# MAXIFLO Inhaler (Formoterol fumarate + Fluticasone propionate)

## Composition

<table>
<thead>
<tr>
<th>MAXIFLO-125 Inhaler</th>
<th>MAXIFLO-250 Inhaler</th>
</tr>
</thead>
<tbody>
<tr>
<td>Each actuation delivers:</td>
<td>Each actuation delivers:</td>
</tr>
<tr>
<td>Formoterol Fumarate Dihydrate IP.................6 mcg</td>
<td>Formoterol Fumarate IP.................6 mcg</td>
</tr>
<tr>
<td>Fluticasone Propionate IP.........................125 mcg</td>
<td>Fluticasone Propionate IP.................250 mcg</td>
</tr>
<tr>
<td>Suspended in propellant HFA 134a ...............q.s.</td>
<td>Suspended in propellant HFA 134a ...............q.s.</td>
</tr>
</tbody>
</table>

## 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. As with other combinations of inhaled corticosteroids and long-acting beta₂-adrenergic agonists, the additive effect produces a reduction in the exacerbation of asthma.

## 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 beta₂-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. Fluticasone propionate reduces the symptoms, improves lung function and prevents exacerbations of asthma, with fewer adverse effects than when corticosteroids are administered systemically. The use of an inhaled steroid improves symptomatic...
control of asthma, should reduce the need for short-acting bronchodilators and may limit the reduction in lung function over time.  

*Formoterol Fumarate*

Formoterol fumarate is a potent long-acting, selective beta$_2$-adrenergic agonist with a rapid onset of action. Inhaled formoterol fumarate acts locally in the lungs as a bronchodilator, which provides symptomatic relief. After a single dose, onset of bronchodilation occurs rapidly within 1-3 minutes, with duration of effect of at least 12 hours. *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. Formoterol has been studied in the treatment of conditions associated with chronic obstructive pulmonary disease (COPD), and has been shown to improve symptoms and pulmonary function and quality of life. Formoterol acts on the reversible component of the disease.

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 adenylyl 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.

### Pharmacokinetics

*Fluticasone Propionate:*

**Absorption:** Fluticasone propionate acts locally in the lung; therefore, plasma levels do not predict therapeutic effect. Absorption is initially rapid then prolonged. 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. Absorption is initially rapid then prolonged.

**Distribution:** Following intravenous administration, fluticasone propionate is extensively distributed in the body. 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 91%. Fluticasone propionate is weakly and reversibly bound to erythrocytes.

**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 17beta-carboxylic acid derivative of fluticasone propionate, which is formed through the cytochrome P450 3A4 isoform subfamily (CYP 3A4) pathway. This metabolite has only very weak affinity glucocorticoid receptor of human lung cytosol *in vitro*

**Elimination:** 87-100% of an oral dose is excreted in the faeces, up to 75% as parent compound. There is also a non-active major metabolite. 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 healthy subjects, formoterol was rapidly absorbed into plasma, reaching a maximum drug concentration of 91.6 pg/mL within 5 minutes of inhalation. 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 8.9 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 studies investigating the cumulative urinary excretion of formoterol and/or its (RR) and (SS)-enantiomers, absorption increased linearly with the dose after inhalation of 12-96 micrograms of dry powder or aerosol formulations. After 12 weeks’ administration of 12 or 24 mcg formoterol powder twice daily the urinary excretion of unchanged formoterol increased by 63-73% in adult patients with asthma, by 19-38% in adult patients with COPD and by 18-84% in children. These results suggested a modest and self-limiting accumulation of formoterol in plasma after repeated dosing.

**Distribution:** The binding of formoterol to human plasma proteins in vitro was 34% primarily to albumin. There is no saturation of binding sites in the concentration range reached with therapeutic doses. 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 with O-demethylation followed by further glucuronidation being another pathway. Minor pathways involve sulfate conjugation of formoterol and deformylation followed by sulfate conjugation. Multiple isozymes catalyse the glucuronidation (UGT1A1, 1A3, 1A6, 1A7, 1A8, 1A9, 1A10, 2B7 and 2B15) and four cytochrome P450 isozymes (CYP2D6, CYP2C19, CYP2C9 and CYP2A6) are involved in the O-demethylation of formoterol and consequently the potential for metabolic drug-drug interaction is low. Formoterol did not inhibit CYP450 isozymes at therapeutically relevant concentrations. The kinetics of formoterol is similar after single and repeated administration, indicating no auto-induction or inhibition of metabolism.

**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 $^{3}$H-formoterol,, 59%-62% of the dose was recovered in the urine and 32%-34% in the feces. Renal clearance of formoterol was about 150 mL/min.

From urinary excretion rates measured in these subjects, the mean terminal elimination half-lives for the (R,R)- and (S,S)-enantiomers were determined to be 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 maintenance 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 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 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. 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.

Patients should not be initiated on MAXIFLO Inhaler 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 fluticasone propionate/formoterol fumarate combination. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation on MAXIFLO Inhaler.

Increasing use of short-acting bronchodilators to relieve asthma symptoms indicates a deterioration of asthma control, and these patients should be reviewed by a physician. Sudden and progressive deterioration in the control of asthma is potentially life-threatening and these patients require urgent medical assessment. Patients should be medically reviewed when their current dosage of MAXIFLO Inhaler fails to give adequate control of asthma. Consideration should be given to either increasing, or to additional corticosteroid therapies. 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 physician.

To Avoid Overtreatment and Unnecessary Adverse Effects

Initiate therapy with sufficient medication to achieve best lung function promptly after about 3 months of good control (which is characterised by few symptoms, minimal use of short-acting beta, agonists, and no exercise limitation), reduce inhaled corticosteroids to the minimum dose needed to maintain adequate asthma control (‘stepping down’).

Consider seasonal adjustment of doses as the minimum required dose may vary.

As with all inhaled medication containing corticosteroids, MAXIFLO Inhaler should be administered with caution in patients with pulmonary tuberculosis, untreated systemic infections, ocular herpes simplex or patients with fungal, viral or other infections of the airway. Any such infections must always be adequately treated if MAXIFLO Inhaler is being used.

An exacerbation of the clinical symptoms of asthma may be due to acute respiratory tract bacterial infection and treatment may require appropriate antibiotics, increased inhaled corticosteroids and a short course of oral corticosteroids. A rapid-acting inhaled bronchodilator should be used as rescue medication.

The prophylactic use of fluticasone propionate/formoterol fumarate combination in exercise-induced asthma has not
been studied. For such use, a separate rapid-acting bronchodilator should be considered.

### Cardiovascular

Cardiovascular effects such as increases in systolic blood pressure and heart rate, may occasionally be seen with all sympathomimetic drugs, especially at higher than therapeutic doses. For this reason, MAXIFLO Inhaler should be administered with caution in patients with pre-existing cardiovascular disorders, including prolongation of the QTc interval. Formoterol itself may induce prolongation of the QTc interval.

A transient decrease in serum potassium may occur with all sympathomimetic drugs at higher therapeutic doses.

MAXIFLO Inhaler should be used with caution in patients with a history of thyrotoxicosis, phaeochromocytoma diabetes mellitus, untreated hypokalaemia, patients predisposed to low levels of serum potassium, hypertrophic obstructive cardiomyopathy, idiopathic sub-valvular aortic stenosis, aneurysm, or other severe cardiovascular disorders, such as ischaemic heart disease, cardiac arrhythmias, severe heart failure, or severe hypertension.

As for all beta₂-agonists, additional blood sugar controls should be considered in diabetic patients.

Potentially serious hypokalaemia may result from systemic beta₂-agonist therapy, but following inhalation at therapeutic doses, plasma levels of formoterol are very low.

Concomitant treatment of beta₂-agonists with drugs which can induce or potentiate a hypokalaemic effect. e.g. xanthine derivatives, steroids and diuretics, may add to a possible hypokalemic effect of the beta₂-agonist. Particular caution is recommended in unstable asthma with variable use of rescue bronchodilators, in acute severe asthma as the associated risk may be augmented by hypoxia and in other conditions when the likelihood for hypokalaemia adverse effects is increased. It is recommended that serum potassium levels are monitored during these circumstances. 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.

As with other inhalation therapies, paradoxical bronchospasm may occur, with an immediate increase in wheezing after dosing. In such a case, MAXIFLO Inhaler should be discontinued immediately, the patient assessed and alternative therapy instituted, if necessary. Patients should be advised to seek immediate attention if their condition deteriorates.

### Possible Systemic Effects, Including Adrenocortical Function, Bone Density and Growth

Inhaled steroids are designed to direct glucocorticoid delivery to the lungs in order to reduce overall systemic glucocorticoid exposure and side effects. With sufficient doses however, all inhaled steroids can have adverse effects.

Possible systemic effects include Cushing's syndrome, Cushingoid features, depression of the hypothalamic-pituitary adrenal, 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).

The lowest dose of inhaled fluticasone that causes suppression of the HPA axis (as indicated by the 24-hour urinary cortisol concentrations), and effects the bone mineral levels or growth retardation in children has not yet been established. Some depression of plasma cortisol may occur in a small number of adult patients on higher doses (e.g. >1 mg/day). In situations of possible impaired adrenal function, HPA axis function should be monitored regularly. Adrenal function and adrenal reserve usually remain within normal range on inhaled fluticasone propionate therapy. However, prolonged treatment with high doses of inhaled corticosteroids may result in adrenal suppression and acute adrenal crisis.

Data regarding the effect of long term use of inhaled fluticasone on bone mineral density in elderly patients are limited.

Patients in a medical or surgical emergency, who have required high dose of inhaled steroids therapy and/or intermittent treatment with oral steroids 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 adrenocortical (HPA) axis function should be monitored regularly.

In rare cases, inhaled therapy may unmask underlying eosinophilic conditions (e.g. Churg Strauss syndrome). These cases have usually been associated with reduction or withdrawal of oral corticosteroid therapy. A direct causal relationship has not been established.

These patients may require specialised advice to determine the extent of adrenal impairment before elective procedures. The possibility of residual impaired adrenal response should always be considered in an emergency (medical or surgical) and elective situations likely to produce stress, and appropriate corticosteroid treatment considered.

It is recommended that the height of children and adolescents receiving prolonged treatment with inhaled corticosteroids is regularly monitored. If growth is slowed, therapy should be reviewed with the aim of reducing the dose of inhaled corticosteroid, if possible to the lowest dose at which effective control is maintained. In addition, consideration should be given to referring the patient to a paediatric respiratory specialist.

### 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.

### Effects on Laboratory Tests

A transient decrease in serum potassium may occur with all sympathomimetic drugs (formoterol, a component of MAXIFLO Inhaler) at higher therapeutic doses.

Concomitant treatment with ketoconazole or other potent CYP3A4 inhibitors should be avoided unless the benefit outweighs the increased risk of systemic side effects of corticosteroids.

The benefits of inhaled fluticasone should minimize the need for oral steroids. However, patients transferred from oral steroids remain at risk of impaired adrenal reserve for a considerable time after transferring to inhaled fluticasone. The possibility of respective symptoms may persist for some time.

### Transferring Patients being treated with Oral Corticosteroids

The benefits of inhaled corticosteroids should minimise the need for oral steroids. However, patients transferred from oral steroids, remain at risk of impaired adrenal reserve for a considerable time after transferring to inhaled corticosteroid. The possibility of adverse effects may persist for some time. These patients may require specialised advice to determine the extent of adrenal impairment before elective procedures. The possibility of residual impaired adrenal response should always be considered in emergency (medical or surgical) and elective situations likely to produce stress, and appropriate corticosteroid treatment considered.

Lack of response or severe exacerbations of asthma should be treated by increasing the dose of inhaled corticosteroid and, if necessary, by giving a systemic steroid and/or an antibiotic if there is an infection. The transfer of oral steroid-dependent patients to inhaled fluticasone, and their subsequent management, needs special care as recovery from impaired adrenocortical function, caused by prolonged systemic steroid therapy, may take a considerable time.

Patients, who have been treated with systemic steroids for long periods of time, or at a high dose, may have adrenocortical suppression. With these patients adrenocortical function should be monitored regularly and their dose of systemic steroid reduced cautiously.

After approximately a week, gradual withdrawal of the systemic steroid is started by reducing the dose by 1 mg
prednisolone per week, or its equivalent. For maintenance doses of prednisolone in excess of 10 mg daily, it may be appropriate to cautiously use larger reductions in dose at weekly intervals.

Some patients feel unwell in a non-specific way during the withdrawal phase despite maintenance or even improvement of respiratory function. They should be encouraged to persevere with inhaled fluticasone and to continue withdrawal of systemic steroid, unless there are objective signs of adrenal insufficiency.

Patients transferred from oral steroids whose adrenocortical function is still impaired should carry a steroid warning card indicating that they need supplementary systemic steroid during periods of stress, e.g. chest infections, major intercurrent illness, surgery, trauma, etc.

Replacement of systemic steroid treatment with inhaled therapy sometimes unmasks allergies such as allergic rhinitis or eczema previously controlled by systemic drug.

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.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

**Drug Interactions**

No formal drug interaction studies have been performed with fluticasone propionate/formoterol fumarate combination, hence the drug interactions with individual component of the formulation have been considered here.

**CYP34A Inhibitors**

There is an increased risk of systemic side-effects when combining fluticasone propionate with potent CYP3A4 inhibitors. Fluticasone propionate, an individual component of MAXIFLO Inhaler, is a substrate of CYP 3A4. Caution needs to be taken in long-term coadministration of strong CYP 3A4 inhibitors (e.g. ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nelfinavir, saquinavir, ketoconazole, telithromycin) together with MAXIFLO Inhaler and co-administration with such drugs should be avoided if possible. Particularly co-medication of ritonavir should be avoided unless the benefit outweighs the increased risks. 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.

**Potassium Sparing Diuretics**

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 beta agonists, 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 co-administration of a beta agonist with non-potassium sparing diuretics.

**Xanthine Derivatives and Glucocorticosteroids**

Xanthine derivatives and glucocorticosteroids may add to a possible hypokalaemic effect of the beta agonists as discussed above.

**L-Dopa, L-Thyroxine, Oxytocin and Alcohol**

L-Dopa, L-thyroxine, oxytocin and alcohol can impair cardiac tolerance towards beta, sympathomimetics.

**Monoamine Oxidase Inhibitors**

Concomitant treatment with monoamine oxidase inhibitors (MAOIs), including agents with similar properties such as furazolidone and procarbazine, may precipitate hypertensive reactions.

**Halogenated Hydrocarbon Anaesthetics**

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

**Drugs known to Prolong QTc interval**
Formoterol fumarate, as with other beta₂-agonists, should be administered with extreme caution to patients being treated with MAOIs or tricyclic antidepressants (or within two weeks of their discontinuation), or drugs known to prolong the electrocardiographic QTc interval such as quinidine, disopyramide, procainamide, phenothiazines and antihistamines. Drugs that are known to prolong the QTc interval increase the risk of ventricular arrhythmias.

Adrenergic Drugs
If additional adrenergic drugs are to be administered by any route, they should be used with caution, because the pharmacologically predictable sympathetic effects of formoterol may be potentiated. Concomitant use of beta-adrenergic drugs can have a potentially additive effect.

Beta-Blockers
Beta-adrenergic receptor antagonists (beta-blockers) and formoterol fumarate may inhibit the effect of each other when administered concurrently. Beta-blockers may also produce severe bronchospasm in asthmatic patients. Therefore, patients with asthma should not normally be treated with beta-blockers and this includes beta-blockers used as eye drops for treatment of glaucoma. However, under certain circumstances, e.g. as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-blockers in patients with asthma. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

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

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, an increased exposure can be expected in patients with severe hepatic impairment.

Pregnancy
There are no adequate and well-controlled studies with fluticasone propionate/formoterol fumarate combination in pregnant women. Studies in animals have shown reproductive toxicity. Administration MAXIFLO Inhaler are not recommended during pregnancy and should be considered only if the expected benefit to the expectant mother is greater than any possible risk to the foetus.

Labour
Because of the potential for beta-agonist interference with uterine contractility, use of MAXIFLO Inhaler for the management of asthma during labour should be restricted to those patients in whom the benefit outweighs the risks, and the lowest effective dose needed to maintain adequate asthma control should be used.

Lactation
It is not known whether fluticasone propionate or formoterol fumarate or their metabolites, are excreted in human breast milk. Such excretion has been demonstrated for both drugs in lactating rats. In addition, growth and survival of pups were found to be decreased when lactating rats were given formoterol fumarate at oral doses greater than 1 mg/kg/day. 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.
**Paediatric Use**

The safety and efficacy of fluticasone propionate/formoterol fumarate have not been assessed in children under 12 years of age. Therefore, MAXIFLO Inhaler is not recommended for children under 12 years.

**Geriatric Use**

There is no need to adjust the dose in elderly patients.

**Undesirable Effects**

Adverse effects of fluticasone propionate/formoterol fumarate combination are listed by system organ class (SOC), in order of decreasing seriousness within each SOC in Table 1.

**Table 1: Adverse Effects Associated with Fluticasone Propionate/Formoterol Fumarate Combination**

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Adverse Effect</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Oral candidiasis</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>Oral fungal infection</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sinusitis</td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Hyperglycaemia</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Sleep disorders including insomnia</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Abnormal dreams</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>Agitation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Psychomotor hyperactivity, anxiety, depression, aggression, behavioural changes (predominantly in children)</td>
<td>Not known</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Tremor</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dysgeusia</td>
<td></td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Vertigo</td>
<td>Rare</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Palpitations</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Ventricular extrasystoles</td>
<td></td>
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<tr>
<td></td>
<td>Angina pectoris</td>
<td></td>
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<tr>
<td></td>
<td>Tachycardia</td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypertension</td>
<td>Rare</td>
</tr>
<tr>
<td>-------------------</td>
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<td>------</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Exacerbation of asthma, Dysphonia, Throat irritation</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Dyspnoea, Cough</td>
<td>Rare</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Dry mouth</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Diarrhoea, Dyspepsia</td>
<td>Rare</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Pruritus</td>
<td>Rare</td>
</tr>
<tr>
<td>Musculoskeletal connective tissue disorders</td>
<td>Muscle spasms</td>
<td>Rare</td>
</tr>
<tr>
<td>General and administration site disorders</td>
<td>Peripheral oedema</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Asthenia</td>
<td>Rare</td>
</tr>
</tbody>
</table>

**Frequency:** very common (≥ 1/10); common (≥ 1/100 and <1/10); uncommon (≥ 1/1,000 and <1/100); rare (≥ 1/10,000 and < 1/1,000); very rare (<1/10,000 including isolated reports); not known (cannot be estimated from the available data).

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 inhaled bronchodilator and should be treated immediately. Inhalation therapy should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.

The common adverse events that occur with ≥1% incidence in any treatment group in the pooled analysis were as follows:

**Infections and Infestations**
Bronchitis, ear infection, gastroenteritis viral, influenza, laryngitis, nasopharyngitis, pharyngitis, pneumonia pneumococcal, respiratory infection, rhinitis, sinusitis, tonsillitis, upper respiratory tract infection, urinary tract infection, viral infection,

**Respiratory thoracic and mediastinal disorders:** Asthma, cough, dyspnea, dysphonia, rhinitis allergic, rhinitis seasonal

**Nervous system disorders:** Headache

**Psychiatric disorders:** Depression

**Renal and urinary disorders:** Dysuria

**Reproductive and breast disorders:** Adenomyosis

**Gastrointestinal disorders:** Abdominal pain upper, diarrhea, vomiting

**Musculoskeletal and connective tissue disorder:** Arthralgia, back pain, myalgia, pain in extremity

**Injury, poisoning and procedural complications:** Fall, neck injury

**Metabolism and nutrition disorders:** Hypercholesterolaemia, hyperlipidaemia

**Vascular disorders:** Hypertension
Neoplasms benign, malignant and unspecified (including cysts and polyps): Melanocytic naevus, prostatic adenoma, skin papilloma

Surgical and medical procedures: Dental prosthesis placement

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**

Hypersensitivity reactions (including hypotension, angioneurotic oedema, pruritus, exanthema), QTc interval prolongation, hypokalaemia, nausea, myalgia, increased blood lactate levels have been reported with formoterol fumarate. Treatment with beta-agonists such as formoterol may result in an increase in blood levels of insulin, free fatty acids, glycerol and ketone bodies.

Hypersensitivity reactions have been reported in patients using inhaled sodium cromoglycate as an active ingredient. Whilst MAXIFLO Inhaler contains only a low concentration of sodium cromoglycate as an excipient, it is unknown if hypersensitivity reactions are dose dependent.

**Fluticasone Propionate**

Hypersensitivity reactions including urticaria, pruritus, angioedema (mainly facial and oropharyngeal), and anaphylactic reactions have been reported with fluticasone propionate. Systemic effects of inhaled corticosteroids may occur, particularly at high dosages prescribed for prolonged periods. These may include Cushing’s syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma, sleep disorders, contusion, skin atrophy and susceptibility to infections. The ability to adapt to stress may be impaired. The systemic effects described, however, are much less likely to occur with inhaled corticosteroids than with oral corticosteroids. Prolonged treatment with high doses of inhaled corticosteroids may result in clinically significant adrenal suppression and acute adrenal crisis. Additional systemic corticosteroid cover may be required during periods of stress (trauma, surgery, infection).

### Postmarketing Experience

Eye disorders: vision blurred

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 or you can report to Cipla Ltd on 18002677779. 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 fluticasone propionate/formoterol fumarate combination. Information on overdose with both single drugs is given below:

**Fluticasone Propionate**

*Symptoms:* Acute inhalation of fluticasone propionate doses in excess of those recommended may lead to temporary 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 typically vague and may include 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.

**Treatment:** In cases of fluticasone propionate overdose the dose of Maxiflo Inhaler should be tapered. 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. Therapy with MAXIFLO Inhaler may still be continued with an inhaled corticosteroid at the recommended dose for symptom control.

▶ Formoterol Fumarate

**Symptoms:** An overdose of formoterol would likely lead to an exaggeration of effects that are typical for beta₂ 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:** Treatment of formoterol overdose consists of discontinuation of the medication together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of cardio selective beta 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.

**Storage And Handling Instructions**

Store below 30ºC.
Do not freeze.

**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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