Disease and Acute Episodes**

Fluticasone/salmeterol combination should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of asthma or COPD. Fluticasone/salmeterol combination has not been studied in subjects with acutely deteriorating asthma or COPD. The initiation of fluticasone/salmeterol combination in this setting is not appropriate.

Serious acute respiratory events, including fatalities, have been reported when salmeterol, a component of fluticasone/salmeterol combination, has been initiated in patients with significantly worsening or acutely deteriorating asthma. In most cases, these have occurred in patients with severe asthma (e.g., patients with a history of corticosteroid dependence, low pulmonary function, intubation, mechanical ventilation, frequent hospitalizations, previous life-threatening acute asthma exacerbations) and in some patients with acutely deteriorating asthma (e.g., patients with significantly increasing symptoms; increasing need for inhaled, short-acting beta₂-agonists; decreasing response to usual medications; increasing need for systemic corticosteroids; recent emergency room visits; deteriorating lung function).
However, these events have occurred in a few patients with less severe asthma as well. It was not possible from these reports to determine whether salmeterol contributed to these events. Increasing use of inhaled, short-acting beta\textsubscript{2}-agonists is a marker of deteriorating asthma. In this situation, the patient requires immediate reevaluation with reassessment of the treatment regimen, giving special consideration to the possible need for replacing the current strength of fluticasone/salmeterol combination with a higher strength, adding additional ICS, or initiating systemic corticosteroids. Patients should not use more than 1 inhalation twice daily of fluticasone/salmeterol combination.

Fluticasone/salmeterol combination should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. Fluticasone/salmeterol combination has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta\textsubscript{2}-agonist.

When beginning treatment with fluticasone/salmeterol combination, patients who have been taking oral or inhaled, short-acting beta\textsubscript{2}-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs.

Fluticasone/salmeterol combination should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using fluticasone/salmeterol combination should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.

In clinical trials, the development of localized infections of the mouth and pharynx with Candida albicans has occurred in subjects treated with fluticasone/salmeterol combination. When such an infection develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while treatment with fluticasone/salmeterol combination continues, but at times therapy with fluticasone/salmeterol combination may need to be interrupted. Advise the patient to rinse his/her mouth with water without swallowing following inhalation to help reduce the risk of oropharyngeal candidiasis.

Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of pneumonia and exacerbations frequently overlap. Lower respiratory tract infections, including pneumonia, have been reported in patients with COPD following the inhaled administration of corticosteroids, including fluticasone propionate and fluticasone/salmeterol combination.

Persons who are using drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In such children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If a patient is exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If a patient is exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. If chickenpox develops, treatment with antiviral agents may be
ICS should be used with caution, if at all, in patients with active or quiescent tuberculosis infections of the respiratory tract; systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

### Transferring Patients from Systemic Corticosteroid Therapy

Particular care is needed for patients who have been transferred from systemically active corticosteroids to ICS because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available ICS. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function. Patients who have been previously maintained on 20 mg or more of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although fluticasone/salmeterol combination may control asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of glucocorticoid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies.

During periods of stress or a severe asthma attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic corticosteroids during periods of stress or a severe asthma attack.

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to fluticasone/salmeterol combination. Prednisone reduction can be accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during therapy with fluticasone/salmeterol combination. Lung function (mean forced expiratory volume in 1 second or morning peak expiratory flow), beta-agonist use, and asthma symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition, patients should be observed for signs and symptoms of adrenal insufficiency, such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

Transfer of patients from systemic corticosteroid therapy to fluticasone/salmeterol combination may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy (e.g., rhinitis, conjunctivitis, eczema, arthritis, eosinophilic conditions).

### Hypercorticism and Adrenal Suppression

Fluticasone propionate, a component of fluticasone/salmeterol combination, will often help control asthma symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Since fluticasone propionate is absorbed into the circulation and can be systemically active at higher doses, the beneficial effects of fluticasone/salmeterol combination in minimizing HPA dysfunction may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose. A relationship between plasma levels of fluticasone propionate and inhibitory effects on stimulated cortisol production has been shown after 4 weeks of treatment with fluticasone propionate inhalation aerosol. Since individual sensitivity to effects on cortisol production exists, physicians should consider this information when prescribing fluticasone/salmeterol combination.

Because of the possibility of significant systemic absorption of ICS in sensitive patients, patients treated with fluticasone/salmeterol combination should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal
closely) may appear in a small number of patients who are sensitive to these effects. If such effects occur, fluticasone/salmeterol combination should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids, and other treatments for management of asthma symptoms should be considered.

### Drug Interactions with Strong Cytochrome P450 3A4 Inhibitors

The use of strong cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, saquinavir, ketoconazole, telithromycin) with fluticasone/salmeterol combination is not recommended because increased systemic corticosteroid and increased cardiovascular adverse effects may occur (see Drug Interactions).

### Paradoxical Bronchospasm and Upper Airway Symptoms

As with other inhaled medicines, fluticasone/salmeterol combination can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with fluticasone/salmeterol combination, it should be treated immediately with an inhaled, short-acting bronchodilator; fluticasone/salmeterol combination should be discontinued immediately; and alternative therapy should be instituted. Upper airway symptoms of laryngeal spasm, irritation, or swelling, such as stridor and choking, have been reported in patients receiving fluticasone/salmeterol combination.

### Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions (e.g., urticaria, angioedema, rash, bronchospasm, hypotension), including anaphylaxis, may occur after administration of fluticasone/salmeterol combination. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of powder products containing lactose; therefore, patients with severe milk protein allergy should not use fluticasone/salmeterol combination (see CONTRAINDICATIONS).

### Cardiovascular and Central Nervous System Effects

Excessive beta-adrenergic stimulation has been associated with seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, palpitation, nausea, dizziness, fatigue, malaise, and insomnia (see OVERDOSAGE). Therefore, fluticasone/salmeterol combination, like all products containing sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, hypertension, diabetes mellitus, thyrotoxicosis, uncorrected hypokalaemia or patients predisposed to low levels of serum potassium.

Salmeterol, a component of fluticasone/salmeterol combination, can produce a clinically significant cardiovascular effect in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of salmeterol at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiogram (ECG) changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Large doses of inhaled or oral salmeterol (12 to 20 times the recommended dose) have been associated with clinically significant prolongation of the QTc interval, which has the potential for producing ventricular arrhythmias. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

### Reduction in Bone Mineral Density

Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing ICS. The clinical significance of small changes in BMD with regard to long-term consequences such as fracture is unknown. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of
osteoporosis, postmenopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids), should be monitored and treated with established standards of care. Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended prior to initiating fluticasone/salmeterol combination and periodically thereafter. If significant reductions in BMD are seen and fluticasone/salmeterol combination is still considered medically important for that patient’s COPD therapy, use of medicine to treat or prevent osteoporosis should be strongly considered.

**Effect on Growth**

Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth of pediatric patients receiving fluticasone/salmeterol combination routinely (e.g., via stadiometry). To minimize the systemic effects of orally inhaled corticosteroids, including fluticasone/salmeterol combination, titrate each patient’s dosage to the lowest dosage that effectively controls his/her symptoms (see DOSAGE AND ADMINISTRATION, Use in Specific Populations).

**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.

**Eosinophilic Conditions and Churg-Strauss Syndrome**

In rare cases, patients on inhaled fluticasone propionate, a component of fluticasone/salmeterol combination, may present with systemic eosinophilic conditions. Some of these patients have clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of fluticasone propionate. Cases of serious eosinophilic conditions have also been reported with other ICS in this clinical setting. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between fluticasone propionate and these underlying conditions has not been established.

**Coexisting Conditions**

Fluticasone/salmeterol combination, like all medicines containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related beta2-adrenoceptor agonist salbutamol when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

**Hypokalemia and Hyperglycemia**

Beta-adrenergic agonist medicines may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects (see PHARMACOLOGY). The decrease in serum potassium is usually transient, not requiring supplementation. Clinically significant changes in blood glucose and/or serum potassium were seen infrequently during clinical trials with fluticasone/salmeterol combination at recommended doses.

**Drug Interactions**

Fluticasone/salmeterol combination has been used concomitantly with other drugs, including short-acting beta2-agonists, methylxanthines, and intranasal corticosteroids, commonly used in patients with asthma or COPD without adverse drug
reactions (see PHARMACOLOGY). No formal drug interaction trials have been performed with fluticasone/salmeterol combination.

**Strong Cytochrome P450 3A4 Inhibitors**

Fluticasone and salmeterol are substrates of CYP3A4. The use of strong cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, ketoconazole, telithromycin) with fluticasone/salmeterol combination is not recommended because increased systemic corticosteroid and increased cardiovascular adverse effects may occur.

**Monoamine Oxidase Inhibitors and Tricyclic Antidepressants**

Fluticasone/salmeterol combination should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of salmeterol, a component of fluticasone/salmeterol combination, on the vascular system may be potentiated by these agents.

**Beta-adrenergic Receptor Blocking Agents**

Beta-blockers not only block the pulmonary effect of beta-agonists, such as salmeterol, a component of fluticasone/salmeterol combination, but may also produce severe bronchospasm in patients with asthma or COPD. Therefore, patients with asthma or COPD should not normally be treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents for these patients; cardioselective beta-blockers could be considered, although they should be administered with caution.

**Non-Potassium-Sparing Diuretics**

The ECG changes and/or hypokalemia that may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, such as salmeterol, a component of fluticasone/salmeterol combination, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of fluticasone/salmeterol combination with non-potassium-sparing diuretics.

**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**

Administration of SEROFLO Autohaler 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**

There are no data available for human breast milk. Both salmeterol and fluticasone propionate and their metabolites are excreted into breast milk in rats. Administration of SEROFLO Autohaler to women who are breastfeeding should only be considered if the expected benefit to the mother is greater than any possible risk to the child. Caution should be exercised when SEROFLO Autohaler is administered to a nursing woman.
Geriatric

As with other products containing beta,-agonists, special caution should be observed when using Fluticasone/salmeterol in geriatric patients who have concomitant cardiovascular disease that could be adversely affected by beta2-agonists. Based on available data for fluticasone/salmeterol or its active components, no adjustment of dosage of Fluticasone/salmeterol in geriatric patients is warranted.

Pediatrics

The safety and effectiveness of fluticasone/salmeterol combination in children with asthma younger than 4 years have not been established. ICS, including fluticasone propionate, a component of the formulation, may cause a reduction in growth velocity in children and adolescents. The growth of pediatric patients receiving orally inhaled corticosteroids, including fluticasone/salmeterol combination, should be monitored. If a child or adolescent on any corticosteroid appears to have growth suppression, the possibility that he/she is particularly sensitive to this effect of corticosteroids should be considered. The potential growth effects of prolonged treatment should be weighed against the clinical benefits obtained. To minimize the systemic effects of orally inhaled corticosteroids, including fluticasone/salmeterol combination, each patient should be titrated to the lowest strength that effectively controls his/her asthma.

Undesirable Effects

As SEROFLO Autohaler 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. Use of long-acting beta agonist may result into:

- Serious asthma-related events including hospitalizations, intubations and death, cardiovascular and central nervous system effects
- Systemic and local corticosteroid use may result in the following: Candida albicans infection, pneumonia in patients with COPD, immunosuppression, hypercorticism and adrenal suppression, reduction in bone mineral density, growth retardation, glaucoma and cataracts.
- Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse events that occurred in the groups receiving salmeterol/fluticasone in trials, with an incidence of 3% or more and at a greater incidence than with placebo were:

**Ear, nose, and throat:** Upper respiratory tract infection, pharyngitis, upper respiratory inflammation, sinusitis, hoarseness/dysphonia, candidiasis of mouth/throat, throat irritation

**Lower respiratory:** Viral respiratory infections, bronchitis, cough

**Neurology:** Headache, dizziness

**Gastrointestinal:** Nausea and vomiting, gastrointestinal discomfort and pain, diarrhea, viral gastrointestinal infections

**Non-site specific:** Candidiasis unspecified site, fever, malaise, and fatigue

**Musculoskeletal:** Musculoskeletal pain, muscle cramps and spasms, traumatic fractures, arthralgia, myalgia

Other adverse reactions not previously listed, whether considered drug-related or not by the investigators, that were
reported more frequently by subjects with asthma treated or COPD treated with fluticasone/salmeterol combination compared with subjects treated with placebo include the following: palpitations, tachycardia, cardiac arrhythmias (including supraventricular tachycardia and extrasystoles), atrial fibrillation, angina pectoris lymphatic signs and symptoms; muscle injuries; fractures; wounds and lacerations; contusions and hematomas; ear signs and symptoms; nasal signs and symptoms; nasal sinus disorders; nasopharyngitis; nasal congestion; paradoxical bronchospasm; keratitis and conjunctivitis; dental discomfort and pain; gastrointestinal signs and symptoms; oral ulcerations; oral discomfort and pain; lower respiratory signs and symptoms; pneumonia; back pain; muscle stiffness, tightness, and rigidity; bone and cartilage disorders; sleep disorders; compressed nerve syndromes; viral infections; pain; chest symptoms; fluid retention; bacterial infections; unusual taste; viral skin infections; skin flakiness and acquired ichthyosis; disorders of sweat and sebum, hypothyroidism, dry eyes, edema and swelling, hypersensitivity reactions including; dyspnea, bronchospasm, anaphylactic reactions including anaphylactic shock, angioedema, Cushing’s syndrome, Cushingoid features, adrenal suppression, hypokalemia, hypoglycemia, anxiety, sleep disorders, behavioral changes including psychomotor hyperactivity and irritability (predominantly in children), growth retardation in children, decreased bone mineral density, depression, aggression (predominantly in children), tremor, cataract, glaucoma, vision blurred

Common adverse reactions (≥3% and greater than placebo) seen in the pediatric subjects but not reported in the adult and adolescent clinical trials include: throat irritation and ear, nose, and throat infections.

Laboratory Test Abnormalities

Elevation of hepatic enzymes was reported in ≥1% of subjects in clinical trials. The elevations were transient and did not lead to discontinuation from the trials. In addition, there were no clinically relevant changes noted in glucose or potassium.

Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during postapproval use of any formulation of fluticasone propionate, and/or salmeterol regardless of indication. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to fluticasone propionate, and/or salmeterol or a combination of these factors.

Cardiac Disorders: Arrhythmias (including atrial fibrillation, extrasystoles, supraventricular tachycardia), ventricular tachycardia

Endocrine Disorders: Cushing’s syndrome, Cushingoid features, growth velocity reduction in children/adolescents, hypercorticism

Eye Disorders: Glaucoma

Gastrointestinal Disorders: Abdominal pain, dyspepsia, xerostomia

Immune System Disorders: Immediate and delayed hypersensitivity reaction (including very rare anaphylactic reaction). Very rare anaphylactic reaction in patients with severe milk protein allergy

Infections and Infestations: Esophageal candidiasis

Metabolic and Nutrition Disorders: Hyperglycemia, weight gain

Musculoskeletal, Connective Tissue, and Bone Disorders: Arthralgia, cramps, myositis, osteoporosis

Nervous System Disorders: Paresthesia, restlessness

Psychiatric Disorders: Agitation, aggression, depression, behavioral changes, including hyperactivity and irritability have been reported very rarely and primarily in children.

Reproductive System and Breast Disorders: Dysmenorrhea
**Respiratory, Thoracic, and Mediastinal Disorders:** Chest congestion; chest tightness; dyspnea; facial and oropharyngeal edema, immediate bronchospasm; paradoxical bronchospasm; tracheitis; wheezing; reports of upper respiratory symptoms of laryngeal spasm, irritation, or swelling such as stridor or choking

**Skin and Subcutaneous Tissue Disorders:** Ecchymoses, photodermatitis.

**Vascular Disorders:** Pallor

If you experience any side-effects, talk to your doctor or pharmacist or write to drugsafety@cipla.com. You can also report side effects directly via the national pharmacovigilance program of India by calling on 1800 180 3024. By reporting side-effects, you can help provide more information on the safety of this product.

### Overdosage

There are no data available from clinical trials on overdose with salmeterol/fluticasone; 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. The preferred antidotes are cardioselective beta-blocking agents, which should be used with caution in patients with a history of bronchospasm. If SEROFLO Autohaler 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

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.

In cases of both acute and chronic fluticasone propionate overdose SEROFLO Autohaler therapy may still be continued at a suitable dosage for symptom control.

### Storage and Handling Informations

Store below 30°C. Do not freeze. The canister is pressurized and must be kept away from direct sunlight. The canister must not be punctured, broken or incinerated even when apparently, empty. Keep away from eyes. Keep away from children.

### Packaging Information

SEROFLO 250 Autohaler

Each sales pack is available as canisters containing 200 metered doses.

Last Updated: September 2018

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**SEROFLO Autohaler**

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