Professional Information

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

TIZAGLENN CO 12 µg/ 250 µg (Powder for inhalation)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TIZAGLENN CO: Each capsule contains formoterol fumarate 12 µg and fluticasone propionate 250 µg.

Contains sugar: lactose monohydrate 24,74 mg per capsule.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for inhalation (capsules).

Inhalation device with 2 bottles containing 30 capsules each.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TIZAGLENN CO is intended for the regular treatment of bronchial asthma in adults over 18 years of age:

- in patients with inadequate disease control on monotherapy with inhaled corticosteroids and 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.

4.2 Posology and method of administration

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Posology:

TIZAGLENN CO is for oral inhalation use only.

The recommended dose for adults over 18 years of age is one **TIZAGLENN CO** capsule by oral inhalation 12 hourly.

There are no data available for use in children.

Special populations

Elderly patients

The normal adult dosage is applicable.

Renal patients

The normal adult dosage is applicable.

Hepatic patients

No dose adjustment is required in patients with hepatic impairment. As formoterol is primarily eliminated via hepatic metabolism, an increased exposure can be expected in patients with severe liver diseases (see section 5.2).

Method of administration:

Do not swallow capsules as the intended effects on the lungs will not be obtained, capsules should only be used with the inhaler device.

The amount of medicine delivered to the lungs will depend on patient factors, such as inspiratory flow and peak inspiratory flow (PIF) through the delivery system, which may vary for COPD and other patient populations under posology and method of administration.

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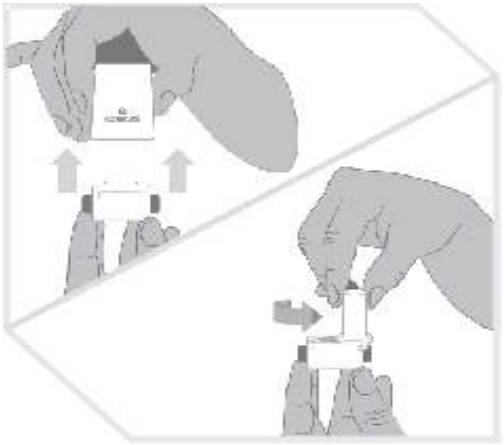
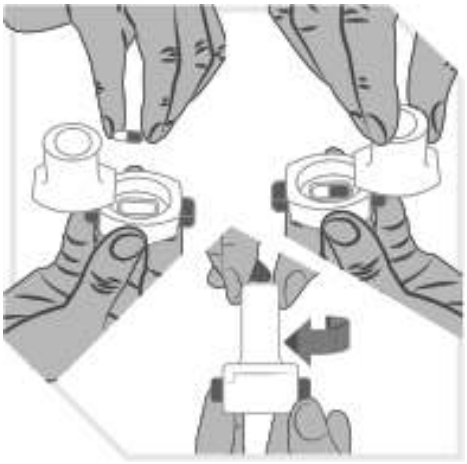
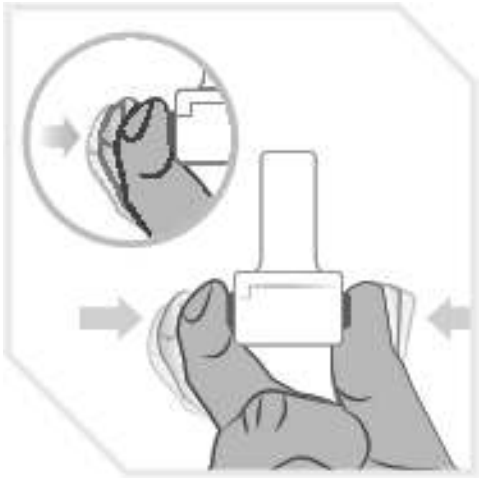
1. Remove the protective cover from device. Hold the base firmly and turn the mouthpiece in the direction given on the device.



2. Insert the capsule into the slot in the chamber. Rotate the mouthpiece back in position to close the device.



3. Hold the lever between your thumb and index finger. In order to evenly puncture the capsule, make sure that you push both the buttons inwards, simultaneously.



4. Breathe out (exhale) as much air as you can – Your lungs should be as empty as possible right before you breathe in your medicine.

5. Grip the mouthpiece between your teeth and close your lips firmly around the device so that no air or medicine can escape out. Tilt your head upwards.

6. Using only your mouth, breathe in deep and fast. Continue breathing in, until your lungs are completely full of air.

7. Take your mouth off the mouthpiece and hold your breath for 10 seconds or as long as possible. Slowly breathe out through your nose. Check that the capsule is empty and the total dose is consumed. If any dose remains in the capsule, repeat steps until you have taken the number of doses, as prescribed by your doctor. Ensure that you leave an interval of 1 minute between two doses.

8. Remove the empty capsule and put the protective cover back. Store in safe and dry place.

9. After taking the dose, rinse your mouth and brush your teeth.

4.3 Contraindications

TIZAGLENN CO is contraindicated in patients with:

- known hypersensitivity to formoterol fumarate or fluticasone propionate or to any of the excipients in the **TIZAGLENN CO** formulation (see *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.

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TIZAGLENN CO should not be used to treat acute asthma symptoms. Patients should be advised to have their 'reliever' medicine available at all times, in case required for relief in an acute asthma attack.

The prophylactic use of **TIZAGLENN CO** 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 **TIZAGLENN CO** maintenance dose as prescribed, even when asymptomatic.

Patients should not be initiated on **TIZAGLENN CO** 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 **TIZAGLENN CO.** Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation on **TIZAGLENN CO**.

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 **TIZAGLENN CO** has failed to give adequate control of asthma. Consideration should be given to additional corticosteroid therapies.

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Once asthma symptoms are controlled, consideration may be given to gradually reducing the dose of **TIZAGLENN CO**. Regular review of patients as treatment is stepped down is important. The lowest effective dose of **TIZAGLENN CO** should be used (see section 4.2).

Treatment with **TIZAGLENN CO** should not be stopped abruptly due to risk of exacerbation. Therapy should be downtitrated under the supervision of a doctor.

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, **TIZAGLENN CO** 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 **TIZAGLENN CO** is being used.

TIZAGLENN CO 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 β2 agonists. Concomitant treatment of β2 agonists with medicines 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 β2 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 β2 agonists, additional blood sugar controls should be considered in diabetic patients.

Care should be taken when transferring patients to **TIZAGLENN CO** therapy, particularly if there is any reason to suppose that adrenal function is impaired from previous systemic steroid 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. **TIZAGLENN CO** 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. 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 (see section 4.5).

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

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.

Excipients

TIZAGLENN CO contains lactose monohydrate up to 27,74 mg/capsule. This amount does not normally cause problems in lactose intolerant people. The excipient lactose contains small amounts of milk proteins, which may cause allergic reactions.

4.5 Interaction with other medicines and other forms of interaction

No formal drug interaction studies have been performed with **TIZAGLENN CO**.

Fluticasone propionate:

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 ECG changes and/or hypokalaemia that may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by β agonists, especially when the recommended dose of the β agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the co-administration of a β agonist with non-potassium sparing diuretics. Xanthine derivates and glucocorticosteroids may add to a possible hypokalaemic effect of the β agonists.

In addition, L-Dopa, L-thyroxine, oxytocin and alcohol can impair cardiac tolerance towards β2 sympathomimetics.

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

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

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

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

Formoterol fumarate:

Formoterol fumarate 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 medicines known to prolong the QTc interval such as antipsychotics (including phenothiazines), quinidine, disopyramide, procainamide, and antihistamines. Medicines that are known to prolong the QTc interval can increase the risk of ventricular arrhythmias.

If additional adrenergic medicines 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, in pregnant women.

The use of **TIZAGLENN CO** is not recommended during pregnancy.

Because of the potential for β agonist interference with uterine contractility, use of **TIZAGLENN CO** for management of asthma during labour should be restricted.

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.

Fertility

There are no data available on effects of **TIZAGLENN CO** on fertility. 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

TIZAGLENN CO is unlikely to produce an effect, as it has no or negligible influence on the ability to drive and use machines.

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4.8 Undesirable effects

a. Tabulated summary of adverse reactions

Undesirable effects which have been associated with **TIZAGLENN CO** 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 (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1,000 and <1/100), rare (≥1/10,000 < 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.

Table 1: TIZAGLENN CO adverse reactions

MedDRA SOC	**Frequency**	**Adverse events**
Infections and Infestations	Rare	Oral candidiasis Oral fungal infections Sinusitis
Metabolism and Nutrition Disorders	Rare	Hyperglycaemia
Psychiatric Disorders	Uncommon	Sleep disorders including insomnia
	Rare	Abnormal dreams Agitation
	Not known	Psychomotor hyperactivity, anxiety, depression, aggression, behavioural changes (predominantly in children)
Nervous System Disorders	Uncommon	Headache Tremor Dizziness
	Rare	Dysgeusia
Eye disorders	Not known	Vision blurred

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Ear and labyrinth disorders	Rare	Vertigo
Cardiac Disorders	Uncommon	Palpitations Ventricular extrasystoles
	Rare	Angina pectoris Tachycardia
Vascular disorders	Rare	Hypertension
Respiratory, Thoracic and Mediastinal Disorders	Uncommon	Exacerbation of asthma Dysphonia Throat irritation
	Rare	Dyspnoea Cough
Gastrointestinal disorders	Uncommon	Dry mouth
	Rare	Diarrhoea Dyspepsia
Skin and subcutaneous tissue disorders	Uncommon	Rash
	Rare	Pruritus
Musculoskeletal and Connective Tissue Disorders	Rare	Muscle spasms
General disorders and administration site conditions	Rare	Peripheral oedema Asthenia

Description of selected adverse reactions

Since **TIZAGLENN CO** contains both fluticasone propionate and formoterol fumarate, the same pattern of undesirable effects as reported for these individual medicines may occur. The following undesirable effects are associated with fluticasone propionate and formoterol fumarate, but have not been seen during the clinical development of **TIZAGLENN CO**:

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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 β2 agonists such as formoterol may result in an increase in blood levels of insulin, free fatty acids, glycerol and ketone bodies.

In the event of a hypersensitivity reaction to **TIZAGLENN CO** 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. **TIZAGLENN CO** 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 **TIZAGLENN CO**.

<u>Reporting of suspected adverse reactions</u>

Professional Information

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/ risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

There are no data available from clinical trials on overdose with **TIZAGLENN CO**, however, data on overdose with both individual components are given below:

Formoterol fumarate:

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

Treatment of formoterol overdose consists of discontinuation of the medication together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of 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 **TIZAGLENN CO** has to be withdrawn due to overdose of the β agonist component of the medicine, provision of appropriate replacement steroid therapy should be considered. Serum potassium levels should be monitored as hypokalaemia can occur. Potassium replacement should be considered.

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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

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A. 21.5.4 Corticosteroids - Other combinations.

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

ATC Code: R03AK11

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 β2 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, using the press-and-breathe inhaler, 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 using the press-and-breathe inhaler 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 press-and-breathe inhaler versus fluticasone propionate and formoterol fumarate are not available. There were no signs of

attenuation of therapeutic effects of the press-and-breathe inhaler in trials lasting up to 12 months including adult and adolescent patients.

Dose-response trends for the press-and-breathe inhaler were evident for symptom-based endpoints, with incremental benefits from high versus low dose the press-and-breathe inhaler being most likely in patients with more severe asthma.

A single dose pharmacokinetic/ pharmacodynamic study was performed to compare the pharmacokinetics and pharmacodynamics of fluticasone propionate and formoterol fumarate delivered by fixed dose combination and by the press-and-breathe combined inhaler (with and without spacer). The pharmacokinetic data from this study is discussed in *Section 5.2*. The pharmacodynamic part of the study evaluated the effect of formoterol fumarate delivered by the breath-triggered inhaler on serum potassium, serum glucose, heart rate, systolic blood pressure and diastolic blood pressure. For each of these parameters, formoterol fumarate delivered by the breath-triggered inhaler was found to have effects of a magnitude which were not clinically relevant and intermediate between those of the press-and-breathe inhaler with and without a spacer

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.

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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, 1093 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 17β-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:

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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 µg 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 µg 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 µg) or aerosol formulations (12-96 µg), showed that absorption increased linearly with the dose.

After 12 weeks administration of 12 µg or 24 µg 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 µg dose.

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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 µg. 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 µg) 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

Two single-dose pharmacokinetic studies have been performed to investigate the pharmacokinetics of fluticasone propionate and formoterol fumarate delivered by fixed dose combination (Formoterol fumarate and Fluticasone propionate). The first study compared the pulmonary bioavailability of fluticasone propionate and formoterol fumarate delivered by either fixed dose combination (Formoterol fumarate and Fluticasone propionate) or the press-and-breathe inhaler (with and without spacer) whilst using a charcoal block method to prevent formoterol absorption from the gastrointestinal tract. The second study compared the total systemic bioavailability of fluticasone propionate and formoterol fumarate delivered by fixed dose combination (Formoterol fumarate and Fluticasone propionate) with that delivered by the press-and-breathe inhaler (with and without spacer),and included a pharmacodynamic comparison stage if pharmacokinetic equivalence failed to be demonstrated for either of the components.

These studies demonstrated that the pulmonary bioavailability of and total systemic exposure to fluticasone propionate with usage of fixed dose combination (Formoterol fumarate and Fluticasone propionate) is intermediate between that attained with the press-and-breathe inhaler with and without spacer. The pulmonary bioavailability of formoterol with usage of fixed dose combination (Formoterol fumarate and Fluticasone propionate) is greater than that attained with the press-and-breathe inhaler, and equivalent to that attained with the press-and-breathe inhaler plus spacer. Total systemic exposure to formoterol with the fixed dose combination (Formoterol fumarate and Fluticasone propionate) is similar to that with the press-and-breathe inhaler (although bioequivalence was not confirmed), and greater than attained with the press-and-breathe inhaler plus spacer (which precludes appreciable oral absorption of formoterol). Overall these data,

supplemented by pharmacodynamic safety data, indicate that fixed dose combination (Formoterol fumarate and Fluticasone propionate) will have an efficacy and safety profile consistent with that demonstrated for the fluticasone propionate and formoterol fumarate press-and-breathe inhaler, with and without a spacer.

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

Fluticasone propionate

Following inhalation of a 250 µg dose of fluticasone propionate from 2 actuations of fixed dose combination (Formoterol fumarate and Fluticasone propionate) 125 µg /5 µg by healthy volunteers who had previously been administered a charcoal block, fluticasone propionate was rapidly absorbed into the plasma, mean maximum plasma fluticasone concentration of 25,0 pg/mL occurred approximately 1,3 hours after inhalation.

Following inhalation of a 250 µg dose of fluticasone propionate from 2 actuations of fixed dose combination (Formoterol fumarate and Fluticasone propionate) 125 µg /5 µg by healthy volunteers, fluticasone propionate was rapidly absorbed into the plasma, mean maximum plasma fluticasone concentration of 17,6 pg/mL occurred at 1,25 hours after inhalation.

Formoterol fumarate

Following inhalation of a 10 µg dose of formoterol fumarate from 2 actuations of fixed dose combination (Formoterol fumarate and Fluticasone propionate) 125 µg /5 µg by healthy volunteers who had previously been administered a charcoal block, mean maximum plasma formoterol

concentration of 7,8 pg/mL occurred approximately 6 minutes after inhalation, representing formoterol fumarate bioavailability from pulmonary absorption.

Following inhalation of a 10 µg dose of formoterol fumarate from 2 actuations of fixed dose combination (Formoterol fumarate and Fluticasone propionate) 125 µg /5 µg by healthy volunteers, mean maximum plasma formoterol concentration of 6,0 pg/mL occurred approximately 10 minutes after inhalation, representing formoterol fumarate bioavailability from both pulmonary and gastrointestinal 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 2 actuations of fixed dose combination (Formoterol fumarate and Fluticasone propionate) 125 µg /5 µg, fluticasone propionate has a terminal elimination half-life of approximately 13 h.

Formoterol fumarate

Professional Information

Following inhalation of 2 actuations of fixed dose combination (Formoterol fumarate and Fluticasone propionate) 125 µg /5 µg, formoterol fumarate has a terminal elimination half-life of approximately 9,2 h.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C. Keep the container tightly closed in its original package.

6.5 Nature and contents of container

Available as 30 capsules with one silica gel canister packed in a white, opaque HDPE round container and induction sealed. Such two HDPE containers are packed in a carton with a device and pack insert.

Dry Powder Inhaler device: Made up of material ABS (Acrylonitrile Butadiene Styrene). Consisting of cap & body fitted with piercing needles.

6.6 Special precautions for disposal and other handling

No special requirements. Any unused product or waste material should be disposed of in accordance with local requirements.

Professional Information

7. HOLDER OF CERTIFICATE OF REGISTRATION

Glenmark Pharmaceuticals South Africa (Pty) Ltd

2nd Floor, Building D,

Stoneridge Office Park,

8 Greenstone Place,

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Gauteng, 1609

8. REGISTRATION NUMBER(S)

57/10.2.1/0339

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22 April 2025

10. DATE OF REVISION OF TEXT

27 November 2024