For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

Fluticasone Propionate and Formoterol Fumarate Inhaler

Maxiflo-M

inhaler

COMPOSITION

Maxiflo-M-125 Inhaler

Each actuation delivers

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

Maxiflo-M – 250 Inhaler

Each actuation delivers

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

DOSAGE FORM

Inhalation Aerosol

DESCRIPTION

Maxiflo-M Inhaler is a combination of fluticasone propionate, a synthetic corticosteroid and formoterol; a selective long acting β_2-agonist.

Fluticasone propionate is a synthetic, trifluorinated glucocorticoid with potent anti-inflammatory activity. Formoterol is a very potent long-acting β_2-adrenoceptor agonist with a high intrinsic activity and a rapid onset of action.

PHARMACOLOGY

Pharmacodynamics

Maxiflo-M Inhaler contains both fluticasone and formoterol; therefore, the mechanisms of action described below for the individual components apply to **Maxiflo-M Inhaler**. These drugs represent two classes of medications (a synthetic corticosteroid and a long-acting, selective β_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 β_2-adrenergic agonist with a rapid onset of action. The onset of action is observed within one to three minutes. Significant bronchodilation is still present 12 hours after inhalation. 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 β_2-receptors than at β_1-receptors. The *in vitro* binding selectivity to β_2-adrenoceptors over β_1-adrenoceptors is higher for formoterol than for salbutamol (5 times), whereas salmeterol has a higher (3 times) β_2-selectivity ratio than formoterol.

Although β_1-receptors are the predominant adrenergic receptors in bronchial smooth muscle and β_1-receptors are the predominant receptors in the heart, there are also β_1-receptors in the human heart, which comprise 10–50% of the total β-adrenergic receptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective β_2-agonists may have cardiac effects.

The pharmacological effects of β_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.

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: Following oral administration of 80 mcg of radiolabeled formoterol fumarate to 2 healthy subjects, 59%-62% of the radioactivity was eliminated in the urine and 32%-34% in the feces over a period of 104 hours. Renal clearance of formoterol from blood in these subjects was about 150 mL/min. Following inhalation of a 12 mcg or 24 mcg dose by 16 patients with asthma, about 10% and 15%-18% of the total dose was excreted in the urine as unchanged formoterol and direct conjugates of formoterol, respectively. Following inhalation of 12 mcg or 24 mcg dose by 18 patients with COPD the corresponding values were 7% and 6-9% of the dose, respectively.

Based on plasma concentrations measured following inhalation of a single 120 mcg dose by 12 healthy subjects, the mean terminal elimination half-life was determined to be 10 hours. 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. The (R,R)- and (S,S)-enantiomers represented about 40% and 60% of unchanged drug excreted in the urine, respectively, following single inhaled doses between 12 and 120 mcg in healthy volunteers and single and repeated doses of 12 and 24 mcg in patients with asthma. Thus, the relative proportion of the two enantiomers remained constant over the dose range studied and there was no evidence of relative accumulation of one enantiomer over the other after repeated dosing.

INDICATIONS

Maxiflo-M Inhaler is indicated in the regular treatment of asthma, where use of a combination (long-acting β_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-M-125: 1-2 inhalations twice daily
MAXIFLO-M-250: 1-2 inhalations twice daily

COPD

MAXIFLO-M-125: Two inhalations twice daily
MAXIFLO-M-250: Two inhalations twice daily

CONTRAINDICATIONS

Maxiflo-M 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-M Inhaler** must be used daily for optimum benefit, even when asymptomatic.

Maxiflo-M 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-M Inhaler** should be administered with caution in patients with pulmonary tuberculosis.

Maxiflo-M Inhaler should be administered with caution in patients with severe cardiovascular disorders, including heart rhythm abnormalities, diabetes mellitus, untreated hypokalaemia, thyrotoxicosis and phaeochromocytoma. Potentially serious hypokalaemia may result from systemic β_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-M 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 adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cushing's syndrome, cushingoid features, cataract, and glaucoma. It is important, therefore, that the dose is titrated to the lowest dose at which effective control is maintained.

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. 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-M Inhaler** is coadministered with ketoconazole and other known potent cytochrome P450 3A4 inhibitors.

β-adrenergic blockers may weaken or antagonize the effect of **Maxiflo-M Inhaler.** Therefore β-adrenergic blockers (including eye drops) 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 β_2-agonists. Concomitant administration of other sympathomimetic agents may potentiate the undesirable effects of formoterol.

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-M Inhaler** in pregnancy should be considered only if the expected benefit to the expectant mother is greater than any possible risk to the foetus.

Lactation

Use of **Maxiflo-M 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 excercised if **Maxiflo-M inhaler** is administered to nursing women.

UNDESIRABLE EFFECTS

As **Maxiflo-M 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, hallucinations, headache, palpitations, tachycardia, tachyarrhythmia, ventricular extrasystoles, angina pectoris, atrial fibrillation, cough, throat irritation, exacerbation of asthma, nausea, hyperhidrosis, urticaria, angioedema, myalgia, nephritis and oedema peripheral.

Fluticasone Propionate

Adverse events that occurred in >3% of patients: Urinary tract infection, throat irritation, sinusitis/sinus infection, upper respiratory inflammation, 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, viral respiratory 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.

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.

OVERDOSAGE

The signs and symptoms of **Maxiflo-M Inhaler** overdose are tremor, headache, tachycardia, nausea, vomiting, somnolence, palpitations, ventricular arrhythmias, angina, hypertension or hypotension, metabolic acidosis, hypokalaemia, hyperglycaemia, seizures, muscle cramps, dry mouth, dizziness, fatigue, malaise and insomnia. Metabolic acidosis may also occur. The preferred antidotes are cardioselective β-blocking agents, which should be used with caution in patients with a history of bronchospasm. If a higher than recommended dosage is continued over prolonged periods, some degree of adrenal suppression may result. Monitoring of adrenal reserve may be necessary.

INCOMPATIBILITY: None known

SHELF-LIFE : See on pack

STORAGE AND HANDLING INSTRUCTIONS:

Store below 30˚C. Do not freeze

PRESENTATION:

Canister containing 120 metered dose

Last updated: Feb. 2012

Cipla **CIPLA LTD.** INDIA

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Fluticasone Propionate and Formoterol Fumarate Inhaler

Maxiflo-M inhaler

with dose indicator

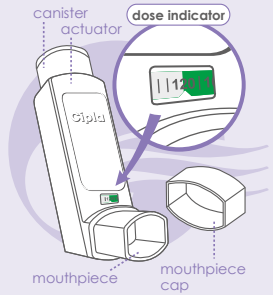
patient information leaflet

please read this leaflet completely before use

CFC-FREE

ABOUT YOUR MAXIFLO-M INHALER

PARTS OF THE INHALER



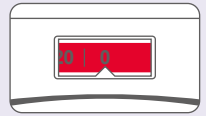
Your **MAXIFLO-M** inhaler now comes with a dose indicator. It shows the number of puffs in the inhaler. As you use the inhaler, the dose indicator will countdown and indicate the number of puffs remaining.

HOW TO KNOW THAT YOUR MAXIFLO-M INHALER IS GETTING OVER

When there are 40 puffs remaining, the colour on the dose indicator will change from green to red.

This indicates that fewer doses are remaining in the inhaler. You should now consider getting a new inhaler or ask your doctor if you need another one.

When the dose indicator displays '0', this means that there is no more medicine left in the inhaler & you need to discard the inhaler. Your inhaler may not feel empty & it may continue to operate, but you will not get the right amount of medicine, if you keep using it beyond '0'.



BEFORE USING YOUR MAXIFLO-M INHALER

1 Remove the cap from the mouthpiece & make sure that the mouthpiece is clean.

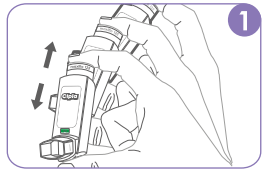
2 Hold the inhaler away from your face. Shake it well & release two puffs into the air.

3 The dose indicator will show the number '120', indicating the number of puffs in the inhaler. Now your **MAXIFLO-M** inhaler is ready for use.

IF you have not used your inhaler for a week or more, shake well and release one puff into the air.

USING YOUR MAXIFLO-M INHALER

1 Sit or stand upright. Remove the mouthpiece cap & shake the inhaler well. Hold it upright as shown, with your thumb at the base below the mouthpiece. Place either one or two fingers on top of the canister.

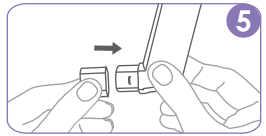


2 Breathe out fully, through your mouth.

3 Place the mouthpiece of the inhaler in your mouth between your teeth & close your lips around it (do not bite it). **Start breathing in slowly through your mouth. Press down the canister firmly & fully to release one spray while continuing to breathe in slowly & deeply.**

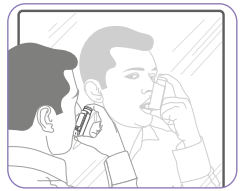
4 Remove the inhaler from your mouth & hold your breath for 10 seconds, or for as long as is comfortable. Breathe out normally.

5 If another puff is required, wait for at least 1 minute. Shake inhaler well & repeat steps 2 to 4. After use, replace the mouthpiece cap firmly & snap it into position.

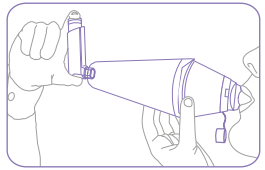


6 After taking each dose, rinse your mouth with water & spit it out.

IMPORTANT:
Do not rush steps 2, 3 & 4. It is important that you start to breathe in slowly before releasing a puff.
To ensure correct use of the inhaler, use it in front of a mirror for the first few times. If you see 'mist' coming out from the top of the inhaler or the sides of your mouth, start again from step 1. This escaping mist indicates incorrect technique.



In case of difficulty in using the inhaler correctly, you may use it along with a spacer device.



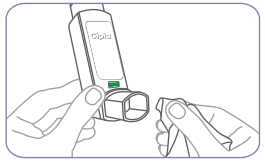
FOR CHILDREN:
Parents must assist those children who need help in using the **MAXIFLO-M** inhaler correctly with/without a spacer.

CLEANING YOUR MAXIFLO-M INHALER

It is important to keep your inhaler clean. Clean your inhaler atleast once a week.

1 Take the mouthpiece cap off. **DO NOT take the metal canister out of the actuator.**

2 Wipe the inside & the outside of the mouthpiece with a clean, dry cloth.



3 Replace the mouthpiece cap.

4 DO NOT wash or soak any part of the inhaler in water.

STORING YOUR MAXIFLO-M INHALER

Store below 30°C.

Do not freeze.

Keep the inhaler in an upright position, with the mouthpiece down.

DO NOT

- × *Spray the inhaler in your eyes.*
- × *Exceed the recommended dose.*
- × *Change/tamper with the numbers on the dose indicator.*
- × *Puncture or burn the inhaler even when empty as it is pressurized.*

Keep the inhaler out of the reach of children.

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