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Psychiatric Disorders	Anxiety Sleep disorders Behavioural changes, including psychomotor hyperactivity and irritability (predominantly in children) Depression, aggression (predominantly in children)	Uncommon Uncommon Rare Not Known
Nervous System Disorders	Headache Tremor	Very Common[1] Uncommon
Eye disorder	Cataract Glaucoma	Uncommon Rare
Cardiac Disorders	Palpitations Tachycardia Cardiac arrhythmias (including supraventricular tachycardia and extrasystoles). Atrial fibrillation Angina pectoris	Uncommon Uncommon Rare Uncommon Uncommon
Respiratory, Thoracic & Mediastinal Disorders	Nasopharyngitis Throat irritation Hoarseness/dysphonia Sinusitis Paradoxical bronchospasm	Very Common[2,3] Common Common Common[1,3] Rare
Skin and subcutaneous tissue disorders	Contusions	Common[1,3]
Musculoskeletal & Connective Tissue Disorders	Muscle cramps Traumatic fractures Arthralgia Myalgia	Common Common[1,3] Common Common

1. Reported commonly in placebo
2. Reported very commonly in placebo
3. Reported over 3 years in a COPD study

Description of selected adverse reactions
The pharmacological side effects of β2 agonist treatment, such as tremor, palpitations and headache, have been reported, but tend to be transient and reduce with regular therapy.
As with other inhalation therapy paradoxical bronchospasm may occur with an immediate increase in wheezing and shortness of breath after dosing. Paradoxical bronchospasm responds to a rapid-acting bronchodilator and should be treated straightaway. Salmeterol + Fluticasone (Salflusol MDI) should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.
Due to the fluticasone propionate component, hoarseness and candidiasis (thrush) of the mouth and throat and, rarely, of the oesophagus can occur in some patients. Both hoarseness and incidence of mouth and throat candidiasis may be relieved by rinsing the mouth with water and/or brushing the teeth after using the product. Symptomatic mouth and throat candidiasis can be treated with topical anti-fungal therapy whilst still continuing with the Salmeterol + Fluticasone (Salflusol MDI).
Paediatric population
Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression and growth retardation in children and adolescents. Children may also experience anxiety, sleep disorders and behavioural changes, including hyperactivity and irritability.

OVERDOSE:
There are no data available from clinical trials on overdose with Salmeterol + Fluticasone (Salflusol MDI), 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. If Salmeterol + Fluticasone (Salflusol MDI) therapy has to be withdrawn due to overdose of the β agonist component of the drug, provision of appropriate replacement steroid therapy should be considered. Additionally, hypokalaemia can occur and therefore serum potassium levels should be monitored. 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, Salmeterol + Fluticasone (Salflusol MDI) therapy should be continued at a suitable dosage for symptom control.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph.

STORAGE CONDITIONS:
Store at temperatures not exceeding 30°C. Do not freeze.
The canister contains a pressurised liquid. Do not expose to temperatures higher than 50°C, protect from direct sunlight. Do not pierce or burn the canister even when empty.
As with most inhaled medicinal products in pressurised canisters, the therapeutic effect of this medicinal product may decrease when the canister is cold.

AVAILABILITY:
Salflusol MDI (25/125)
14mL Anodised aluminum container with 50µL metered valve; 14mL, 0.48mm orifice white body actuator with Pantone 569C Green dust cap containing 120 metered doses; box of 1s.

Salflusol MDI (25/250)
14mL Anodised aluminum container with 50µL metered valve; 14mL, 0.48mm orifice white body actuator with Pantone 569C Green dust cap containing 120 metered doses; box of 1s.

REG NO.:

Salfusol MDI (25/125) DRP -7591
Date of First Authorization: 29 December 2017
Date of Revision: 30 July 2020

Salfusol MDI (25/250) DRP -7592
Date of First Authorization: 29 December 2017
Date of Revision: 30 July 2020

MANUFACTURED & EXPORTED BY:
medisol
LIFESCIENCE PVT. LTD.
23/2, 26/P, Alkara, Tal: Umargam, Dist: Valsad, Gujarat, India - 396 105.

REGISTERED OFFICE:
228, Pragati Industrial Estate, N.M. Joshi Marg, Lower Parel (E), Mumbai, India - 400 011

IMPORTED & DISTRIBUTED BY:
biocare
LIFESCIENCES INC
4th Floor, 393 Goodwill Bldg., Senator Gil Puyat Ave., Brgy Bel-Air, Makat City

PMML213

SALMETEROL XINAFOATE + FLUTICASONE PROPIONATE

SALFLUSOL MDI

25+50 mcg/dose, 25 + 125 mcg/dose & 25 + 250 mcg/dose
METERED DOSE INHALER
SELECTIVE BETA-2-ADRENORECEPTOR AGONIST/ CORTICOSTEROID

FORMULATION:
Each metered dose (ex valve) contains:
Salflusol MDI (25/50)
Salmeterol (as Salmeterol xinafoate, B.P.)……25 mcg
Fluticasone (as Fluticasone propionate, B.P.)……50 mcg
Propellant HFA 134a……q.s.
Salflusol MDI (25/125)
Salmeterol (as Salmeterol xinafoate, B.P.)……25 mcg
Fluticasone (as Fluticasone propionate, B.P.)……125 mcg
Propellant HFA 134a…… q.s.
Salflusol MDI (25/250)
Salmeterol (as Salmeterol xinafoate, B.P.)……25 mcg
Fluticasone (as Fluticasone propionate, B.P.)……250 mcg
Propellant HFA 134a……q.s.

PHARMACEUTICAL FORM:
Pressurised inhalation, suspension.
The canister contains a white to off white suspension.
The canisters are fitted into white actuators incorporating an atomising orifice and fitted with dustcaps.

INDICATIONS:
Salmeterol + Fluticasone (Salflusol MDI) is indicated in the regular treatment of asthma where use of a combination product (long-acting β2 agonist and inhaled corticosteroid) is appropriate:
patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short-acting β2 agonist, or
patients already adequately controlled on both inhaled corticosteroid and long-acting β2 agonist

DOSAGE AND ADMINISTRATION:
Posology
Route of administration: Inhalation use.
Patients should be made aware that Salmeterol + Fluticasone (Salflusol MDI) must be used daily for optimum benefit, even when asymptomatic.
Patients should be regularly reassessed by a doctor, so that the strength of Salmeterol + Fluticasone (Salflusol MDI) 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 the lowest strength of the combination given twice daily then the next step could include a test of inhaled corticosteroid alone. As an alternative, patients requiring a long-acting β2 agonist could be titrated to Salmeterol + Fluticasone (Salflusol MDI) given once daily if, in the opinion of the prescriber, it would be adequate to maintain disease control. 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 daytime symptoms the dose should be given in the morning.
Patients should be given the strength of Salmeterol + Fluticasone (Salflusol MDI) containing the appropriate fluticasone propionate dosage for the severity of their disease. Note: Salmeterol + Fluticasone (Salflusol MDI) 25 microgram/50 microgram strength is not appropriate for adults and children with severe asthma. If an individual patient should require dosages outside the recommended regimen, appropriate doses of β2 agonist and/or corticosteroid should be prescribed.
Recommended Doses:
Adults and adolescents 12 years and older:
- Two inhalations of 25 micrograms salmeterol and 50 micrograms fluticasone propionatetwice daily, or
- Two inhalations of 25 micrograms salmeterol and 125 micrograms fluticasone propionate twice daily, or
- Two inhalations of 25 micrograms salmeterol and 250 micrograms fluticasone propionate twice daily.

A short-term trial of Salmeterol + Fluticasone (Salflusol MDI) may be considered as initial maintenance therapy in adults or adolescents with moderate persistent asthma (defined as patients with daily symptoms, daily rescue use and moderate to severe airflow limitation) for whom rapid control of asthma is essential. In these cases, the recommended initial dose is two inhalations of 25 micrograms salmeterol and 50 micrograms fluticasone propionate twice daily. Once control of asthma is attained treatment should be reviewed and consideration given as to whether patients should be stepped down to an inhaled corticosteroid alone. Regular review of patients as treatment is stepped down is important.
A clear benefit has not been shown as compared to inhaled fluticasone propionate alone used as initial maintenance therapy when one or two of the criteria of severity are missing. In general inhaled corticosteroids remain the first line treatment for most patients. Salmeterol + Fluticasone (Salflusol MDI) is not intended for the initial management of mild asthma. Salmeterol + Fluticasone (Salflusol MDI) 25 micrograms/50 micrograms strength is not appropriate in adults and children with severe asthma; it is recommended to establish the appropriate dosage of inhaled corticosteroid before any fixed-combination can be used in patients with severe asthma.
Paediatric population
Children 4 years and older:
- Two inhalations of 25 micrograms salmeterol and 50 micrograms fluticasone propionate twice daily.

The maximum licensed dose of fluticasone propionate delivered by Salmeterol + Fluticasone (Salflusol MDI) inhaler in children is 100 microgram twice daily.
There are no data available for use of Salmeterol + Fluticasone (Salflusol MDI) in children aged under 4 years.
Children <12 years old may have difficulties synchronising aerosol actuation with inspiration of breath. Use of a spacer device with Salmeterol + Fluticasone (Salflusol MDI) is recommended in patients who have, or are likely to have difficulties to coordinate actuation with inspiration.
Patients should be instructed in the proper use and care of their inhaler and spacer and their technique checked to ensure optimum delivery of the inhaled drug to the lungs. Patients should continue to use the same make of spacer device as switching between spacer devices can result in changes in the dose delivered to the lungs (see Special Warnings and Precautions).
Re-titration to the lowest effective dose should always follow the introduction or change of a spacer device.
Special patient groups
There is no need to adjust the dose in elderly patients or in those with renal impairment. There are no data available for use of Salmeterol + Fluticasone (Salflusol MDI) in patients with 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. The inhaler has been designed for use in a vertical position.
Testing the inhaler:
Before using for the first time patients should remove the mouthpiece cover by gently squeezing the sides of the cover, shake the inhaler well, hold the inhaler between the fingers and thumb with their thumb on the base, below the mouthpiece and release puffs into the air to make sure that it works. The inhaler should be shaken immediately before releasing each puff. If the inhaler has not been used for a week or more the mouthpiece cover should be removed, the patient should shake the inhaler well and should release two puffs into the air.
Use of the inhaler:
1. Patients should remove the mouthpiece cover by gently squeezing the sides of the cover
2. Patients should check inside and outside of the inhaler including the mouthpiece for the presence of loose objects.
3. Patients should shake the inhaler well to ensure that any loose objects are removed and that the contents of the inhaler are evenly mixed
4. Patients should hold the inhaler upright between fingers and thumb with their thumb on the base, below the mouthpiece.
5. Patients should breathe out as far as is comfortable and then place the mouthpiece in their mouth between their teeth and close their lips around it, Patients should be instructed not to bite the mouth piece.
6. Just after starting to breathe in through their mouth, patients should press firmly down on the top of the inhaler to release Salmeterol + Fluticasone (Salflusol MDI), while still breathing in steadily and deeply.
7. While holding their breath, patients should take the inhaler from their mouth and take their finger from the top of the inhaler. Patients should continue holding their breath for as long as is comfortable.
8. To take a second inhalation, patients should keep the inhaler upright and wait about half a minute before repeating steps 3 to 7.
9. Patients should immediately replace the mouthpiece cover in the correct orientation by firmly pushing and snapping the cap into position. This does not require excessive force; the cover should click into position.

IMPORTANT
Patients should not rush stages 5, 6 and 7. It is important that patients start to breathe in as slowly as possible just before operating their inhaler. Patients should practice in front of a mirror for the first few times. If they see "mist" coming from the top of their inhaler or the sides of their mouth they should start again from stage 3.
Patients should rinse their mouth out with water and spit out, and/or brush their teeth after each dose of medicine, in order to minimise the risk of oropharyngeal candidiasis and hoarseness.

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Cleaning:
Your inhaler should be cleaned at least once a week.
1. Remove the mouth piece cover.
2. Do not remove the canister from the plastic casing.
3. Wipe the inside and outside of the mouthpiece and the plastic casing with a dry cloth or tissue.
4. Replace the mouthpiece cover in the correct orientation. This does not require excessive force; the cover should click into position.
DO NOT PUT THE METAL CANISTER IN WATER

PHARMACODYNAMICS:
Pharmacotherapeutic Group: Adrenergics in combination with corticosteroids or other drugs, excl. Anticholinergics.
ATC Code: R03AK06
Mechanism of action and pharmacodynamic effects
Salmeterol + Fluticasone (Salflusol MDI) contains salmeterol and fluticasone propionate which have differing modes of action.
The respective mechanisms of action of both drugs are discussed below.
Salmeterol:
Salmeterol is a selective long-acting (12 hour) β2 adrenoceptor agonist with a long side chain which binds to the exo-site of the receptor.
Salmeterol produces a longer duration of bronchodilation, lasting for at least 12 hours, than recommended doses of conventional short-acting β2 agonists.
Fluticasone propionate:
Fluticasone propionate given by inhalation at recommended doses has a glucocorticoid anti-inflammatory action within the lungs, resulting in reduced symptoms and exacerbations of asthma, with less adverse effects than when corticosteroids are administered systemically.

PHARMACOKINETICS:
When salmeterol and fluticasone propionate were administered in combination by the inhaled route, the pharmacokinetics of each component were similar to those observed when the drugs were administered separately. For pharmacokinetic purposes therefore each component can be considered separately.
Salmeterol
Salmeterol acts locally in the lung therefore plasma levels are not an indication of therapeutic effects. In addition there are only limited data available on the pharmacokinetics of salmeterol because of the technical difficulty of assaying the drug in plasma due to the low plasma concentrations at therapeutic doses (approximately 200 picogram/mL or less) achieved after inhaled dosing.
Fluticasone propionate
The absolute bioavailability of a single dose of inhaled fluticasone propionate in healthy subjects varies between approximately 5 to 11% of the nominal dose depending on the inhalation device used. In patients with asthma a lesser degree of systemic exposure to inhaled fluticasone propionate has been observed. Systemic absorption occurs mainly through the lungs and is initially rapid then prolonged. The remainder of the inhaled dose may be swallowed but contributes minimally to systemic exposure due to the low aqueous solubility and pre-systemic metabolism, resulting in oral availability of less than 1%. There is a linear increase in systemic exposure with increasing inhaled dose.
The disposition of fluticasone propionate is characterised by high plasma clearance (1150 mL/min), a large volume of distribution at steady-state (approximately 300 L) and a terminal half-life of approximately 8 hours.
Plasma protein binding is 91%.
Fluticasone propionate is cleared very rapidly from the systemic circulation. The main pathway is metabolism to an inactive carboxylic acid metabolite, by the cytochrome P450 enzyme CYP3A4. Other unidentified metabolites are also found in the faeces.
The renal clearance of fluticasone propionate is negligible. Less than 5% of the dose is excreted in urine, mainly as metabolites. The main part of the dose is excreted in faeces as metabolites and unchanged drug.

CONTRAINDICATIONS:
Hypersensitivity to the active substances or to any of the excipients.

SPECIAL WARNINGS AND PRECAUTIONS:
Salmeterol + Fluticasone (Salflusol MDI) should not be used to treat acute asthma symptoms for which a fast- and short-acting bronchodilator is required.
Patients should be advised to have their inhaler to be used for relief in an acute asthma attack available at all times.
Patients should not be initiated on Salmeterol + Fluticasone (Salflusol MDI) during an exacerbation, or if they have significantly worsening or acutely deteriorating asthma.
Serious asthma-related adverse events and exacerbations may occur during treatment with Salmeterol + Fluticasone (Salflusol MDI). Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation on Salmeterol + Fluticasone (Salflusol MDI).
Increased requirements for use of reliever medication (short-acting bronchodilators), or decreased response to reliever medication indicate deterioration of asthma control and patients should be reviewed by a physician.
Sudden and progressive deterioration in control of asthma is potentially life-threatening and the patient should undergo urgent medical assessment. Consideration should be given to increasing corticosteroid therapy.
Once asthma symptoms are controlled, consideration may be given to gradually reducing the dose of Salmeterol + Fluticasone (Salflusol MDI). Regular review of patients as treatment is stepped down is important. The lowest effective dose of Salmeterol + Fluticasone (Salflusol MDI) should be used.
Treatment with Salmeterol + Fluticasone (Salflusol MDI) should not be stopped abruptly due to risk of exacerbation. Therapy should be down-titrated under physician supervision.
As with all inhaled medication containing corticosteroids, Salmeterol + Fluticasone (Salflusol MDI) should be administered with caution in patients with active or quiescent pulmonary tuberculosis and fungal, viral or other infections of the airway. Appropriate treatment should be promptly instituted, if indicated.
Rarely, Salmeterol + Fluticasone (Salflusol MDI) may cause cardiac arrhythmias e.g. supraventricular tachycardia, extrasystoles and atrial fibrillation, and a mild transient reduction in serum potassium at high therapeutic doses. Salmeterol + Fluticasone (Salflusol MDI) should be used with caution in patients with severe cardiovascular disordersor heart rhythm abnormalities and in patients with diabetes mellitus, thyrotoxicosis, uncorrected hypokalaemia or patients predisposed to low levels of serum potassium.
There have been very rare reports of increases in blood glucose levels and this should be considered when prescribing to patients with a history of diabetes mellitus.
As with other inhalation therapy paradoxical bronchospasm may occur with an immediate increase in wheezing and shortness of breath after dosing. Paradoxical bronchospasm responds to a rapid-acting bronchodilator and should be treated straightaway. Salmeterol + Fluticasone (Salflusol MDI) should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.
The pharmacological side effects of β2 agonist treatment, such as tremor, palpitations and headache, have been reported, but tend to be transient and reduce with regular therapy.
Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, decrease in bone mineral density, cataract and glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children) (see Paediatric population sub-heading below for information on the systemic effects of inhaled corticosteroids in children and adolescents). It is important, therefore, that the patient is reviewed regularly and the dose of inhaled corticosteroid is reduced to the lowest dose at which effective control of asthma is maintained.
Prolonged treatment of patients with high doses of inhaled corticosteroids may result in adrenal suppression and acute adrenal crisis. Very rare cases of adrenal suppression and acute adrenal crisis have also been described with doses of fluticasone propionate between 500 and less than 1000 micrograms. Situations, which could potentially trigger acute adrenal crisis, include trauma, surgery, infection or any rapid reduction in dosage. Presenting symptoms are typically vague and may include anorexia, abdominal pain, weight loss, tiredness, headache, nausea, vomiting, hypotension, decreased level of consciousness, hypoglycaemia, and seizures. Additional systemic corticosteroid cover should be considered during periods of stress or elective surgery.
Systemic absorption of salmeterol and fluticasone propionate is largely through the lungs. As the use of a spacer device with a metered dose inhaler may increase drug delivery to the lungs it should be noted that this could potentially lead to an increase in the risk of systemic adverse effects.
The benefits of inhaled fluticasone propionate therapy should minimise the need for oral steroids, but patients transferring from oral steroids may remain at risk of impaired adrenal reserve for a considerable time. Therefore these patients should be treated with special care and adrenocortical function regularly monitored. Patients who have required high dose emergency corticosteroid therapy in the past may also be at risk. This possibility of residual impairment should always be borne in mind in emergency and elective situations likely to produce stress, and appropriate corticosteroid treatment must be considered. The extent of the adrenal impairment may require specialist advice before elective procedures.
Ritonavir can greatly increase the concentration of fluticasone propionate in plasma. Therefore, concomitant use should be avoided, unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects. There is also an increased risk of systemic side effects when combining fluticasone propionate with other potent CYP3A inhibitors.

There was an increased reporting of lower respiratory tract infections (particularly pneumonia and bronchitis) in a 3-year study in patients with Chronic Obstructive Pulmonary Disease (COPD) receiving salmeterol and fluticasone propionate as a fixed-dose combination administered via the Diskus/Accuhalercompared with placebo. In a 3-year COPD study, older patients, patients with a lower body mass index (<25 kg/m2) and patients with very severe disease (FEV1<30% predicted) were at greatest risk of developing pneumonia regardless of treatment. Physicians should remain vigilant for the possible development of pneumonia and other lower respiratory tract infections in patients with COPD as the clinical features of such infections and exacerbation frequently overlap. If a patient with severe COPD has experienced pneumonia the treatment with Salmeterol + Fluticasone (Salflusol MDI) should be re-evaluated. The safety and efficacy of Salmeterol + Fluticasone (Salflusol MDI) has not been established in patients with COPD and therefore Salmeterol + Fluticasone (Salflusol MDI) is not indicated for use in the treatment of patients with COPD.
Concomitant use of systemic ketoconazole significantly increases systemic exposure to salmeterol. This may lead to an increase in the incidence of systemic effects (e.g. prolongation in the QTc interval and palpitations). Concomitant treatment with ketoconazole or other potent CYP3A4 inhibitors should therefore be avoided unless the benefits outweigh the potentially increased risk of systemic side effects of salmeterol treatment.
Paediatric population
Children and adolescents <16 years taking high doses of fluticasone propionate (typically ≥ 1000 micrograms/day) may be at particular risk of systemic effects. Systemic effects may occur, particularly at high doses prescribed for long periods. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, acute adrenal crisis and growth retardation in children and adolescents and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression. Consideration should be given to referring the child or adolescent to a paediatric respiratory specialist.
It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroid is regularly monitored. The dose of inhaled corticosteroid should be reduced to the lowest dose at which effective control of asthma is maintained.

INTERACTIONS:
β adrenergic blockers may weaken or antagonise the effect of salmeterol. Both non-selective and selective β blockers should be avoided in patients with asthma, unless there are compelling reasons for their use. Potentially serious hypokalaemia may result from β2 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.
Concomitant use of other β adrenergic containing drugs can have a potentially additive effect.
Fluticasone Propionate
Under normal circumstances, low plasma concentrations of fluticasone propionate are achieved after inhaled dosing, due to extensive first pass metabolism and high systemic clearance mediated by cytochrome P450 3A4 in the gut and liver. Hence, clinically significant drug interactions mediated by fluticasone propionate are unlikely.
In an interaction study in healthy subjects with intranasal fluticasone propionate, ritonavir (a highly potent cytochrome P450 3A4 inhibitor) 100 mg b.i.d. increased the fluticasone propionate plasma concentrations several hundred fold, resulting in markedly reduced serum cortisol concentrations. Information about this interaction is lacking for inhaled fluticasone propionate, but a marked increase in fluticasone propionate plasma levels is expected. Cases of Cushing's syndrome and adrenal suppression have been reported. The combination should be avoided unless the benefit outweighs the increased risk of systemic glucocorticoid side effects.
In a small study in healthy volunteers, the slightly less potent CYP3A inhibitor ketoconazole increased the exposure of fluticasone propionate after a single inhalation by 150%. This resulted in a greater reduction of plasma cortisol as compared with fluticasone propionate alone. Co-treatment with other potent CYP3A inhibitors, such as itraconazole, and moderate CYP3A inhibitors, such as erythromycin, is also expected to increase the systemic fluticasone propionate exposure and the risk of systemic side effects. Caution is recommended and long-term treatment with such drugs should if possible be avoided.
Salmeterol
Potent CYP3A4 inhibitors
Co-administration of ketoconazole (400 mg orally once daily) and salmeterol (50 micrograms inhaled twice daily) in 15 healthy subjects for 7 days resulted in a significant increase in plasma salmeterol exposure (1.4-fold Cmax and 15-fold AUC). This may lead to an increase in the incidence of other systemic effects of salmeterol treatment (e.g. prolongation of QTc interval and palpitations) compared with salmeterol or ketoconazole treatment alone.
Clinically significant effects were not seen on blood pressure, heart rate, blood glucose and blood potassium levels. Co-administration with ketoconazole did not increase the elimination half-life of salmeterol or increase salmeterol accumulation with repeat dosing.
The concomitant administration of ketoconazole should be avoided, unless the benefits outweigh the potentially increased risk of systemic side effects of salmeterol treatment. There is likely to be a similar risk of interaction with other potent CYP3A4 inhibitors (e.g. itraconazole, telithromycin, ritonavir).
Moderate CYP 3A4 inhibitors
Co-administration of erythromycin (500 mg orally three times a day) and salmeterol (50 micrograms inhaled twice daily) in 15 healthy subjects for 6 days resulted in a small but non-statistically significant increase in salmeterol exposure (1.4-fold Cmax and 1.2-fold AUC). Co-administration with erythromycin was not associated with any serious adverse effects.

FERTILITY PREGNANCY AND LACTATION:
Fertility
There are no data in humans. However, animal studies showed no effects of salmeterol or fluticasone propionate on fertility.
Pregnancy
A moderate amount of data on pregnant women (between 300 to 1000 pregnancy outcomes) indicate no malformative or feto/neonatal toxicity of salmeterol and fluticasone propionate. Animal studies have shown reproductive toxicity after administration of β2 adrenoreceptor agonists and glucocorticosteroids.
Administration of Salmeterol + Fluticasone (Salflusol MDI) to pregnant women should only be considered if the expected benefit to the mother is greater than any possible risk to the fetus.
The lowest effective dose of fluticasone propionate needed to maintain adequate asthma control should be used in the treatment of pregnant women.
Breastfeeding
It is unknown whether salmeterol and fluticasone propionate/metabolites are excreted in human milk.
Studies have shown that salmeterol and fluticasone propionate, and their metabolites, are excreted into the milk of lactating rats.
A risk to breastfed newborns/infants cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue Salmeterol + Fluticasone (Salflusol MDI) therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:
Salmeterol + Fluticasone (Salflusol MDI) has no or negligible influence on the ability to drive and use machines.

ADVERSE EFFECTS:
As Salmeterol + Fluticasone (Salflusol MDI) contains salmeterol and fluticasone propionate, the type and severity of adverse reactions associated with each of the compounds may be expected. There is no incidence of additional adverse events following concurrent administration of the two compounds.
Adverse events which have been associated with salmeterol/fluticasone propionate are given below, listed by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000) and not known (cannot be estimated from the available data). Frequencies were derived from clinical trial data. The incidence in placebo was not taken into account.

System Organ Class	Adverse Event	Frequency
Infections & Infestations	Candidiasis of the mouth and throat Pneumonia Bronchitis Oesophageal candidiasis	Common Common[1,3] Common[1,3] Rare
Immune System Disorders	Hypersensitivity reactions with the following manifestations: Cutaneous hypersensitivity reactions Angioedema (mainly facial and oropharyngeal oedema) Respiratory symptoms (dyspnoea) Respiratory symptoms (bronchospasm) Anaphylactic reactions including anaphylactic shock	Uncommon Rare Uncommon Rare Rare
Endocrine Disorders	Cushing's syndrome, Cushingoid features, Adrenal suppression, Growth retardation in children and adolescents, Decreased bone mineral density	Rare
Metabolism & Nutrition Disorders	Hypokalaemia Hyperglycaemia	Common[2] Uncommon