

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Formoterol Fumarate and Fluticasone Propionate Powder for Inhalation (12 + 250 mcg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains:

Formoterol Fumarate Dihydrate BP 12 mcg

Fluticasone Propionate BP..... 250 mcg

Inactive Ingredients: Lactose Monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for Inhalation (in Capsule)

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

The drug is intended for the regular treatment of bronchial asthma in adults over 18 years of age, if the combination therapy is indicated with beta 2-adrenergic agonist long-acting and inhaled corticosteroid:

- in patients with insufficient disease control against the background of continuous monotherapy with inhaled corticosteroids with occasional use of short-acting beta 2 – adrenergic agonists;
- patients with adequate control of the disease during therapy with an inhaled corticosteroid and beta 2-adrenergic agonists;
- as a starting maintenance therapy in patients with persistent bronchial asthma in the presence of indications for the initiation of inhaled glucocorticosteroid to achieve disease control.

4.2 Posology and method of administration

Recommended dose for adults over 18 years:

The recommended dose for adults over 18 years of age is one capsule of the combination (Formoterol and Fluticasone Propionate) by oral inhalation twice daily, one in the morning and another at night.

There are no data available for use in children.

It is recommended for use in adults aged 18 years and above. Method of administration

For inhalation use. The patient should be trained how to use the inhaler correctly by a physician or other healthcare professional.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1..

4.4 Special warnings and precautions for use

The management of asthma should normally follow a stepwise programme and patients' responses should be monitored clinically and by lung function tests.

Fixed dose combination (Formoterol Fumarate and Fluticasone Propionate) 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 medicine to be used for relief in an acute asthma attack available at all times.

The prophylactic use of Fixed dose combination (Formoterol Fumarate and Fluticasone Propionate) in exercise-induced asthma has not been studied. For such use, a separate rapid-acting bronchodilator should be considered.

Patients should be reminded to take their Fixed dose combination (Formoterol Fumarate and Fluticasone Propionate) maintenance dose as prescribed, even when asymptomatic.

Patients should not be initiated on Fixed dose combination (Formoterol Fumarate and Fluticasone Propionate) 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 Fixed dose combination (Formoterol Fumarate and Fluticasone Propionate). Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation on Fixed dose combination (Formoterol Fumarate and Fluticasone Propionate).

Fixed dose combination (Formoterol Fumarate and Fluticasone Propionate) should not be used as the first treatment for asthma.

If increasing use of short-acting bronchodilators to relieve asthma is required, if short-acting bronchodilators become less effective, or ineffective or if asthma symptoms persist, the patient should be reviewed by their doctor as soon as possible as any of these may indicate a deterioration in asthma control and their treatment may need to be changed.

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

Consideration should be given to increasing corticosteroid therapy. The patient should also be medically reviewed when the current dosage of Fixed dose combination (Formoterol Fumarate and Fluticasone Propionate) has failed to give adequate control of asthma. Consideration should be given to additional corticosteroid therapies.

Once asthma symptoms are controlled, consideration may be given to gradually reducing the dose of Fixed dose combination (Formoterol Fumarate and Fluticasone Propionate). Regular review of patients as treatment is stepped down is important. The lowest effective dose of Fixed dose combination (Formoterol Fumarate and Fluticasone Propionate) should be used.

Treatment with Fixed dose combination (Formoterol Fumarate and Fluticasone Propionate) 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.

An exacerbation of the clinical symptoms of asthma may be due to an 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. As with all inhaled medication containing corticosteroids, Fixed dose combination (Formoterol Fumarate and Fluticasone Propionate) should be administered with caution in patients with pulmonary tuberculosis, quiescent tuberculosis or patients with fungal, viral or other infections of the airway. Any such infections must always be adequately treated if Fixed dose combination (Formoterol Fumarate and Fluticasone Propionate) is being used.

Fixed dose combination (Formoterol Fumarate and Fluticasone Propionate) should be used with caution in patients with thyrotoxicosis, phaeochromocytoma, diabetes mellitus, uncorrected hypokalaemia or patients predisposed to low levels of serum potassium, hypertrophic obstructive cardiomyopathy, idiopathic subvalvular aortic stenosis, severe hypertension, aneurysm or other severe cardiovascular disorders, such as ischaemic heart disease, cardiac arrhythmias or severe heart failure.

Potentially serious hypokalaemia may result from high doses of β_2 agonists. Concomitant treatment of β_2 agonists with drugs which can induce hypokalaemia or potentiate a hypokalaemic effect, e.g. xanthine derivatives, steroids and diuretics, may add to a possible hypokalaemic effect of the β_2 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.

Caution must be observed when treating patients with existing prolongation of the QTc interval. Formoterol itself may induce prolongation of the QTc interval.

As for all β_2 agonists, additional blood sugar controls should be considered in diabetic patients.

Care should be taken when transferring patients to Fixed dose combination (Formoterol Fumarate and Fluticasone Propionate) therapy, particularly if there is any reason to suppose that adrenal function is impaired from previous systemic steroid therapy.

As with other inhalation therapy paradoxical bronchospasm may occur with an immediate increase in wheezing and shortness of breath after dosing. Paradoxical bronchospasm responds to a rapid-acting inhaled bronchodilator and should be treated straight away. Fixed dose combination (Formoterol Fumarate and Fluticasone Propionate) should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.

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.

Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children). It is important, therefore, that the patient is reviewed regularly and the dose of inhaled corticosteroid is reduced to the lowest dose at which effective control of asthma is maintained.

Prolonged treatment of patients with high doses of inhaled corticosteroids may result in adrenal suppression and acute adrenal crisis. Children and adolescents <16 years taking high doses of fluticasone propionate (typically ≥ 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.

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 adrenocortical (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.

Use of a spacer device may lead to a possible increase in pulmonary deposition and a potential increase in systemic absorption and systemic adverse events.

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. Interaction with other medicinal products and other forms of interaction

4.5 Interaction with other medicinal products and other forms of interaction

No formal drug interaction studies have been performed with Fixed dose combination (Formoterol Fumarate and Fluticasone Propionate).

Fluticasone propionate, an individual component of Fixed dose combination (Formoterol Fumarate and Fluticasone Propionate), is a substrate of CYP 3A4. Co-treatment with CYP3A inhibitors (e.g. ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nelfinavir, saquinavir, ketoconazole, telithromycin, cobicistat) is expected to increase the risk of systemic side-effects. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid side-effects.

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 derivatives 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 β_2 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.

Concomitant use of other β adrenergic drugs can have a potentially additive effect.

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

Formoterol fumarate, as with other β_2 agonists, should be administered with caution to patients being treated with tricyclic antidepressants or monoamine oxidase inhibitors, and during the immediate two week period following their discontinuation, or other drugs known to prolong the QTc interval such as antipsychotics (including phenothiazines), quinidine, disopyramide, procainamide, and antihistamines. Drugs that are known to prolong the QTc interval can increase the risk of ventricular arrhythmias.

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.

Beta adrenergic receptor antagonists (β 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 β blockers and this includes β 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 β blockers in patients with asthma. In this setting, cardioselective β blockers could be considered, although they should be administered with caution.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data on the use of fluticasone propionate and formoterol fumarate, either administered alone or together but administered from separate inhalers, or on the use of this fixed-dose combination, Fixed dose combination (Formoterol Fumarate and Fluticasone Propionate) in pregnant women. Studies in animals have shown reproductive toxicity.

Administration of Fixed dose combination (Formoterol Fumarate and Fluticasone Propionate) is not recommended during pregnancy, and should only be considered if expected benefit to the mother is greater than any possible risk to the fetus. If this is the case, then the lowest effective dose needed to maintain adequate asthma control should be used.

Because of the potential for β agonist interference with uterine contractility, use of Fixed dose combination (Formoterol Fumarate and Fluticasone Propionate) for management of asthma during labour should be restricted to those patients in whom the benefit outweighs the risks.

Breastfeeding

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. Therefore, a decision must be made whether to discontinue breastfeeding or to discontinue/abstain from Fixed dose combination (Formoterol Fumarate and Fluticasone Propionate) therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility

There are no data available on effects on fertility following administration of Fixed dose combination (Formoterol Fumarate and Fluticasone Propionate). In animal studies, no effects on fertility have been seen following administration of the individual active substances at clinically relevant doses.

4.7 Effects on ability to drive and use machines

Fixed dose combination (Formoterol Fumarate and Fluticasone Propionate) has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Undesirable effects which have been associated with Fixed dose combination (Formoterol Fumarate and Fluticasone Propionate) during clinical development are given in the table below, listed by system organ class. The following frequency categories form the basis for classification of the undesirable effects as: very common ($\geq 1/10$), common ($\geq 1/100$ and $< 1/10$), uncommon ($\geq 1/1,000$ and $< 1/100$), rare ($\geq 1/10,000$ and $< 1/1,000$), very rare ($< 1/10,000$) and not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	Adverse Event	Frequency
Infections and Infestations	Oral candidiasis Oral fungal infections Sinusitis	Rare
Metabolism and Nutrition Disorders	Hyperglycaemia	Rare
Psychiatric Disorders	Sleep disorders including insomnia	Uncommon
	Abnormal dreams Agitation	Rare
	Psychomotor hyperactivity, anxiety, depression, aggression, behavioural changes (predominantly in children)	Not known
Nervous System Disorders	Headache Tremor Dizziness	Uncommon
	Dysgeusia	Rare
Eye disorders	Vision blurred	Not known
Ear and labyrinth disorders	Vertigo	Rare
Cardiac Disorders	Palpitations Ventricular extrasystoles	Uncommon
	Angina pectoris Tachycardia	Rare
Vascular disorders	Hypertension	Rare
Respiratory, Thoracic and Mediastinal Disorders	Exacerbation of asthma Dysphonia Throat irritation	Uncommon
	Dyspnoea Cough	Rare
Gastrointestinal disorders	Dry mouth	Uncommon
	Diarrhoea Dyspepsia	Rare
Skin and subcutaneous tissue disorders	Rash	Uncommon
	Pruritus	Rare
Musculoskeletal and Connective Tissue	Muscle spasms	Rare

Disorders		
General disorders and administration site conditions	Peripheral oedema Asthenia	Rare

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 straight away. Fixed dose combination (Formoterol Fumarate and Fluticasone Propionate) should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.

Since Fixed dose combination (Formoterol Fumarate and Fluticasone Propionate) contains both fluticasone propionate and formoterol fumarate, the same pattern of undesirable effects as reported for these substances may occur. The following undesirable effects are associated with fluticasone propionate and formoterol fumarate, but have not been seen during the clinical development of Fixed dose combination (Formoterol Fumarate and Fluticasone Propionate):

Fluticasone propionate:

Hypersensitivity reactions including, urticaria, pruritus, angioedema (mainly facial and oropharyngeal), anaphylactic reactions. Systemic effects of inhaled corticosteroids may occur, particularly at high doses 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, 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).

Formoterol fumarate:

Hypersensitivity reactions (including hypotension, urticaria, angioneurotic oedema, pruritus, exanthema), QTc interval prolongation, hypokalaemia, nausea, myalgia, increased blood lactate levels. Treatment with β_2 agonists such as formoterol may result in an increase in blood levels of insulin, free fatty acids, glycerol and ketone bodies.

In the unlikely event of a hypersensitivity reaction to Fixed dose combination (Formoterol Fumarate and Fluticasone Propionate), treatment should be initiated in accordance with standard treatment for any other hypersensitivity

reaction, which may include the use of antihistamines and other treatment as required. Fixed dose combination (Formoterol Fumarate and Fluticasone Propionate) may need to be discontinued immediately and an alternative asthma therapy may need to be initiated if necessary.

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 anti-fungal therapy whilst continuing the treatment with Fixed dose combination (Formoterol Fumarate and Fluticasone Propionate).

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) <https://pv.pharmacyboardkenya.org>

4.9 Overdose

There are no data available from clinical trials on overdose with Fixed dose combination (Formoterol Fumarate and Fluticasone Propionate), 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 β_2 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 cardio selective 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 Fixed dose combination (Formoterol Fumarate and Fluticasone Propionate) 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Drugs for obstructive airways, adrenergics in combination with corticosteroids or other drugs excl. anticholinergics

ATC code: R03AK11

Mechanism of Action and Pharmacodynamic Effects

Fixed dose combination (Formoterol Fumarate and Fluticasone Propionate) contains both fluticasone propionate and formoterol fumarate. The mechanisms of action are described below for the individual components. These drugs represent two classes of medications (a synthetic corticosteroid and a selective, long-acting β_2 adrenergic receptor agonist) and as with other inhaled corticosteroid and long-acting β_2 adrenergic agonist combinations additive effects are seen in terms of a reduction in asthma exacerbations.

Fluticasone propionate

Fluticasone propionate is a synthetic, trifluorinated glucocorticoid with potent

anti-inflammatory activity in the lungs when given by inhalation. Fluticasone propionate reduces symptoms and exacerbations of asthma with less adverse effects than when corticosteroids are administered systemically.

Formoterol fumarate

Formoterol fumarate is a long-acting selective β_2 adrenergic receptor agonist. Inhaled formoterol fumarate acts locally in the lung as a bronchodilator. The onset of bronchodilating effect is rapid, within 1 - 3 minutes, and the duration of effect is at least 12 hours after a single dose.

Clinical study

In 12-week clinical trials in adults and adolescents, the addition of formoterol to fluticasone propionate improved asthma symptoms and lung function and reduced exacerbations. Therapeutic effect of the combination of fluticasone propionate and formoterol fumarate exceeded that of fluticasone propionate alone. There are no long-term data comparing the combination of fluticasone propionate and formoterol fumarate with fluticasone propionate.

In an 8-week clinical trial the effect on lung function with combination of fluticasone propionate and formoterol fumarate was at least equal to that of the combination of fluticasone propionate and formoterol fumarate when administered as separate inhalers. Long-term comparative data of the combination of fluticasone propionate and formoterol fumarate versus fluticasone propionate and formoterol fumarate are not available. There were no signs of attenuation of therapeutic effects of combination of fluticasone propionate and formoterol fumarate in trials lasting up to 12 months including adult and adolescent patients.

Dose-response trends for combination of fluticasone propionate and formoterol fumarate were evident for symptom-based endpoints, with incremental benefits from high versus low dose

combination of fluticasone propionate and formoterol fumarate being most likely in patients with more severe asthma.

5.2 Pharmacokinetic properties

Fluticasone propionate:

Absorption

Following inhalation, systemic absorption of fluticasone propionate occurs mainly through the lungs and has been shown to be linearly related to dose over the dose range 500 to 2000 micrograms. Absorption is initially rapid then prolonged.

Published studies using oral dosing of labelled and unlabelled drug have demonstrated that the absolute oral systemic bioavailability of fluticasone propionate is negligible (<1%) due to a combination of incomplete absorption from the GI tract and extensive first-pass metabolism.

Distribution

Following intravenous administration, fluticasone propionate is extensively distributed in the body. The initial disposition phase for fluticasone propionate is rapid and consistent with its high lipid solubility and tissue binding. The volume of distribution averages 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 and is not significantly bound to human transcortin.

Biotransformation

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 very high clearance rate indicates extensive hepatic clearance. The only circulating metabolite detected in man is the 17 β -carboxylic acid derivative of fluticasone propionate, which is formed through the cytochrome P450 3A4 isoform subfamily (CYP 3A4) pathway. This metabolite has less affinity (approximately 1/2000) than the parent drug for the glucocorticoid receptor of human lung cytosol *in vitro*. Other metabolites detected *in vitro* using cultured human hepatoma cells have not been detected in man.

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 shows polyexponential kinetics and has a terminal elimination half-life of approximately 7.8 hours. Less than 5% of a radiolabelled dose is excreted in the urine as metabolites, and the remainder is excreted in the faeces as parent drug and metabolites.

Formoterol fumarate:

Data on the plasma pharmacokinetics of formoterol were collected in healthy volunteers after inhalation of doses higher than the recommended range and in COPD patients after inhalation of therapeutic doses.

Absorption

Following inhalation of a single 120 microgram dose of formoterol fumarate by healthy volunteers, formoterol was rapidly absorbed into plasma, reaching a maximum concentration of 91.6 pg/mL within 5 minutes of inhalation. In

COPD patients treated for 12 weeks with formoterol fumarate 12 or 24 micrograms b.i.d. the plasma concentrations of formoterol ranged between 4.0 and 8.9 pg/mL and 8.0 and 17.3 pg/mL respectively at 10 minutes, 2 hours and 6 hours post inhalation.

Studies investigating the cumulative urinary excretion of formoterol and/or its (RR) and (SS)-enantiomers, after inhalation of dry powder (12 - 96 micrograms) or aerosol formulations (12-96 micrograms), showed that absorption increased linearly with the dose.

After 12 weeks administration of 12 micrograms or 24 micrograms formoterol powder b.i.d., 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, suggesting a modest and self-limiting accumulation of formoterol in plasma after repeated dosing.

Distribution

The plasma protein binding of formoterol is 61 - 64% (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 microgram dose.

Biotransformation

Formoterol is eliminated primarily by metabolism, direct glucuronidation being the major pathway of biotransformation, with O-demethylation followed by further glucuronidation being another pathway. Minor pathways involve sulphate conjugation of formoterol and deformylation followed by sulphate conjugation. Multiple isozymes catalyze the glucuronidation (UGT1A1, 1A3, 1A6, 1A7, 1A8, 1A9, 1A10, 2B7 and 2B15) and O-demethylation (CYP 2D6, 2C19, 2C9 and 2A6) of formoterol, and so consequently the potential for metabolic drug-drug interaction is low. Formoterol did not inhibit cytochrome P450 isozymes at therapeutically relevant concentrations. The kinetics of formoterol is similar after single and repeated administration, indicating no auto-induction or inhibition of metabolism.

Elimination

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 ^3H -formoterol, 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.

Fluticasone propionate/formoterol fumarate combination

A number of studies have examined the pharmacokinetic characteristics of fluticasone propionate and formoterol fumarate from fixed dose combination (Formoterol fumarate and Fluticasone propionate) compared with the individual components, given both together and separately.

There is a high variability both within and between the pharmacokinetic studies however, in general there is a trend for the systemic exposure of fluticasone and formoterol to be less from this fixed combination of fluticasone propionate and formoterol fumarate than from the individual components given together.

Pharmacokinetic equivalence between fixed dose combination (Formoterol fumarate and Fluticasone propionate) and the constituent monoproducts has not been demonstrated. Long-term comparative data of fixed dose combination (Formoterol fumarate and Fluticasone propionate) versus fluticasone propionate and formoterol fumarate are not available.

Absorption

Fixed dose combination (Formoterol fumarate and Fluticasone propionate) - fluticasone propionate

Following inhalation of a single 250 microgram dose of fluticasone propionate from 2 actuations of fixed dose combination (Formoterol fumarate and Fluticasone propionate) 125 microgram/5 microgram by healthy volunteers

fluticasone propionate was rapidly absorbed into the plasma, reaching a mean maximum plasma fluticasone concentration of 32.8 pg/mL within 45 minutes of inhalation. In asthma patients who received single doses of fluticasone propionate from fixed dose combination (Formoterol fumarate and Fluticasone propionate), mean maximum plasma concentrations of 15.4 pg/mL and 27.4 pg/mL were achieved within 20 minutes and 30 minutes for 100 microgram/10microgram (2 actuations of fixed dose combination of Formoterol fumarate and Fluticasone propionate 50 microgram/5 microgram inhaler) and 250 microgram/10 microgram (2 actuations of fixed dose combination of Formoterol fumarate and Fluticasone propionate 125 microgram/5 microgram inhaler) doses respectively.

In multiple dose studies in healthy volunteers, fixed dose combination (Formoterol fumarate and Fluticasone propionate) doses of 100 microgram/10 micrograms, 250 microgram/10 microgram and 500 microgram/20 microgram resulted in mean maximum plasma fluticasone concentrations of 21.4, 25.9 to 34.2 and 178 pg/mL respectively. The data for the 100 microgram/10 microgram and 250 microgram/10 microgram doses were generated by use of a device without a spacer and the data for the 500 microgram/20 microgram dose were generated by use of a device with a spacer. Use of a device plus spacer increases mean systemic (which equates to pulmonary absorption) bioavailability of fluticasone by 35% in healthy volunteers compared to administration of fixed dose combination (Formoterol fumarate and Fluticasone propionate) via a pMDI alone.

Fixed dose combination (Formoterol fumarate and Fluticasone propionate) - formoterol fumarate

Following a single dose of Fixed dose combination (Formoterol fumarate and Fluticasone propionate) in healthy volunteers, a dose of 20 micrograms of formoterol fumarate from 2 actuations of Fixed dose combination (Formoterol fumarate and Fluticasone propionate) 250 microgram/10 microgram inhaler resulted in a mean maximum plasma formoterol concentration of 9.92 pg/mL within 6 minutes of inhalation. Following multiple doses, 20 micrograms of formoterol fumarate from 2 actuations of Fixed dose combination (Formoterol fumarate and Fluticasone propionate) 250 microgram/10 microgram inhaler resulted in a mean maximum plasma formoterol concentration of 34.4 pg/mL.

Use of a device plus spacer decreases mean systemic bioavailability of formoterol by 25% in healthy volunteers compared to administration of Fixed dose combination (Formoterol fumarate and Fluticasone propionate) via a pMDI alone. This is likely to be due to a reduction in absorption from the gastrointestinal tract when the spacer is used, offsetting the expected corresponding increase in pulmonary absorption.

Distribution

There is currently no plasma protein binding information specific to fluticasone propionate or formoterol fumarate from fixed dose combination (Formoterol fumarate and Fluticasone propionate).

Biotransformation

There are currently no data relating to the metabolism of fluticasone propionate or formoterol fumarate specifically from the inhalation of fixed dose combination (Formoterol fumarate and Fluticasone propionate).

Elimination

Fluticasone propionate

Following inhalation of fluticasone propionate from 2 actuations of fixed dose combination (Formoterol fumarate and Fluticasone propionate) 250 microgram/10 microgram, fluticasone propionate has a terminal elimination half-life of approximately 14.2 h.

Formoterol fumarate

Following inhalation of formoterol fumarate from 2 actuations of fixed dose combination (Formoterol fumarate and Fluticasone propionate) 250 microgram/10 microgram, formoterol fumarate has a terminal elimination half-life of approximately 6.5 h. Less than 2% of a single dose of formoterol fumarate from fixed dose combination (Formoterol fumarate and Fluticasone propionate) is excreted in the urine.

5.3 Preclinical safety data

The toxicity observed in animal studies with formoterol fumarate and fluticasone propionate, given in combination or separately consisted mainly of effects associated with exaggerated pharmacological activity. Effects on the cardiovascular system are related to formoterol administration and included hyperaemia, tachycardia, arrhythmias and myocardial lesions. Neither increase in toxicity nor occurrence of unexpected findings was observed upon administration of the combination.

Reproduction studies in rats and rabbits with fluticasone propionate and formoterol fumarate confirmed the known embryo-fetal effects of the two individual components including fetal growth retardation, incomplete ossification, embryo lethality, cleft palate, oedema and skeletal variations. These effects were seen at lower exposures than those expected by using the clinical maximum recommended dose. A somewhat reduced fertility in male rats was observed at very high systemic exposure to formoterol.

Neither formoterol fumarate nor fluticasone propionate were found to be genotoxic in standard *in vitro* and *in vivo* tests, when tested individually. No carcinogenicity studies have been performed with the combination. No carcinogenic potential has been identified for fluticasone propionate. A slight increase in the incidence of benign tumours was observed in the reproductive tract of female mice and rats following administration of formoterol. This effect is looked upon as a class effect in rodents after long exposure to high doses of β_2 agonists and does not suggest any potential risk of carcinogenicity in man.

Pre-clinical studies with HFA 227 reveal no special hazard for man based on studies of repeated-dose toxicity, genotoxicity, carcinogenicity and toxicity to reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose Monohydrate, Isopropyl Alcohol, Methylene Chloride.

6.2 Incompatibilities

None reported.

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store below 30°C. Protect from heat and moisture.

6.5 Nature and contents of container

30 Size "3", capsule with orange red colored imprinted with logo "G", "F+F" and "12+250" in black on cap and clear transparent body, filled with white to off white powder are packed in one PP container and closed with cap having inbuilt silica gel. Label on each container. Two such containers are packed in one printed carton along with one instahaler – P device and one leaflet.

6.6 Special precautions for disposal

No special requirements

7. MARKETING AUTHORISATION HOLDER

Glenmark Pharmaceuticals
Ltd. B/2, Mahalaxmi
Chambers,
22, Bhulabhai Desai road,
Mumbai – 400 026.

Manufactured at:

Glenmark Pharmaceuticals Ltd.
Unit- III, Village Kishanpura, Baddi- Nalagarh
Road, Tehsil Baddi, Distt. Solan (H.P.) 173 205

8. MARKETING AUTHORISATION NUMBER

H2015/CTD2678/300

9. DATE OF MARKETING AUTHORISATION/RENEWAL OF THE AUTHORISATION

August 2023

10. DATE OF REVISION OF THE TEXT

August 2023, 12th August 2026