Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Iffeza 125 microgram/5 microgram per metered dose pressurised inhalation, suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each metered dose (ex-valve) contains:

125 micrograms of fluticasone propionate and 5 micrograms of formoterol fumarate dihydrate. This is equivalent to a delivered dose (ex-actuator) of approximately 115 microgram of fluticasone propionate/4.5 microgram of formoterol fumarate dihydrate.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Pressurised inhalation, suspension

The canister contains white to off white liquid suspension. The canister is in a white actuator with a grey integrated dose indicator and a light grey mouthpiece cover.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

This fixed-dose combination of fluticasone propionate and formoterol fumarate (Iffeza inhaler) is indicated in the regular treatment of asthma where the use of a combination product (an inhaled corticosteroid and a long-acting β_2 agonist) is appropriate:

- For patients not adequately controlled with inhaled corticosteroids and 'as required' inhaled short-acting β_2 agonist.

  Or
- For patients already adequately controlled on both an inhaled corticosteroid and a long-acting β_2 agonist.

Iffeza 125 microgram /5 microgram inhaler is indicated in adults and adolescents aged 12 years and above.

4.2 Posology and method of administration

Posology

For inhalation use.

Patients will need to be trained on the use of the inhaler and their asthma should be regularly reassessed by a doctor, so that the strength of Iffeza inhaler they are receiving remains optimal and is only changed on medical advice. The dose should be titrated to the lowest dose at which effective control of symptoms is maintained. Once control of asthma is achieved with the lowest strength of Iffeza inhaler administered twice daily treatment should be reviewed and consideration given as to whether patients should be stepped down to an inhaled corticosteroid alone. As a general principle the dose should be titrated to the lowest dose at which effective control of symptoms is maintained. Regular review of patients as treatment is stepped down is extremely important.

There are no data available for use of Iffeza inhaler in patients with COPD. Iffeza inhaler should not be used in patients with COPD.

Patients should be given the strength of Iffeza inhaler containing the appropriate fluticasone propionate dosage for the severity of their disease. Note: Iffeza 50 microgram/5 microgram per metered dose, strength is not appropriate in adults and adolescents with severe asthma. Prescribers should be aware that, in patients with asthma, fluticasone propionate is as effective as some other inhaled steroids when administered at approximately half the total daily dose (in micrograms). If an individual patient should require doses outside the recommended dose regimens, appropriate doses of the β_2 agonist and the inhaled corticosteroid in separate inhalers, or appropriate doses of the inhaled corticosteroid alone, should be prescribed.

Iffeza inhaler is delivered by a press-and-breathe pressurised metered dose inhaler (pMDI) which also contains an integrated dose indicator. Each inhaler will provide at least 120 actuations (60 doses).

Recommended dose for adults and adolescents aged 12 years and above:
Iffeza 125 microgram/5 microgram inhaler - two inhalations (puffs) twice daily normally taken in the morning and in the evening.

Patients may be transferred to a lower strength of this combination product i.e. Iffeza 50 microgram/5 microgram inhaler, if their asthma is adequately controlled. A patient's dose should be titrated to the lowest dose at which effective control of symptoms is maintained.

For adults only:
The total daily dose can be further increased if asthma still remains poorly controlled by administering the highest strength of this combination product – i.e. Iffeza 250 microgram/10 microgram inhaler- two inhalations (puffs) twice daily. This highest strength is for use in adults only, it should not be used in adolscents aged 12 years and above.

Children under 12 years:
No data are available for this strength of Iffeza inhaler in children. Experience in children under the age of 12 years is limited (see sections 4.4, 4.8, 5.1 & 5.3). Iffeza inhaler in any strength is not recommended for use in children less than 12 years of age; **Iffeza inhaler should not be used in this young age group**.

Special patient groups:
There is no need to adjust the dose in elderly patients.

There are no data available for use of Iffeza inhaler in patients with hepatic or renal impairment (see section 5.2). These patients should be regularly monitored by a physician to ensure titration to the lowest dose at which effective control of symptoms is maintained. 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.

General information:
Inhaled corticosteroids alone are the first line of treatment for most patients. Iffeza inhaler is not intended for the initial treatment of mild asthma. For patients with severe asthma the inhaled corticosteroid therapy should be established before prescribing a fixed-dose combination product.

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

Patients using Iffeza inhaler should not use additional long-acting β_2 agonists for any reason. If asthma symptoms arise in the period between doses, an inhaled, short-acting β_2 agonist should be taken for immediate relief.

For patients who are currently receiving medium to high doses of inhaled corticosteroid therapy, and whose disease severity clearly warrants treatment with two maintenance therapies, the recommended starting dose is two inhalations twice daily of Iffeza 125 microgram /5 microgram inhaler.

Use of a spacer device with Iffeza inhaler is recommended in patients who find it difficult to synchronise aerosol actuation with inspiration of breath. The AeroChamber Plus is the only spacer device recommended for use with Iffeza inhaler.

Patients should be instructed in the proper use and care of their inhaler and spacer and their technique checked to ensure optimum delivery of the inhaled drug to the lungs.

Re-titration to the lowest effective dose should always follow the introduction of a spacer device.

Method of administration

To ensure proper administration of the drug, the patient should be shown how to use the inhaler correctly by a physician or other health professionals. The correct use of the pressurised metered dose inhaler (pMDI) is essential for successful treatment. The patient should be advised to read the Patient Information Leaflet carefully and follow the instructions for use and pictograms in the leaflet.

The actuator has an integrated dose indicator which counts down the number of actuations (puffs) remaining. When this is getting near to zero the patient should be advised to contact their prescriber for a replacement inhaler. The inhaler must not be used after the dose indicator reads “0”.

Priming the inhaler

Before using the inhaler for the first time, or if the inhaler has not been used for 3 days or more, or after exposure to freezing or refrigerated conditions (see section 6.4) the inhaler must be primed before use:

- Remove the mouthpiece cover and shake the inhaler well.
- Actuate (puff) the inhaler whilst pointing it away from the face. This step must be performed 4 times.
- The inhaler should always be shaken immediately before use.

Whenever possible patients should stand or sit in an upright position when inhaling from the inhaler.

Steps to follow when using the inhaler:

1. Remove the mouthpiece cover and check that the mouthpiece is clean, and free from dust and dirt. The inhaler should be shaken immediately before releasing each actuation (puff).
2. Breathe out as far as is comfortable and as slowly and deeply as possible.
3. Hold the canister vertically with its body upwards and put the lips around the mouthpiece. Hold the inhaler upright with a thumb(s) on the base of the mouthpiece and a forefinger/index finger(s) on the top of the inhaler. Do not bite the mouthpiece.
4. At the same time, breathe in slowly and deeply through the mouth. After starting to breathe in press down on the top of the inhaler to release one actuation (puff) and continue to breathe in steadily and deeply.
5. Patients should continue to hold their breath for as long as is comfortable (optimally about 10 seconds), then breathe out slowly. Do not breathe out into the inhaler.
6. Keep the inhaler in a vertical position for about half a minute, shake the inhaler, and repeat steps 2 to 5.
7. After use, replace the mouthpiece cover

IMPORTANT: Do not perform steps 2 to 5 too quickly.

Patients may be advised to practise their technique in front of a mirror. If a mist appears following inhalation, either from the inhaler or from the sides of the mouth, the procedure should be repeated from step 2.

For patients with weak hands, it may be easier to hold the inhaler with both hands. Therefore the index fingers should be placed on the top of the inhaler canister and both thumbs on the base of the inhaler.

Patients should rinse their mouth, gargle with water or brush the teeth after inhaling and spit out the residue to minimise the risk of oral candidiasis or dysphonia.

Cleaning:

Patients should be advised to read the Patient Information Leaflet carefully for cleaning instructions:

The inhaler should be cleaned once a week.

- Remove the mouthpiece cover.
- Do not remove the canister from the plastic casing.
- Wipe the inside and outside of the mouthpiece and the plastic casing with a dry cloth or tissue.
- Replace the mouthpiece cover in the correct orientation.
- Do not put the metal canister into water.

If a patient requires an AeroChamber Plus spacer device then they must be advised to read the instructions provided by the manufacturer to ensure they use it and clean and maintain it properly.

4.3 Contraindications

Hypersensitivity to any of the active substances or to any of the excipients (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.

Iffeza 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 medicine to be used for relief in an acute asthma attack available at all times.

The prophylactic use of Iffeza inhaler 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 Iffeza inhaler maintenance dose as prescribed, even when asymptomatic.

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

Serious asthma-related adverse events and exacerbations may occur during treatment with Iffeza inhaler. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation on Iffeza inhaler.

Iffeza inhaler 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 Iffeza inhaler 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 Iffeza inhaler. Regular review of patients as treatment is stepped down is important. The lowest effective dose of Iffeza inhaler should be used (see section 4.2).

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

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, Iffeza inhaler 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 Iffeza inhaler is being used.

Iffeza inhaler 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 Iffeza 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. Iffeza inhaler should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.

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 (see section 4.5).

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.

Patients should be advised that the Iffeza inhaler contains a small amount of ethanol (approximately 1.00 mg per actuation); however this amount of ethanol is negligible and does not pose a risk to patients.

Paediatric population
It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids is regularly monitored. If growth is slowed, therapy should be reviewed with the aim of reducing the dose of inhaled corticosteroid, if possible, to the lowest dose at which effective control of asthma is maintained. In addition, consideration should be given to referring the patient to a paediatric respiratory specialist.
Only limited data are available in respect of the use of Iffeza inhaler in children under 12 years of age. Iffeza inhaler is NOT recommended for use in children under 12 years of age until further data become available.

4.5 Interaction with other medicinal products and other forms of interaction

No formal drug interaction studies have been performed with Iffeza inhaler.

Iffeza inhaler contains sodium cromoglicate at non-pharmacological levels. Patients should not discontinue any cromoglicate containing medication.

Fluticasone propionate, an individual component of Iffeza, is a substrate of CYP 3A4. The effects of short-term co-administration of strong CYP 3A4 inhibitors (e.g. ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nelfinavir, saquinavir, ketoconazole, telithromycin) together with Iffeza is of minor clinical relevance, but caution needs to be taken in long-term treatment and co-administration with such drugs should be avoided if possible. Particularly co-medication of ritonavir should be avoided unless the benefit outweighs the increased risk of systemic glucocorticoid side-effects. Information about this interaction is lacking for inhaled fluticasone propionate, but a marked increase in fluticasone propionate plasma levels is expected. Cases of Cushing's syndrome and adrenal suppression have been reported.

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 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 extreme 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 (see section 4.4).

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, Iffeza in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Administration of Iffeza inhaler 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 agonists interference with uterine contractility, use of Iffeza inhaler for management of asthma during labour should be restricted to those patients in whom the benefit outweighs the risks.

Lactation
It is not known whether fluticasone propionate or formoterol fumarate are excreted in human breast milk. A risk to the suckling child cannot be excluded. Therefore, a decision must be made whether to discontinue breastfeeding or to discontinue/abstain from Iffeza 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 Iffeza. In animal studies, no effects on fertility have been seen following administration of the individual active substances at clinically relevant doses (see section 5.3).

4.7 Effects on ability to drive and use machines

Iffeza has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Undesirable effects which have been associated with Iffeza inhaler 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.

System Organ Class	Adverse Event	Frequency
Infections and Infestations	Oral candidiasis Acute sinusitis	Rare
Metabolism and Nutrition Disorders	Hyperglycaemia	Uncommon
Psychiatric Disorders	Abnormal dreams Agitation Insomnia	Rare
	Psychomotor hyperactivity, anxiety, depression, aggression, behavioural changes (predominantly in children)	Not known
Nervous System Disorders	Headache Tremor Dizziness Dysgeusia	Uncommon
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	Rare
Musculoskeletal and Connective Tissue Disorders	Muscle spasms	Rare
General disorders and administration site conditions	Peripheral oedema	Uncommon
	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. Iffeza inhaler should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.

Since Iffeza inhaler 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 Iffeza inhaler:

Fluticasone propionate: Hypersensitivity reactions including, urticaria, pruritus, angiooedema (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, sleep disorders, contusion, skin atrophy and susceptibility to infections. The ability to adapt to stress may be impaired. The systemic effects described, however, are much less likely to occur with inhaled corticosteroids than with oral corticosteroids. Prolonged treatment with high doses of inhaled corticosteroids may result in clinically significant adrenal suppression and acute adrenal crisis. Additional systemic corticosteroid cover may be required during periods of stress (trauma, surgery, infection).

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.

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

In the unlikely event of a hypersensitivity reaction to Iffeza inhaler, 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. Iffeza inhaler 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 Iffeza inhaler.

4.9 Overdose

There are no data available from clinical trials on overdose with Iffeza inhaler; however, data on overdose with both single drugs are given below:

Formoterol fumarate:
An overdose of formoterol would likely lead to an exaggeration of effects that are typical for 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 Iffeza 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 (see section 4.4).

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: Formoterol and other drugs for obstructive airways diseases

ATC code: R03AK07

Mechanism of Action and Pharmacodynamic Effects
Iffeza inhaler 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 agonists 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.

Iffeza
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 Iffeza exceeded that of fluticasone propionate alone. There are no long-term data comparing Iffeza with fluticasone propionate.

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

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

Paediatric population

In a 12-week paediatric study including a 6-month extension phase for long-term safety 210 children aged 4 − 12 years were treated with a maintenance dose of Iffeza inhaler (2 inhalations of 50/5 micrograms twice daily) or with a fixed combination comparator drug. Lung function was at least equal to that of the fixed combination comparator drug during the 12-week study duration. Following the 12-week core phase, patients could enter into a 6-month extension phase. Two hundred and five patients treated with Iffeza inhaler completed the 6-month extension phase during which Iffeza was safe and well tolerated.

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.

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 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:

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.

Metabolism
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 ^{3}H-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.

<u>Iffeza - (fluticasone propionate/formoterol fumarate combination)</u>

A number of studies have examined the pharmacokinetic characteristics of fluticasone propionate and formoterol fumarate from Iffeza 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 Iffeza and the constituent monoproducts has not been demonstrated. Long-term comparative data of Iffeza versus fluticasone proprinate and formoterol fumerate are not available (see section 5.1).

Absorption

Iffeza – fluticasone propionate

Following inhalation of a single 250 microgram dose of fluticasone propionate from 2 actuations of Iffeza 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 Iffeza, 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/10 microgram (2 actuations of Iffeza 50 microgram/5 microgram) and 250 microgram/10 microgram (2 actuations of Iffeza 125 microgram/5 microgram) doses respectively.

In multiple dose studies in healthy volunteers, Iffeza inhaler doses of 100 microgram/10 microgram, 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 an AeroChamber Plus spacer increases mean systemic (which equates to pulmonary absorption) bioavailability of fluticasone by 35% in healthy volunteers compared to administration of Iffeza inhaler via a pMDI alone.

Use of an AeroChamber Plus spacer decreases mean systemic bioavailability of formoterol by 25% in healthy volunteers compared to administration of Iffeza inhaler 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.

Iffeza – formoterol fumarate

Following a single dose of Iffeza inhaler in healthy volunteers, a dose of 20 micrograms of formoterol fumarate from 2 actuations of Iffeza 250 microgram/10 microgram 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 Iffeza 250 microgram/10 microgram resulted in a mean maximum plasma formoterol concentration of 34.4 pg/mL.

Distribution

There is currently no plasma protein binding information specific to fluticasone propionate or formoterol fumarate from Iffeza.

Metabolism

There are currently no data relating to the metabolism of fluticasone propionate or formoterol fumarate specifically from the inhalation of Iffeza.

Elimination

Fluticasone propionate

Following inhalation of fluticasone propionate from 2 actuations of Iffeza 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 Iffeza 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 Iffeza 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 Iffeza 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

Sodium Cromoglicate
Ethanol Anhydrous
Apaflurane HFA 227

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 Years
In use shelf – life: 3 months after opening the foil pouch.

6.4 Special precautions for storage

Do not store above 25°C. Do not refrigerate or freeze. If the inhaler is exposed to freezing conditions then the patient must be advised to allow the inhaler to warm at room temperature for 30 minutes then re−prime the inhaler (see section 4.2).
The canister contains a pressurised liquid. Do not expose to temperatures higher than 50°C. Do not puncture, break or burn, even when apparently empty

6.5 Nature and contents of container

120 actuations per inhaler

The actuator is white with a grey integrated dose indicator and a light grey mouthpiece cover. The suspension is contained in an aluminium pressurised canister crimped with a standard metering valve. This canister is inserted into a press-and-breathe actuator fitted with a mouthpiece cover (both made of polypropylene) and an integrated dose indicator which indicates the number of actuations (puffs) remaining. Each container delivers 120 actuations. The assembled MDI inhaler is pouched in an aluminium foil laminate and is packed in a cardboard carton.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

For detailed instructions on the use of the medicinal product refer to section 4.2 (posology and method of administration).

7 MARKETING AUTHORISATION HOLDER

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10 DATE OF REVISION OF THE TEXT