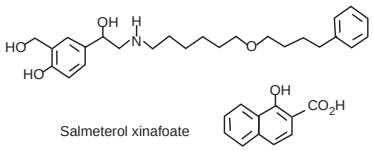
Saltrol™

[Salmeterol+Fluticasone propionate]

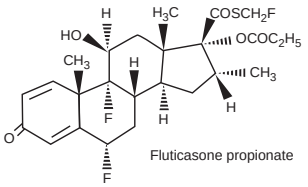
CFC Free Inhaler
25mcg + 125mcg & 25mcg + 250mcg

DESCRIPTION
Saltrol is a combination of Salmeterol xinafoate and Fluticasone propionate. Salmeterol xinafoate is a ß$_2$ adrenergic bronchodilator. It is the racemic form of the 1-hydroxy-2-naphthoic acid salt of Salmeterol. The chemical name of Salmeterol xinafoate is 4-hydroxy-α1-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol, 1-hydroxy-2-naphthalenecarboxylate. Its molecular formula is $C_{25}H_{37}NO_4.C_{11}H_8O_3$ and the structural formula is:



Salmeterol xinafoate

Fluticasone propionate is a corticosteroid having the chemical name S-(fluoromethyl) 6α,9-difluoro-11ß,17-dihydroxy-16α-methyl-3oxoandrosta-1,4-diene-17ß-carbothioate, 17-propionate. Its molecular formula is $C_{25}H_{31}F_3O_5S$ and the structural formula is:



Fluticasone propionate

QUALITATIVE & QUANTITATIVE COMPOSITION
Saltrol (Salmeterol + Fluticasone propionate) inhaler is available for administration as:

Saltrol Inhaler 25mcg + 125mcg
Each metered dose contains:
Salmeterol xinafoate Ph. Eur. equivalent to Salmeterol… 25mcg
Fluticasone propionate Ph. Eur…. 125mcg

Saltrol Inhaler 25mcg + 250mcg
Each metered dose contains:
Salmeterol xinafoate Ph. Eur. equivalent to Salmeterol… 25mcg
Fluticasone propionate Ph. Eur…. 250mcg

CLINICAL PHARMACOLOGY
Mechanism of Action
Salmeterol:
Salmeterol is a selective long-acting (12 hour) ß$_2$ adrenoceptor agonist with a long side chain which binds to the exo-site of the receptor. The pharmacologic effects of ß$_2$ adrenoceptor agonist drugs, including salmeterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes 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.

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
Salmeterol:
Salmeterol acts locally in the lung therefore plasma levels are not an indication of therapeutic effects. The percentage of salmeterol bound to human plasma proteins averages 96% in vitro over the concentration range of 8 to 7,722ng of salmeterol base per milliliter. Salmeterol 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.

Fluticasone propionate:
Fluticasone propionate acts locally in the lung therefore plasma levels do not predict therapeutic effects. Oral systemic bioavailability of Fluticasone propionate is negligible (less than 1%) primarily due to incomplete absorption and presystemic metabolism in the gut and liver. 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 feces. The renal clearance of Fluticasone propionate is negligible. Less than 5% of the dose is excreted in urine, mainly as metabolites. The main part of the dose is excreted in feces as metabolites and unchanged drug.

THERAPEUTIC INDICATIONS
Asthma
Saltrol (Salmeterol + Fluticasone propionate) is indicated for the regular treatment of asthma (Reversible Obstructive Airways Disease), where use of a combination product (bronchodilator and inhaled corticosteroid) is appropriate. This may include:
- Patients on effective maintenance doses of both long-acting ß-agonists and inhaled corticosteroids using separate products.
- Patients who are not adequately controlled on current inhaled corticosteroid therapy.
- Patients who are not adequately controlled on "as needed" short-acting ß-agonists, as an alternative to initiation of maintenance therapy with moderate or high doses of inhaled corticosteroid alone.

Saltrol (Salmeterol + Fluticasone propionate) should not typically be used for the initial management of asthma, unless symptoms are severely uncontrolled, nor in patients whose asthma can be managed by occasional use of short-acting ß$_2$ agonists.

Saltrol (Salmeterol + Fluticasone propionate) should not be used in the treatment of acute asthmatic symptoms.

Chronic Obstructive Pulmonary Disease (COPD)
Saltrol (Salmeterol + Fluticasone propionate) is indicated for the symptomatic treatment of patients with moderate to severe COPD (pre-bronchodilator FEV_1<60% predicted normal), who have significant symptoms despite bronchodilator therapy.

DOSAGE AND ADMINISTRATION
Saltrol (Salmeterol + Fluticasone propionate) Inhaler is for inhalation only. Patients should be made aware that Saltrol (Salmeterol + Fluticasone propionate) Inhaler must be used regularly for optimum benefit, even when asymptomatic. Patients must be warned not to stop therapy or reduce it without medical advice, even if they feel better on Saltrol (Salmeterol + Fluticasone propionate). Patients should be regularly reassessed by a doctor, so that the strength of Saltrol (Salmeterol + Fluticasone propionate) they are receiving remains optimal and is only changed on medical advice.

The dose should be titrated to the lowest dose at which effective control of symptoms is maintained. Where the control of symptoms is maintained with twice daily Saltrol (Salmeterol + Fluticasone propionate), titration to the lowest effective dose could include Saltrol (Salmeterol + Fluticasone propionate) given once daily. In the event of once daily dosing when the patient has a history of nocturnal symptoms, the dose should be given at night; and when the patient has a history of mainly day-time symptoms, the dose should be given in the morning. Regular review of patients as treatment is stepped down is important.

Asthma
Patients should be given the strength of Saltrol (Salmeterol + Fluticasone propionate) containing the appropriate fluticasone propionate dosage for the severity of their disease. Patients should be instructed not to take additional doses to treat symptoms but to take a short-acting inhaled ß$_2$ agonist.

Adults and adolescents 12 years and older:
Two inhalations of 25mcg salmeterol and 125mcg fluticasone propionate twice daily.
or
Two inhalations of 25mcg salmeterol and 250mcg fluticasone propionate twice daily.

Chronic Obstructive Pulmonary Disease (COPD)
2 inhalations of 25mcg +125mcg twice daily. For patients who require additional symptomatic control replace the 25mcg +125mcg strength with the 25mcg +250mcg strength. The maximum daily dose is 2 inhalations 25mcg +250mcg twice daily.

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

Instructions for Use
Patients should be instructed in the proper use of their inhaler. During inhalation, the patient should preferably sit or stand.

Testing the inhaler:
Before using for the first time or if your inhaler has not been used for a week or more remove the mouthpiece cover by gently squeezing the sides of the cover, shake the inhaler well, and release one puff into the air to make sure that it works.

Cleaning:
Your inhaler should be cleaned at least once a week.
- Remove the mouthpiece cover.
- Do not remove the canister from the plastic casing.
- Wipe the inside and outside of the mouthpiece and the plastic casing with a dry cloth, tissue or cotton bud.
- Replace the mouthpiece cover.

Do not put metal canister in water.

ADVERSE REACTIONS
Very common:
Headache and nasopharyngitis.

Common:
Candidiasis of the mouth and throat, pneumonia, bronchitis, hypokalemia, throat irritation, hoarseness/dysphonia, sinusitis, contusions, muscle cramps, traumatic fractures, arthralgia and myalgia.

Uncommon:
Cutaneous hypersensitivity reactions, respiratory symptoms (dyspnoea), hyperglycemia, anxiety, sleep disorders, tremor, cataract, palpitations, tachycardia, atrial fibrillation and angina pectoris.

Rare:
Oesophageal candidiasis, angioedema (mainly facial and oropharyngeal oedema), respiratory symptoms (bronchospasm), anaphylactic reactions including anaphylactic shock, cushing's syndrome, cushingoid features, adrenal suppression, growth retardation in children and adolescents, decreased bone mineral density, behavioural changes, including psychomotor hyperactivity and irritability (predominantly in children), glaucoma, cardiac arrhythmias (including supraventricular tachycardia and extrasystoles) and paradoxical bronchospasm.

CONTRAINDICATIONS
Saltrol (Salmeterol + Fluticasone propionate) is contraindicated in patients with a history of hypersensitivity to salmeterol xinafoate, fluticasone propionate or any of the excipients.

PRECAUTIONS
General
Patients should be advised that this product contains small amount of ethanol. At normal doses, the amounts of ethanol are negligible and do not pose a risk to patients.

Asthma-Related Death
Long-acting ß$_2$ adrenergic agonists (LABA), such as salmeterol, increase the risk of asthma-related death. When treating patients with asthma, only prescribe Salmeterol + Fluticasone propionate inhaler for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid, or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and a LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue Salmeterol + Fluticasone propionate inhaler) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use Salmeterol + Fluticasone propionate inhaler for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.

Deterioration of Disease and Acute Episodes
Salmeterol + Fluticasone propionate inhaler should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of asthma. It should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. When beginning treatment with Salmeterol + Fluticasone propionate inhaler, patients who have been taking oral or inhaled, short-acting ß$_2$ agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs.

Excessive Use of Salmeterol + Fluticasone propionate inhaler and Use with Other Long-Acting ß$_2$ Agonists
Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using Salmeterol + Fluticasone propionate inhaler should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.

Local Effects of Inhaled Corticosteroids
Candida albicans infection of the mouth and pharynx may occur in subjects treated with Salmeterol + Fluticasone propionate inhaler. Monitor patients periodically. Advise the patient to rinse his/her mouth with water without swallowing after inhalation to help reduce the risk.

Pneumonia
Lower respiratory tract infections, including pneumonia, have been reported in patients with chronic obstructive pulmonary disease (COPD) following the inhaled administration of corticosteroids, including fluticasone propionate. Monitor patients with signs and symptoms of pneumonia.

Immunosuppression
Persons who are using drugs that suppress the immune system are more susceptible to infections than healthy individuals. Inhaled corticosteroids 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. More serious or even fatal course of chickenpox or measles can occur in susceptible patients.

Transferring Patients from Systemic Corticosteroid Therapy
Particular care is needed for patients who have been transferred from systemically active corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. Taper patients slowly from systemic corticosteroids if transferring to Salmeterol + Fluticasone propionate inhaler.

Hypercorticism and Adrenal Suppression
It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear with very high dosages or at the regular dosage in susceptible individuals. If such effects occur, Salmeterol + Fluticasone propionate inhaler should be reduced slowly.

Paradoxical Bronchospasm and Upper Airway Symptoms
As with other inhaled medicines, Salmeterol + Fluticasone propionate inhaler can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs discontinue Salmeterol + Fluticasone propionate inhaler and institute alternative therapy.

Immediate Hypersensitivity Reactions
Immediate hypersensitivity reactions (e.g., urticaria, angioedema, rash, bronchospasm, hypotension), including anaphylaxis, may occur after administration of Salmeterol + Fluticasone propionate inhaler.

Cardiovascular and Central Nervous System Effects
Salmeterol + Fluticasone propionate inhaler should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension because of ß adrenergic stimulation.

Reduction in Bone Mineral Density
Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids. Patients should be assessed for decrease in bone mineral density initially and periodically thereafter.

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 Salmeterol + Fluticasone propionate inhaler routinely.

Glaucoma and Cataracts
Glaucoma and cataracts have been reported in patients with asthma following the long-term administration of inhaled corticosteroids, including fluticasone propionate. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts.

Eosinophilic Conditions and Churg-Strauss Syndrome
In rare cases, patients on inhaled fluticasone propionate, may present with systemic eosinophilic conditions. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients.

Coexisting Conditions
Salmeterol + Fluticasone propionate inhaler should be used with caution in patients with convulsive disorders or thyrotoxicosis, diabetes mellitus and ketoacidosis.

Hypokalemia
ß adrenergic agonist medicines may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects.
Hyperglycemia
There have been very rare reports of increase in blood glucose level and this should be considered when prescribing to patients with a history of diabetes mellitus.

Pregnancy
There are no adequate and well controlled studies with Salmeterol + Fluticasone propionate in pregnant women. Salmeterol + Fluticasone propionate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women should be advised to contact their physicians if they become pregnant while taking Salmeterol + Fluticasone propionate inhaler.

Nursing Mother
It is not known whether Salmeterol and Fluticasone propionate / metabolites are excreted in human milk. A risk to breastfed newborns / infants cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue Salmeterol + Fluticasone propionate therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the women.

DRUG INTERACTIONS
Inhibitors of Cytochrome P450 3A4
Co-administration of ketoconazole and salmeterol resulted in a significant increase in plasma salmeterol exposure (1.4-fold C_{max} and 15-fold AUC). This may lead to prolongation of the QT_c interval. Due to the potential increased risk of cardiovascular adverse events, the concomitant use of salmeterol with strong CYP3A4 inhibitors (e.g. ketoconazole, atazanavir, ritonavir, clarithromycin, indinavir, intraconazole, nefazodone, nelfinavir and saquinavir) is not recommended.

Monoamine Oxidase Inhibitors and Tricyclic Antidepressants
Salmeterol and Fluticasone propionate should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, because the action of Salmeterol on the vascular system may be potentiated by these agents.

ß Adrenergic Receptor Blocking Agents
ß adrenergic blockers may weaken or antagonize the effect of Salmeterol. Both non-selective and selective ß blockers should be avoided in patients with asthma. Potentially serious hypokalemia may result from ß$_2$ agonist therapy. Particular caution is advised in acute severe asthma as this effect may be potentiated by concomitant treatment with xanthine derivatives, steroids and diuretics.

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 ß agonists, such as salmeterol, especially when the recommended dose of the ß agonist is exceeded. Caution is advised in the co-administration of Salmeterol + Fluticasone propionate with non-potassium-sparing diuretics.

OVERDOSAGE
Salmeterol
The signs and symptoms of Salmeterol overdose are dizziness, increases in systolic blood pressure, tremor, headache and tachycardia. If Salmeterol + Fluticasone propionate therapy has to be withdrawn due to overdose of the ß agonist component of the drug, provision of appropriate replacement steroid therapy should be considered. Additionally, hypokalemia can occur and therefore serum potassium levels should be monitored. Potassium replacement should be considered.

Fluticasone propionate:
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 stabilized, treatment should be continued with an inhaled corticosteroid at the recommended dose.

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

STORAGE
Do not store above 30°C.
Protect from direct sunlight, heat and frost.
Shake well before use.

As with most inhaled medicinal products in pressurized canisters, the therapeutic effect of this medicinal product may decrease when the canister is cold. The canister should not be broken, punctured or burnt, even when apparently empty.
The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED
Saltrol (Salmeterol + Fluticasone propionate) Inhaler 25mcg + 125mcg is available in pack of 1's. Each canister provides 120 inhalations.

Saltrol (Salmeterol + Fluticasone propionate) Inhaler 25mcg + 250mcg is available in pack of 1's. Each canister provides 120 inhalations.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

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