Composition

MAXIFLO-125 Inhaler

Each actuation delivers:

Formoterol Fumarate Dihydrate IP ...............6 mcg
Fluticasone Propionate IP .....................125 mcg
Suspended in propellant HFA 134a .............q.s.

MAXIFLO-250 Inhaler

Each actuation delivers:

Formoterol Fumarate Dihydrate IP ...............6 mcg
Fluticasone Propionate IP .....................250 mcg
Suspended in propellant HFA 134a .............q.s.

Dosage Form

Inhalation aerosol

Description

MAXIFLO inhaler is a combination of Fluticasone propionate, a synthetic corticosteroid and formoterol; a selective long acting beta₂-agonist.

Fluticasone propionate is a synthetic, trifluorinated glucocorticoid with potent anti-inflammatory activity. Formoterol is a very potent long-acting adrenoceptor beta₂-agonist with a high intrinsic activity and a rapid onset of action.

Pharmacology
**Pharmacodynamics**

MAXIFLO inhaler contains both fluticasone and formoterol; therefore, the mechanisms of action described below for the individual components apply to MAXIFLO inhaler. These drugs represent two classes of medications (a synthetic corticosteroid and a long-acting, selective beta$_2$-adrenoceptor agonist) that have different effects on the clinical, physiological, and inflammatory indices of asthma.

**Fluticasone propionate**

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

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

Studies in patients with asthma have shown a favorable ratio between topical anti-inflammatory activity and systemic corticosteroid effects with recommended doses of orally inhaled fluticasone propionate. This is explained by a combination of a relatively high local anti-inflammatory effect, negligible oral systemic bioavailability (<1%), and the minimal pharmacological activity of the only metabolite detected in man.

**Formoterol fumarate**

Formoterol fumarate is a long-acting, selective beta$_2$-adrenergic agonist with a rapid onset of action. Inhaled formoterol fumarate acts locally in the lungs as a bronchodilator. *In vitro* studies have shown that formoterol has over 200-fold greater agonist activity at beta$_2$-receptors than at beta$_1$-receptors. The *in vitro* binding selectivity to beta$_2$-adrenoceptors over beta$_1$-adrenoceptors is higher for formoterol than for salbutamol (5 times), whereas salmeterol has a higher (3 times) beta$_2$-selectivity ratio than formoterol.

Although beta$_2$-receptors are the predominant adrenergic receptors in bronchial smooth muscle and beta$_1$-receptors are the predominant receptors in the heart, there are also beta$_2$-receptors in the human heart, which comprise 10–50% of the total beta-adrenergic receptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective beta$_2$-agonists may have cardiac effects.

The pharmacological effects of beta$_2$-adrenoceptor agonist drugs, including formoterol, are, at least in part, attributable to the 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 inhibit the release of mediators of immediate hypersensitivity from the cells, especially from mast cells.

The bronchodilating effect sets in rapidly, within 1-3 minutes after inhalation, and lasts for duration of 12 hours after a single dose.
Pharmacokinetics

Fluticasone Propionate

Absorption

Fluticasone propionate acts locally in the lung; therefore, plasma levels do not predict therapeutic effect. Studies using oral dosing of labeled and unlabeled drug have demonstrated that the oral systemic bioavailability of fluticasone propionate is negligible (<1%), primarily due to incomplete absorption and presystemic metabolism in the gut and liver. In contrast, the majority of the fluticasone propionate delivered to the lung is systemically absorbed.

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 dosage of fluticasone propionate inhalation powder. The mean fluticasone propionate plasma concentration was 110 pg/mL.

Distribution

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.

Metabolism

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 cytochrome P450 3A4 pathway. This metabolite had less affinity (approximately 1/2,000) than the parent drug for the corticosteroid 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.

Elimination

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.

Formoterol Fumarate

Absorption

Following inhalation of a single 120 mcg dose of formoterol fumarate by 12 healthy subjects, formoterol was rapidly absorbed into plasma, reaching a maximum drug concentration of 92 pg/mL within 5 minutes of dosing. In COPD patients treated for 12 weeks with formoterol fumarate 12 or 24 mcg b.i.d., the mean plasma concentrations of formoterol ranged between 4.0 and 8.8 pg/mL and
8.0 and 17.3 pg/mL, respectively, at 10 min, 2 h and 6 h post inhalation.

Following inhalation of 12 to 96 mcg of formoterol fumarate by 10 healthy males, urinary excretion of both (R, R) - and (S, S)-enantiomers of formoterol increased proportionally to the dose. Thus, absorption of formoterol following inhalation appeared linear over the dose range studied.

In a study in patients with asthma, when formoterol 12 or 24 mcg twice daily was given by oral inhalation for 4 weeks or 12 weeks, the accumulation index, based on the urinary excretion of unchanged formoterol ranged from 1.63 to 2.08 in comparison with the first dose. For COPD patients, when formoterol 12 or 24 mcg twice daily was given by oral inhalation for 12 weeks, the accumulation index, based on the urinary excretion of unchanged formoterol was 1.19 - 1.38. This suggests some accumulation of formoterol in plasma with multiple dosing. The excreted amounts of formoterol at steady-state were close to those predicted based on single-dose kinetics. As with many drug products for oral inhalation, it is likely that the majority of the inhaled formoterol fumarate delivered is swallowed and then absorbed from the gastrointestinal tract.

**Distribution**

The binding of formoterol to human plasma proteins *in vitro* was 61%-64% at concentrations from 0.1 to 100 ng/mL. Binding to human serum albumin *in vitro* was 31%-38% over a range of 5 to 500 ng/mL. The concentrations of formoterol used to assess the plasma protein binding were higher than those achieved in plasma following inhalation of a single 120 mcg dose.

**Metabolism**

Formoterol is metabolized primarily by direct glucuronidation at either the phenolic or aliphatic hydroxyl group and O-demethylation followed by glucuronide conjugation at either phenolic hydroxyl groups. Minor pathways involve sulfate conjugation of formoterol and deformylation followed by sulfate conjugation. The most prominent pathway involves direct conjugation at the phenolic hydroxyl group. The second major pathway involves O-demethylation followed by conjugation at the phenolic 2'-hydroxyl group. Four cytochrome P450 isozymes (CYP2D6, CYP2C19, CYP2C9 and CYP2A6) are involved in the O-demethylation of formoterol. Formoterol did not inhibit CYP450 enzymes at therapeutically relevant concentrations. Some patients may be deficient in CYP2D6 or 2C19 or both. Whether a deficiency in one or both of these isozymes results in elevated systemic exposure to formoterol or systemic adverse effects has not been adequately explored.

**Excretion**

In asthmatic and COPD patients treated for 12 weeks with 12 or 24 micrograms formoterol fumarate b.i.d., approximately 10% and 7% of the dose, respectively, were recovered in the urine as unchanged formoterol. In asthmatic children, approximately 6% of the dose was recovered in the urine as unchanged formoterol after multiple dosing of 12 and 24 micrograms. The (R,R) and (S,S)-enantiomers accounted for 40% and 60% respectively of urinary recovery of unchanged formoterol, after single doses (12 to 120 micrograms) in healthy volunteers and after single and repeated doses in asthma patients. After a single oral dose of $^{3}$Hformoterol, 59 - 62% of the dose was recovered in the urine and 32 - 34% in the faeces. Renal clearance of formoterol is 150 mL/min.

After inhalation, plasma formoterol kinetics and urinary excretion rate data in healthy volunteers indicate a biphasic elimination, with the terminal elimination half-lives of the (R, R) - and (S, S)-enantiomers being 13.9 and 12.3 hours, respectively. Peak excretion occurs rapidly, within 1.5 hours. Approximately 6.4 - 8% of the dose was recovered in the urine as unchanged formoterol, with the (R, R) - and (S, S)-enantiomers contributing 40% and 60%, respectively.
**Indications**

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

**Dosage And Administration**

**Asthma**

*Adults and Adolescents (12 years and older)*

**MAXIFLO-125 Inhaler**: 1-2 inhalations twice daily  
**MAXIFLO-250 Inhaler**: 1-2 inhalations twice daily

**COPD**

**MAXIFLO-125 Inhaler**: Two inhalations twice daily  
**MAXIFLO-250 Inhaler**: Two inhalations twice daily

MAXIFLO Inhaler may be used with a Zerostat / Zerostat VT Spacer device in patients who find it difficult to synchronize aerosol actuation with inspiration of breath.

**Contraindications**

MAXIFLO Inhaler is contraindicated in patients with a history of hypersensitivity to formoterol, fluticasone or any other component of the drug product.

**Warnings And Precautions**

Patients should be made aware that MAXIFLO Inhaler must be used daily for optimum benefit, even when asymptomatic.

Patients should not be initiated on MAXIFLO Inhaler during an exacerbation, or if they have significantly worsening or acutely deteriorating asthma.

MAXIFLO Inhaler should not be used to treat acute asthma symptoms for which a fast and short-acting bronchodilator is required. Patients should be advised to have their relief medication available at all times.

As with all inhaled medication containing corticosteroids, MAXIFLO Inhaler should be administered with caution in patients with pulmonary tuberculosis.

MAXIFLO Inhaler should be administered with caution in patients with severe cardiovascular disorders, especially coronary insufficiency, hypertension and heart rhythm abnormalities, diabetes mellitus, hypertrophic obstructive cardiomyopathy, idiopathic subvalvular aortic stenosis, aneurysm, severe heart failure, untreated hypokalaemia, or thyrotoxicosis, and phaeochromocytoma.
Potentially serious hypokalaemia may result from systemic beta\textsubscript{2}-agonist therapy, but following inhalation at therapeutic doses, plasma levels of formoterol are very low.

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

Systemic effects are much less likely to occur with inhaled corticosteroids than with oral corticosteroids. Possible systemic effects include Cushing’s syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children), decrease in bone mineral density, cataract, and glaucoma. It is important, therefore, that the dose is titrated to the lowest dose at which effective control is maintained.

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. 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. In situations of possible impaired adrenal function hypothalamic pituitary adrenal (HPA) axis function should be monitored regularly.

There is an increased risk of systemic side effects when combining fluticasone propionate with potent CYP3A4 inhibitors.

The patient should be made aware that this fixed-dose combination inhaler is a prophylactic therapy and as such has to be used regularly even when asymptomatic for optimum benefit.

Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infections of the respiratory tract; untreated systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

Formoterol may induce prolongation of the QTc-interval. Caution should be observed when treating patients with prolongation of the QTc-interval and in patients treated with drugs affecting the QTc-interval.

As for all beta\textsubscript{2} agonists, additional blood sugar controls should be considered in diabetic patients.

Care should be taken when transferring patients to MAXIFLO Inhaler therapy, particularly if there is any reason to suppose that adrenal function is impaired from previous systemic steroid therapy.

Once asthma symptoms are controlled, consideration may be given to gradually reducing the dose of MAXIFLO Inhaler. Regular review of patients as treatment is stepped down is important. The lowest effective dose of MAXIFLO Inhaler should be used.

Treatment with MAXIFLO Inhaler should not be stopped abruptly in patients with asthma due to risk of exacerbation. Therapy should be down-titrated under the supervision of a prescriber.

Prolonged treatment of patients with high doses of inhaled corticosteroids may result in adrenal suppression and acute adrenal crisis. Children and adolescents <16 years taking high doses of fluticasone propionate (typically $\geq 1000$ micrograms/day) may be at particular risk. 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 treatment should be considered during periods of stress or elective surgery.

Patients should be advised to seek immediate attention if their condition deteriorates.

Sudden and progressive deterioration in control of asthma is potentially life-threatening and the patient should undergo urgent medical assessment.

As the fractions of fluticasone and formoterol which reach systemic circulation are primarily eliminated via hepatic metabolism, an increased exposure can be expected in patients with severe hepatic impairment.

| Drug Interactions |

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

Fluticasone propionate, an individual component of MAXIFLO Inhaler, is a substrate of CYP 3A4. The effects of short-term coadministration of strong CYP 3A4 inhibitors (e.g. ritonavir, atazanavir, clarithromycin, indinavir,itraconazole, nelfinavir, saquinavir, ketoconazole, telithromycin) together with MAXIFLO Inhaler is of minor clinical relevance, but caution needs to be taken in long-term treatment and co-administration with such drugs should be avoided if possible.

The ECG changes and/or hypokalaemia that may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by β agonists, especially when the recommended dose of the β agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the co-administration of a β agonist with non-potassium sparing diuretics. Xanthine derivates and glucocorticosteroids may add to a possible hypokalaemic effect of the β agonists. In addition L-Dopa, L-thyroxine, oxytocin and alcohol can impair cardiac tolerance towards β2 sympathomimetics. Concomitant treatment with monoamine oxidase inhibitors, including agents with similar properties such as furazolidone and procarbazine, may precipitate hypertensive reactions.

There is an elevated risk of arrhythmias in patients receiving concomitant anaesthesia with halogenated hydrocarbons.

Hypokalaemia may increase the risk of arrhythmias in patients who are treated with digitalis glycosides.

There have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing syndrome and adrenal suppression. Therefore, coadministration of fluticasone propionate and ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects. Coadministration of a single dose of orally inhaled fluticasone propionate (1,000 mcg) with multiple doses of ketoconazole (200 mg) to steady state resulted in increased plasma fluticasone propionate concentrations, a reduction in plasma cortisol AUC, and no effect on urinary excretion of cortisol. Caution should be exercised when MAXIFLO Inhaler is coadministered with ketoconazole and other known potent cytochrome P450 3A4 inhibitors.
Beta-adrenergic blockers may weaken or antagonize the effect of MAXIFLO Inhaler. Therefore Beta-adrenergic blockers (including eye drops for treatment of glaucoma) should be avoided, unless there are compelling reasons for their use. Effects of formoterol on the vascular-system may be potentiated in patients receiving concomitant therapy with monoamine oxidase (MAO) inhibitors or tricyclic antidepressants. Concomitant treatment with xanthine derivatives, steroids or diuretics may potentiate possible hypokalaemic effect of \(\beta_2\)-agonists. Concomitant administration of other sympathomimetic agents may potentiate the undesirable effects of formoterol.

In addition L-Dopa, L-thyroxine, oxytocin and alcohol can impair cardiac tolerance towards \(\beta_2\) sympathomimetics.

### Renal Impairment

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

### Hepatic Impairment

Pharmacokinetic studies using formoterol/fluticasone have not been conducted to examine differences in patients with hepatic impairment. The pharmacokinetics of formoterol have not been studied in subjects with hepatic impairment. However, since fluticasone propionate is predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of fluticasone propionate. Therefore, patients with hepatic impairment should be closely monitored.

### Pregnancy

Use of MAXIFLO Inhaler in pregnancy should be considered only if the expected benefit to the expectant mother is greater than any possible risk to the foetus. If this is the case, then the lowest effective dose needed to maintain adequate asthma control should be used.

### Lactation

It is not known whether fluticasone propionate or formoterol fumarate are excreted in human breast milk. A risk to the suckling child cannot be excluded. Use of MAXIFLO Inhaler in women who are breastfeeding should only be considered if the expected benefit to the nursing mother is greater than any possible risk to the infant.

Caution should be exercised if MAXIFLO Inhaler is administered to nursing women.

### Undesirable Effects

As MAXIFLO Inhaler contains formoterol and fluticasone propionate, the type and severity of side effects associated with each of the compounds may be expected.

#### Formoterol fumarate

**Overall adverse events that occur with >1% incidence:** Viral Infection, bronchitis, chest pain, tremors, dyspnea, dizziness, insomnia, tonsillitis, rash, dysphonia.
Adverse events occurring in more than 1% of patients with COPD:Upper respiratory tract infection, pain back, pharyngitis, pain chest, sinusitis, fever, cramps in muscles and leg, anxiety, pruritus, increased sputum and dry mouth.

Other rare and uncommon side effects include thrombopenia, hypokalaemia, hyperglycaemia, restlessness, abnormal behavior, abnormal dreams, hallucinations, headache, palpitations, tachycardia, tachyarrhythmia, ventricular extrasystoles, angina pectoris, atrial fibrillation, cough, throat irritation, exacerbation of asthma, nausea, hyperhidrosis, dysgeusia, vertigo, hypertension, asthenia, urticaria, angioedema, myalgia, nephritis and oedema peripheral.

Rare reports of anaphylactic reactions, including severe hypotension and angioedema, have also been received in association with the use of formoterol fumarate inhalation powder.

Fluticasone propionate

Adverse events that occurred in >3% of patients: Urinary tract infection, throat irritation, sinusitis/sinus infection, nasal congestion/blockage, upper respiratory tract infection and inflammation and, rhinitis, oral candidiasis, pneumonia (in COPD patients), upper respiratory tract infections, hyposalivation, nausea and vomiting, gastrointestinal discomfort and pain, viral gastrointestinal infections, fever, viral infection, cough, bronchitis, headache, muscle injury, musculoskeletal pain.

Other adverse events with an incidence of 1% to 3% and that occurred at a greater incidence than with placebo were:

Cardiovascular: Palpitations, chest symptoms.

Drug Interaction, Overdose, and Trauma: Soft tissue injuries, contusions and hematomas, wounds and lacerations, postoperative complications, burns, poisoning and toxicity, pressure-induced disorders.

Ear, Nose, and Throat: Ear signs and symptoms; rhinorrhea/postnasal drip; hoarseness/dysphonia; epistaxis; tonsillitis; nasal signs and symptoms; laryngitis; unspecified oropharyngeal plaques; otitis; ear, nose, throat, and tonsil signs and symptoms; ear, nose, and throat polyps; allergic ear, nose, and throat disorders; throat constriction.

Endocrine and Metabolic: Fluid disturbances, weight gain, goiter, hyperglycemia, disorders of uric acid metabolism, appetite disturbances, growth velocity reduction in children/adolescents, osteoporosis, adrenal suppression.

Eye: Keratitis and conjunctivitis, blepharoconjunctivitis, cataracts and glaucoma.

Gastrointestinal: Diarrhea, gastrointestinal signs and symptoms, dyspepsia, oral ulcerations, dental discomfort and pain, gastroenteritis, gastrointestinal infections, abdominal discomfort and pain, oral erythema and rashes, mouth and tongue disorders, oral discomfort and pain, tooth decay.

Hepatobiliary Tract and Pancreas: Cholecystitis.

Lower Respiratory: Lower respiratory infections.

Musculoskeletal: Muscle pain, arthralgia and articular rheumatism, muscle cramps and spasms, musculoskeletal inflammation.

Neurological: Dizziness, sleep disorders, migraines, paralysis of cranial nerves.
**Non-Site Specific:** Chest symptoms; malaise and fatigue; pain; edema and swelling; bacterial infections; fungal infections; mobility disorders; cysts, lumps, and masses.

**Psychiatry:** Mood disorders.

**Reproduction:** Bacterial reproductive infections.

**Skin:** Skin rashes, urticaria, photodermatitis, dermatitis and dermatosis, viral skin infections, eczema, fungal skin infections, pruritus, acne and folliculitis.

**Urology:** Urinary infections.

**Eosinophilic Conditions:** In rare cases, patients on inhaled fluticasone propionate may present with systemic eosinophilic conditions, with some patients presenting with 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 inhaled corticosteroids 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.

**Respiratory:** Asthma exacerbation, chest tightness, cough, dyspnea, immediate and delayed bronchospasm and wheeze.

Rare cases of immediate and delayed hypersensitivity reactions, including rash and other rare events of angio-oedema and bronchospasm, have been reported.

**Adverse events during post-approval use of fluticasone propionate in clinical practise include**

**Ear, Nose, and Throat:** aphonia, facial and oropharyngeal edema, throat soreness,

**Endocrine and Metabolic:** Cushingoid features, growth velocity reduction in children/adolescents, hyperglycemia, and osteoporosis;

**Eye:** cataracts;

**Psychiatry:** agitation, aggression, anxiety, depression and restlessness; behavioral changes, including hyperactivity and irritability have been reported very rarely and primarily in children;

**Non-Site Specific:** very rare anaphylactic reaction, very rare anaphylactic reaction in patients with severe milk protein allergy;

**Respiratory:** asthma exacerbation, bronchospasm, chest tightness, dyspnea, immediate bronchospasm, pneumonia, and wheeze;

**Skin:** contusions and ecchymoses. Cases of serious eosinophilic conditions have also been reported with other inhaled corticosteroids, cataract, glaucoma.

Dysphonia and candidiasis may be relieved by gargling or rinsing the mouth with water or brushing the teeth after using the product. Symptomatic candidiasis can be treated with topical antifungal
therapy whilst continuing the treatment with MAXIFLO Inhaler.

**Overdosage**

There are no data available from clinical trials on overdose with MAXIFLO Inhaler, however, data on overdose with both single drugs are given below:

**Formoterol fumarate**

An overdose of formoterol would likely lead to an exaggeration of effects that are typical for β₂ agonists; in which case the following adverse experiences may occur: angina, hypertension or hypotension, palpitations, tachycardia, arrhythmia, prolonged QTc interval, headache, tremor, nervousness, muscle cramps, dry mouth, insomnia, fatigue, malaise, seizures, metabolic acidosis, hypokalaemia, hyperglycaemia, nausea and vomiting.

Treatment of formoterol overdose consists of discontinuation of the medication together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of cardioselective β receptor blockers may be considered, bearing in mind that such medication can induce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial in cases of formoterol overdose. Cardiac monitoring is recommended.

If MAXIFLO Inhaler 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. Serum potassium levels should be monitored as hypokalaemia can occur. Potassium replacement should be considered.

**Fluticasone propionate**

Acute overdose with fluticasone propionate usually does not constitute a clinical problem. The only harmful effect after inhalation of a large amount of the drug over a short period is suppression of hypothalamic pituitary adrenocortical (HPA) axis function. HPA axis function usually recovers in a few days, as verified by plasma cortisol measurements. Treatment with the inhaled corticosteroid should be continued at the recommended dose to control asthma.

There are reports of rare cases of acute adrenal crisis. Children and adolescents <16 years taking high doses of fluticasone propionate: (typically ≥1000 microgram/day) may be at particular risk. Presenting symptoms can be vague (anorexia, abdominal pain, weight loss, tiredness, headache, nausea, vomiting and hypotension). Typical symptoms of an adrenal crisis are decreased level of consciousness, hypoglycaemia and/or seizures.

Following chronic use of very high doses a degree of atrophy of the adrenal cortex and HPA axis suppression may occur. Monitoring of adrenal reserve may be necessary. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma.

In the management of chronic overdose oral or systemic corticosteroids may be required in situations of stress. All patients deemed to be chronically overdosed should be treated as if steroid dependent with a suitable maintenance dose of a systemic corticosteroid. When stabilised, treatment should be continued with an inhaled corticosteroid at the recommended dose for symptom control.
Packaging Information

MAXIFLO-125 Inhaler with dose counter

MAXIFLO-250 Inhaler with dose counter

Sales pack available in a canister containing 120 metered doses

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MAXIFLO Inhaler

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