Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Fostair 200 microgram/6 microgram per actuation pressurised inhalation solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each metered dose (ex-valve) contains:
200 micrograms of beclometasone dipropionate and 6 micrograms of formoterol fumarate dihydrate. This is equivalent to a delivered dose (ex-actuator) of 177.7 micrograms of beclometasone dipropionate and 5.1 micrograms of formoterol fumarate dihydrate.
For the full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Pressurised inhalation solution.
The canister contains a colourless to yellowish solution.
The canisters are fitted into a plastic actuator incorporating a mouthpiece and fitted with dust cap.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Fostair is indicated in the regular treatment of asthma where use of a combination product (inhaled corticosteroid and long-acting beta$_2$-agonist) is appropriate:
-patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled rapid-acting beta$_2$-agonist or
-patients already adequately controlled on both inhaled corticosteroids and long-acting beta$_2$-agonists.
Fostair is indicated in adults.

4.2 Posology and method of administration

Fostair is for inhalation use.
Posology

Asthma
Fostair is not intended for the initial management of asthma. The dosage of the components of Fostair is individual and should be adjusted to the severity of the disease. This should be considered not only when treatment with combination products is initiated but also when the dose is adjusted. If an individual patient should require a combination of doses other than those available in the combination inhaler, appropriate doses of beta$_2$-agonists and/or corticosteroids by individual inhalers should be prescribed.

Beclometasone dipropionate in Fostair is characterised by an extrafine particle size distribution which results in a more potent effect than formulations of beclometasone dipropionate with a non-extrafine particle size distribution (100 micrograms of beclometasone dipropionate extrafine in Fostair are equivalent to 250 micrograms of beclometasone dipropionate in a non-extrafine formulation). Therefore the total daily dose of beclometasone dipropionate administered in Fostair should be lower than the total daily dose of beclometasone dipropionate administered in a non-extrafine beclometasone dipropionate formulation.

This should be taken into consideration when a patient is transferred from a beclometasone dipropionate non-extrafine formulation to Fostair; the dose of beclometasone dipropionate should be lower and will need to be adjusted to the individual needs of the patients.

There are two treatment approaches:

A. Maintenance therapy: Fostair is taken as regular maintenance treatment with a separate as needed rapid-acting bronchodilator.

B. Maintenance and reliever therapy: Fostair is taken as regular maintenance treatment and as needed in response to asthma symptoms.

A. Maintenance therapy

Patients should be advised to have their separate rapid-acting bronchodilator available for rescue use at all times.

Dose recommendations for adults 18 years and above:

One or two inhalations twice daily.

The maximum daily dose is 4 inhalations.

B. Maintenance and reliever therapy

Patients take their daily maintenance dose of Fostair and in addition take Fostairas needed in response to asthma symptoms. Patients should be advised to always haveFostair available for rescue use.

Fostairmaintenance and reliever therapy should especially be considered for patients with :

• not fully controlled asthma and in need of reliever medication

• asthma exacerbations in the past requiring medical intervention

Close monitoring for dose-related adverse effects is needed in patients who frequently take high numbers of Fostair as-needed inhalations.

Dose recommendations for adults 18 years and above:

The recommended maintenance dose is 1 inhalation twice daily (one inhalation in the morning and one inhalation in the evening).

Patients should take 1 additional inhalation as needed in response to symptoms. If symptoms persist after a few minutes, an additional inhalation should be taken.

The maximum daily dose is 8 inhalations.

Patients requiring frequent use of rescue inhalations daily should be strongly recommended to seek medical advice. Their

asthma should be reassessed and their maintenance therapy should be reconsidered.

Dose recommendations for children and adolescents under 18 years:

The safety and efficacy of Fostair in children and adolescents under 18 years of age have not been established. Data available with Fostair in children between 5 and 11 years of age and adolescents between 12 and 17 years of age are described in section 4.8, 5.1 and 5.2, but no recommendation on a posology can be made.

Patients should be regularly reassessed by a doctor, so that the dosage of Fostair 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. When control of symptoms is maintained with the lowest recommended dosage, then the next step could include a test of inhaled corticosteroid alone.

Patients should be advised to take Fostair every day even when asymptomatic.

COPD

Dose recommendations for adults 18 years and above:

Two inhalations twice daily.

Special patient groups:

There is no need to adjust the dose in elderly patients. There are no data available for use of Fostair in patients with hepatic or renal impairment (see section 5.2).

Method of admnistration

To ensure proper administration of the drug, the patient should be shown how to use the inhaler correctly by a physician or other health professional. Correct use of the pressurised metered dose inhaler is essential in order that treatment is successful. The patient should be advised to read the Patient Information Leaflet carefully and follow the instructions for use as given in the Leaflet.

Fostair inhaler is provided with a counter on the back of the actuator, which shows how many doses are left. For the 120 doses presentation each time the patient presses the canister, a puff of medicine is released and the counter counts down by one. For the 180 presentation, each time the patient presses the canister the counter rotates by a small amount and the number of puffs remaining is displayed in intervals of 20. Patients should be advised not to drop the inhaler as this may cause the counter to count down.

Testing the inhaler

Before using the inhaler for the first time or if the inhaler has not been used for 14 days or more, the patient should release one actuation into the air in order to ensure that the inhaler is working properly (priming). Before priming the 120 or 180 actuation pressurised containers, the counter/indicator should read 121 or 180, respectively. After testing the inhaler for the first time, the counter should read 120 or 180.

Whenever possible patients shouldstand or sit in an upright position when inhaling from their inhaler.

Use of the inhaler: 1. Patients should remove the protective cap from the mouthpiece and check that the mouthpiece is clean and free from dust and dirt or any other foreign objects.

2. Patients should breathe out as slowly and deeply as possible.

3. Patients should hold the canister vertically with its body upwards and put the lips around the mouthpiece without biting the mouthpiece

4. At the same time, patients should breathe in slowly and deeply through the mouth. After starting to breathe in, they should press down on the top of the inhaler to release one puff.

5. Patients should hold the breath for as long as possible and, finally, they should remove the inhaler from the mouth and breathe out slowly. Patients should not breathe out into the inhaler.

To inhale a further puff , patients should keep the inhaler in a vertical position for about half a minute and repeat steps 2 to 5.

IMPORTANT: patients should not perform steps 2 to 5 too quickly.

After use, patients should close the inhaler with protective cap and check the dose counter.

Patients should be advised to get a new inhaler when the dose counter or indicator shows the number 20. They should stop using the inhaler when the counter shows 0 as any puffs left in the device may not be enough to release a full dose.

If 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 or gargle with water or brush the teeth after inhaling (see section 4.4).

Cleaning

Patients should be advised to read the Patient Information Leaflet carefully for cleaning instructions. For the regular cleaning of the inhaler, patients should remove the cap from the mouthpiece and wipe the outside and inside of the mouthpiece with a dry cloth. They should not remove the canister from the actuator and should not use water or other liquids to clean the mouthpiece.

Patients who find it difficult to synchronise aerosol actuation with inspiration of breath, may use the AeroChamber Plus® spacer device. They should be advised by their doctor, pharmacist or a nurse 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. This may be obtained by the patients using the AeroChamber Plus® by one continuous slow and deep breath through the spacer, without any delay between actuation and inhalation.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Fostair should be used with caution (which may include monitoring)in patients with cardiac arrhythmias, especially third degree atrioventricular block and tachyarrhythmias, idiopathic subvalvular aortic stenosis, hypertrophic obstructive cardiomyopathy, ischaemic heart disease, severe heart failure, severe arterial hypertension and aneurysm.

Caution should also be observed when treating patients with known or suspected prolongation of the QTc interval, either congenital or drug induced (QTc > 0.44 seconds). Formoterol itself may induce prolongation of the QTc interval.

Caution is also required when Fostair is used by patients with thyrotoxicosis, diabetes mellitus, phaeochromocytoma and untreated hypokalaemia.

Potentially serious hypokalaemia may result from $beta_2$-agonist therapy. Particular caution is advised in severe asthma as this effect may be potentiated by hypoxia.Hypokalaemia may also be potentiated by concomitant treatment with other drugs which can induce hypokalaemia, such as xanthine derivatives, steroids and diuretics (see Section 4.5). Caution is also recommended in unstable asthma when a number of "rescue" bronchodilators may be used. It is recommended that serum potassium levels are monitored in such situations.

The inhalation of formoterol may cause a rise in blood glucose levels. Therefore blood glucose should be closely monitored in patients with diabetes.

If anaesthesia with halogenated anaesthetics is planned, it should be ensured that Fostair is not administered for at least 12 hours before the start of anaesthesia as there is a risk of cardiac arrhythmias.

As with all inhaled medication containing corticosteroids, Fostair should be administered with caution in patients with active or quiescent pulmonary tuberculosis, fungal and viral infections in the airways.

It is recommended that treatment with Fostair should not be stopped abruptly.
If patients find the treatment ineffective medical attention must be sought. Increasing use of rescue bronchodilators indicates a worsening of the underlying condition and warrants a reassessment of the asthma therapy. 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 the need for increased treatment with corticosteroids, either inhaled or oral therapy, or antibiotic treatment if an infection is suspected.

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

As with other inhalation therapy paradoxical bronchospasm may occur with an immediate increase in wheezing and rapidness of breath after dosing. This should be treated immediately with a fast-acting inhaled bronchodilator. Fostair should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.

Fostair should not be used as the first treatment for asthma.

For treatment of acute asthma attacks patients should be advised to have their rapid-acting bronchodilator available at all times.

Patients should be reminded to take Fostair daily as prescribed even when asymptomatic.

Once asthma symptoms are controlled, consideration may be given to gradually reducing the dose of Fostair. Regular review of patients as treatment is stepped down is important. The lowest effective dose of Fostair should be used (a lower strength Fostair 100/6 is available, see also section 4.2).

Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. These effects are much less likely to occur with inhaled than with oral corticosteroids. Possible systemic effects include: Cushing's syndrome, Cushingoid features, adrenal suppression, decrease in bone mineral density, growth retardation in children and adolescents, cataract and glaucoma and more rarely, a range of psycological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children).

Therefore, it is important 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.

Single dose pharmacokinetic data (see section 5.2) have demonstrated that the use of Fostair with Aerochamber Plus® spacer device in comparison to the use of standard actuator, does not increase the total systemic exposure to formoterol and reduces the systemic exposure to beclometasone-17-monopropionate, while there is an increase for unchanged beclometasone dipropionate that reaches systemic circulation from the lung; however, since the total systemic exposure to beclometasone dipropionate plus its active metabolite does not change, there is no increased risk of systemic effects when using Fostair with the named spacer device.

Prolonged treatment of patients with high doses of inhaled corticosteroids may result in adrenal suppression and acute adrenal crisis. Children aged less than 16 years taking/inhaling higher than recommended doses of beclometasone dipropionate may be at particular risk. 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 cover should be considered during periods of stress or elective surgery.

Care should be taken when transferring patients to Fostair therapy, particularly if there is any reason to suppose that adrenal function is impaired from previous systemic steroid therapy.

Patients transferring from oral to inhaled corticosteroids may remain at risk of impaired adrenal reserve for a considerable time. Patients who have required high dose emergency corticosteroid therapy in the past or have received prolonged treatment with high doses of inhaled corticosteroids 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.

Patients should be advised to rinse the mouth or gargle with water or brush the teeth after inhaling the prescribed dose to minimise the risk of oropharyngeal candida infection.

Fostair contains a small amount of ethanol (alcohol), 9 mg per actuation, which is equivalent to 0,25 mg/kg per dose of two actuations. At normal doses the amount of ethanol is negligible and does not pose a risk to patients.

Visual disturbance

Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation

of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions
Beclometasone dipropionate undergoes a very rapid metabolism via esterase enzymes.
Beclometasone is less dependent on CYP3A metabolism than some other corticosteroids, and in general interactions are unlikely; however the possibility of systemic effects with concomitant use of strong CYP3A inhibitors (e.g. ritonavir, cobicistat) cannot be excluded, and therefore caution and appropriate monitoring is advised with the use of such agents.

Pharmacodynamic interactions
Beta-adrenergic blockers can weaken or inhibit the effect of formoterol. Fostair should therefore not be given together with beta-adrenergic blockers (including eye drops) unless there are compelling reasons.

On the other hand, concomitant use of other beta-adrenergic drugs can have potentially additive effects, therefore caution is required when theophylline or other beta-adrenerigic drugs are prescribed concomitantly with formoterol.
Concomitant treatment with quinidine, disopyramide, procainamide, phenothiazines, antihistamines, monoamine oxidase inhibitors and tricyclic antidepressants can prolong the QTc-interval and increase the risk of ventricular arrhythmias.

In addition, L-dopa, L-thyroxine, oxytocin and alcohol can impair cardiac tolerance towards beta$_2$-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 treatment with xanthine derivatives, steroids, or diuretics may potentiate a possible hypokalaemic effect of beta$_2$-agonists (see section 4.4.). Hypokalaemia may increase the disposition towards arrhythmias in patients who are treated with digitalis glycosides.
Fostair contains a small amount of ethanol. There is a theoretical potential for interaction in particularly sensitive patients taking disulfiram or metronidazole.

4.6 Fertility, pregnancy and lactation

Fertility
There are no data in humans. In animal studies in rats, the presence of beclometasone dipropionate at high doses in the combination was associated with reduced female fertility and embryotoxicity (see section 5.3).

Pregnancy
There is no experience with or evidence of safety of propellant HFA-134a in human pregnancy or lactation. However studies of the effect of HFA-134a on reproductive function and embryofetal development in animals have revealed no clinically relevant adverse effects.
There are no relevant clinical data on the use of Fostair in pregnant women. Animal studies using beclometasone dipropionate and formoterol combination showed evidence of toxicity to reproduction after high systemic exposure (see 5.3 Preclinical safety data). Because of the tocolytic actions of beta2-sympathomimetic agents particular care should be exercised in the run up to delivery. Formoterol should not be recommended for use during pregnancy and particularly at the end of pregnancy or during labour unless there is no other (safer) established alternative.
Fostair should only be used during pregnancy if the expected benefits outweigh the potential risks.

Breast feeding
There are no relevant clinical data on the use of Fostair in lactation in humans.
Although no data from animal experiments are available, it is reasonable to assume that beclometasone dipropionate is secreted in milk, like other corticosteroids.
While it is not known whether formoterol passes into human breast milk, it has been detected in the milk of lactating animals.
Administration of Fostair to women who are breast-feeding should only be considered if the expected benefits outweigh the potential risks.
A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Fostair therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

4.7 Effects on ability to drive and use machines

Fostair is unlikely to have any effect on the ability to drive and operate machinery.

4.8 Undesirable effects

As Fostair contains beclometasone dipropionate and formoterol fumarate dihydrate, the type and severity of adverse reactions associated with each of the compounds may be expected. There is no incidence of additional adverse events following concurrent administration of the two compounds.
Undesirable effects which have been associated with beclometasone dipropionate and formoterol administered as a fixed combination (Fostair) and as single agents are given below, listed by system organ class. Frequencies are defined as: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 < 1/1,000) very rare (≥1/10,000) and not known (cannot be estimated from the available data).
Common and uncommon ADRs were derived from clinical trials in asthmatic and COPD patients.

System Organ Class	Adverse Reaction	Frequency
Infections and Infestations	**Pharyngitis, oral candidiasis**	**Common**
	Influenza, oral fungal infection, oropharyngeal candidiasis, oesophageal candidiasis, vulvovaginal candidiasis, gastroenteritis, sinusitis, rhinitis, pneumonia*	**Uncommon**
Blood and lymphatic system disorders	**Granulocytopenia**	**Uncommon**
	Thrombocytopenia	**Very rare**
Immune system disorders	**Dermatitis allergic**	**Uncommon**
	Hypersensitivity reactions, including erythema, lips, face, eye and pharyngeal oedema	**Very rare**
Endocrine disorders	**Adrenal suppression**	**Very rare**
Metabolism and nutrition disorders	**Hypokalaemia, hyperglycaemia**	**Uncommon**
Psychiatric disorders	**Restlessness**	**Uncommon**
	Psychomotor hyperactivity, sleep disorders, anxiety, depression, aggression, behavioural changes(predominantly in children)	**Not known**
Nervous system disorders	**Headache**	**Common**
	Tremor, dizziness	**Uncommon**
Eye disorders	**Glaucoma, cataract**	**Very rare**
	Vision, blurred (see also section 4.4)	**Not known**
Ear and labyrinth disorders	**Otosalpingitis**	**Uncommon**
Cardiac disorders	**Palpitations, electrocardiogram QT corrected interval prolonged, electrocardiogram change, tachycardia, tachyarrhythmia, atrial fibrillation*,**	**Uncommon**
	Ventricular extrasystoles, angina pectoris	**Rare**
Vascular disorders	**Hyperaemia, flushing**	**Uncommon**
Respiratory, thoracic and mediastinal disorders	**Dysphonia**	**Common**

	Cough, productive cough, throat irritation, asthmatic crisis, pharyngeal erythema	**Uncommon**
	Bronchospasm paradoxical	**Rare**
	Dyspnoea, exacerbation of asthma	**Very rare**
Gastrointestinal disorders	**Diarrhoea, dry mouth, dyspepsia, dysphagia, burning sensation of the lips, nausea, dysgeusia**	**Uncommon**
Skin and subcutaneous tissue disorders	**Pruritus, rash, hyperhidrosis, urticaria**	**Uncommon**
	Angioedema	**Rare**
Musculoskeletal and connective tissue disorders	**Muscle spasms, myalgia**	**Uncommon**
	Growth retardation in children and adolescents	**Very rare**
Renal and urinary disorders	**Nephritis**	**Rare**
General disorders and administration site conditions	**Oedema peripheral**	**Very rare**
Investigations	**C-reactive protein increased, platelet count increased, free fatty acids increased, blood insulin increased, blood ketone body increased, blood cortisol decrease***	**Uncommon**
	Blood pressure increased	**Uncommon**
	Blood pressure decreased	**Rare**
	Bone density decreased	**Very rare**

* One related non serious case of pneumonia was reported by one patient treated with Fostair100/6 in a pivotal clinical trial in COPD patients. Other adverse reactions observed with Fostair 100/6 in COPD clinical trials were: reduction of blood cortisol and atrial fibrillation.

As with other inhalation therapy, paradoxical bronchospasm may occur (see 4.4 'Special Warnings and Precautions for Use').
Among the observed adverse reactions those typically associated with formoterol are:
hypokalaemia, headache, tremor, palpitations, cough, muscle spasms and prolongation of QTc interval.
Adverse reactions typically associated with the administration of beclometasone dipropionate are:
oral fungal infections, oral candidiasis, dysphonia, throat irritation.
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 Fostair.
Systemic effects of inhaled corticosteroids (e.g. beclometasone dipropionate) may occur particularly when administered at high doses prescribed for prolonged periods, these may include adrenal suppression, decrease in bone mineral density, growth retardation in children and adolescents, cataract and glaucoma (see also 4.4).
Hypersensitivity reactions including rash, urticaria pruritus, erhythema and oedema of the eyes, face, lips and throat may also occur.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Inhaled doses of Fostair 100/6 up to twelve cumulative actuations (total beclometasone dipropionate 1200 micrograms, formoterol 72 micrograms) have been studied in asthmatic patients. The cumulative treatments did not cause abnormal effect on vital signs and neither serious nor severe adverse events were observed.

Excessive doses of formoterol may lead to effects that are typical of $beta_2$-adrenergic agonists: nausea, vomiting, headache, tremor, somnolence, palpitations, tachycardia, ventricular arrhythmias, prolongation of QTc interval, metabolic acidosis, hypokalaemia, hyperglycaemia.

In case of overdose of formoterol, supportive and symptomatic treatment is indicated. Serious cases should be hospitalised. Use of cardioselective beta-adrenergic blockers may be considered, but only subject to extreme caution since the use of beta-adrenergic blocker medication may provoke bronchospasm.Serum potassium should be monitored.

Acute inhalation of beclometasone dipropionate doses in excess of those recommended may lead to temporary suppression of adrenal function. This does not need emergency action as adrenal function recovers in a few days, as verified by plasma cortisol measurements. In these patients treatment should be continued at a dose sufficient to control asthma.
Chronic overdose of inhaled beclometasone dipropionate: risk of adrenal suppression (see section 4.4.). Monitoring of adrenal reserve may be necessary. Treatment should be continued at a dose sufficient to control asthma.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for obstructive airway diseases; Adrenergics, inhalants
ATC-code: R03 AK08.
Mechanisms of action and pharmacodynamic effects
Fostair contains beclometasone dipropionate and formoterol. These two actives have different modes of action. In common with other inhaled corticosteroids and beta$_2$-agonist combinations, additive effects are seen in respect of reduction in asthma exacerbations.

Beclometasone dipropionate
Beclometasone dipropionate given by inhalation at recommended doses has a glucocorticoid antiinflammatory action within the lungs, resulting in reduced symptoms and exacerbations of asthma with less adverse effects than when corticosteroids are administered systemically.

Formoterol
Formoterol is a selective beta$_2$-adrenergic agonist that produces relaxation of bronchial smooth muscle in patients with reversible airways obstruction. The bronchodilating effect sets in rapidly, within 1-3 minutes after inhalation, and has a duration of 12 hours after a single dose.

Clinical efficacy and safety for Fostair
In clinical trials in adults, the addition of formoterol to beclometasone dipropionate improved asthma symptoms and lung function and reduced exacerbations.
In a 24-week study the effect on lung function of Fostair 100/6 HFA was at least equal to that of the free combination of beclometasone dipropionate and formoterol and exceeded that of beclometasone dipropionate alone.

The efficacy of Fostair 200/6 HFA, 2 puffs twice a day, was evaluated in a 12-week pivotal trial comparing the effect on lung function versus treatment with beclometasone dipriopionate monotherapy in asthmatic patients not adequately controlled with previous treatment (high dose ICS or medium dose-ICS+LABAs combinations). The study demonstrated the superiority of Fostair 200/6 HFA compared to BDP HFA in terms of change from baseline in the average pre-dose morning PEF (adjusted mean difference 18.53 L).

In a 24-week pivotal trial the safety profile of Fostair 200/6 HFA, 2 puffs twice a day, was comparable to that of an approved fixed dose combination (fluticasone/salmeterol 500/50, 1 puff twice daily). No clinically relevant effect was observed with Fostair 200/6 HFA on the HPA axis after 6 months of treatment. The study showed that both Fostair 200/6 µg and the approved fixed dose combination were not superior to non extrafine beclometasone dipriopionate monotherapy (2000 µg/day) on the change in pre-dose morning FEV_1 and percentage of complete days without asthma symptoms.

5.2 Pharmacokinetic properties

The systemic exposure to the active substances beclometasone dipropionate and formoterol in the fixed combination Fostair have been compared to the single components.

In a pharmacokinetic study conducted in healthy subjects treated with a single dose of Fostair fixed combination (4 puffs of 100/6 micrograms) or a single dose of beclometasone dipropionate CFC (4 puffs of 250 micrograms) and Formoterol HFA (4 puffs of 6 micrograms), the Area Under the Curve (AUC) of beclometasone dipropionate main active metabolite (beclometasone-17-monopropionate) and its maximal plasma concentration were, respectively, 35% and 19% lower with the

fixed combination than with non-extrafine beclometasone dipropionate CFC formulation, in contrast, the rate of absorption was more rapid (0.5 vs 2h) with the fixed combination compared to non-extrafine beclometasone dipropionate CFC formulation alone.
For formoterol, maximal plasma concentration was similar after administration of the fixed or the extemporary combination and the systemic exposure was slightly higher after administration of Fostair than with the extemporary combination.

There was no evidence of pharmacokinetic or pharmacodynamic (systemic) interactions between beclometasone dipropionate and formoterol.
A pharmacokinetic study conducted in healthy volunteers with activated charcoal blockade demonstrated that the lung bioavailability of beclometasone-17-monopropionate in the Fostair 200/6 formulation is dose proportional with respect to that of the 100/6 strength for AUC only {mean ratio between systemic bioavailability in the 200/6 formulation and in the 100/6 strength equal to 91.63 (90 % Confidence Interval: 83.79; 100.20)}. For formoterol fumarate the mean ratio between systemic bioavailability in the 200/6 formulation and in the 100/6 strength was equal to 86.15 (90% Confidence Interval: 75.94; 97.74).

In another pharmacokinetic study conducted in healthy volunteers without charcoal blockade, the systemic exposure of beclometasone-17-monopropionate in the Fostair 200/6 formulation was shown to be dose proportional with respect to that of the 100/6 strength {mean ratio between systemic bioavailability in the 200/6 formulation and in the 100/6 strength equal to 89.2 (90 % Confidence Interval: 79.8; 99.7)}. The total systemic exposure of formoterol fumarate was unchanged; {mean ratio between systemic bioavailability in the 200/6 formulation and in the 100/6 strength equal to 102.2 (90% Confidence Interval: 90.4; 115.5)}.

The use of Fostair 200/6 with Aerochamber Plus® spacer increased the lung delivery of beclometasone dipropionate active metabolite beclometasone 17-monopropionate and formoterol in healthy volunteers by 25 % and 32 % respectively,while the total systemic exposure was slightly reduced for beclometasone 17-monopropionate (by 17%)and formoterol (by 17%)and increased for unchanged beclometasone dipropionate (by 54%).

Beclometasone dipropionate

Beclometasone dipropionate is a pro-drug with weak glucocorticoid receptor binding affinity that is hydrolysed via esterase enzymes to an active metabolite beclometasone-17-monopropionate which has a more potent topical anti-inflammatory activity compared with the pro-drug beclometasone dipropionate.

Absorption, distribution and biotransformation

Inhaled beclometasone dipropionate is rapidly absorbed through the lungs; prior to absorption there is extensive conversion to its active metabolite beclometasone-17-monopropionate via esterase enzymes that are found in most tissues. The systemic availability of the active metabolite arises from lung (36 %) and from gastrointestinal absorption of the swallowed dose. The bioavailability of swallowed beclometasone dipropionate is negligible however, pre-systemic conversion to beclometasone-17-monopropionate results in 41%of the dose being absorbed as the active metabolite.
There is an approximately linear increase in systemic exposure with increasing inhaled dose.
The absolute bioavailability following inhalation is approximately 2% and 62% of the nominal dose for unchanged beclometasone dipropionate and beclometasone-17-monopropionate respectively.
Following intravenous dosing, the disposition of beclometasone dipropionate and its active metabolite are characterised by high plasma clearance (150 and 120L/h respectively), with a small volume of distribution at steady state for beclometasone dipropionate (20L) and larger tissue distribution for its active metabolite (424L).
Plasma protein binding is moderately high.

<u>Elimination</u>
Faecal excretion is the major route of beclometasone dipropionate elimination mainly as polar metabolites. The renal excretion of beclometasone dipropionate and its metabolites is negligible. The terminal elimination half-lives are 0.5 h and 2.7 h for beclometasone dipropionate and beclometasone-17-monopropionate respectively.

Special populations

The pharmacokinetics of beclometasone dipropionate in patients with renal or hepatic impairment has not been studied; however, as beclometasone dipropionate undergoes a very rapid metabolism via esterase enzymes present in intestinal fluid, serum, lungs and liver, to originate the more polar products beclometasone-21-monopropionate, beclometasone-17-monopropionate and beclometasone, hepatic impairment is not expected to modify the pharmacokinetics and safety profile of beclometasone dipropionate.
As beclometasone dipropionate or its metabolites were not traced in the urine, an increase in systemic exposure is not envisaged in patients with renal impairment.

Formoterol

Absorption and distribution

Following inhalation, formoterol is absorbed both from the lung and from the gastrointestinal tract. The fraction of an inhaled dose that is swallowed after administration with a metered dose inhaler (MDI) may range between 60% and 90%. At least 65% of the fraction that is swallowed is absorbed from the gastrointestinal tract. Peak plasma concentrations of unchanged drug occur within 0.5 to 1 hours after oral administration. Plasma protein binding of formoterol is 61-64% with 34% bound to albumin. There was no saturation of binding in the concentration range attained with therapeutic doses. The elimination half-life determined after oral administration is 2-3 hours. Absorption of formoterol is linear following inhalation of 12 to 96 µg of formoterol fumarate.

Biotransformation

Formoterol is widely metabolised and the prominent pathway involves direct conjugation at the phenolic hydroxyl group. Glucuronide acid conjugate is inactive. The second major pathway involves O-demethylation followed by conjugation at the phenolic 2'-hydroxyl group. Cytochrome P450 isoenzymes CYP2D6, CYP2C19 and CYP2C9 are involved in the O-demethylation of formoterol. Liver appears to be the primary site of metabolism. Formoterol does not inhibit CYP450 enzymes at therapeutically relevant concentrations.

Elimination

The cumulative urinary excretion of formoterol after single inhalation from a dry powder inhaler increased linearly in the 12 – 96 µg dose range. On average, 8% and 25% of the dose was excreted as unchanged and total formoterol, respectively. Based on plasma concentrations measured following inhalation of a single 120 µg dose by 12 healthy subjects, the mean terminal elimination half-life was determined to be 10 hours. The (R,R)- and (S,S)-enantiomers represented about 40% and 60% of unchanged drug excreted in the urine, respectively. The relative proportion of the two enantiomers remained constant over the dose range studied and there was no evidence of relative accumulation of one enantiomer over the other after repeated dosing.
After oral administration (40 to 80 µg), 6% to 10% of the dose was recovered in urine as unchanged drug in healthy subjects; up to 8% of the dose was recovered as the glucuronide.
A total 67% of an oral dose of formoterol is excreted in urine (mainly as metabolites) and the remainder in the faeces. The renal clearance of formoterol is 150 ml/min.

Special populations

Hepatic/Renal impairment: the pharmacokinetics of formoterol has not been studied in patients with hepatic or renal impairment; however, as formoterol is primarily eliminated via hepatic metabolism, an increased exposure can be expected in patients with severe liver cirrhosis

5.3 Preclinical safety data

The toxicity observed in animal studies with beclometasone dipropionate and formoterol, given in combination or separately, consisted mainly of effects associated with exaggerated pharmacological activity. They are related to the immuno-suppressive

activity of beclometasone dipropionate and to the known cardiovascular effects of formoterol evident mainly in dogs. Neither increase in toxicity nor occurrence of unexpected findings were observed upon administration of the combination.

Reproduction studies in rats showed dose-dependent effects. The combination was associated with reduced female fertility and embryofetal toxicity. High doses of corticosteroids to pregnant animals are known to cause abnormalities of fetal development including cleft palate and intra-uterine growth retardation, and it is likely that the effects seen with the beclometasone dipropionate /formoterol combination were due to beclometasone dipropionate. These effects were noted only with high systemic exposure to the active metabolite beclometasone-17-monopropionate(200 fold the expected plasma levels in patients). Additionally, increased duration of gestation and parturition, an effect attributable to the known tocolytic effects of beta$_2$-sympathomimetics, was seen in animal studies.
These effects were already noted for maternal plasma formoterol levels below the levels expected in patients treated with Fostair.

Genotoxicity studies performed with a beclometasone dipropionate/formoterol combination do not indicate mutagenic potential. No carcinogenicity studies have been performed with the proposed combination. However animal data reported for the individual constituents do not suggest any potential risk of carcinogenicity in man.

Pre-clinical data on the CFC-free propellant HFA-134a reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Norflurane (HFA-134a)
Ethanol anhydrous
Hydrochloric acid

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

21 months

6.4 Special precautions for storage

Prior to dispensing to the patient:
Store in a refrigerator (2-8°C) (for a maximum of 18 months).

After dispensing:
Do not store above 25°C (for a maximum of 3 months).
The canister contains a pressurised liquid. Do not expose to temperatures higher than 50°C. Do not pierce the canister.

6.5 Nature and contents of container

The inhalation solution is contained in a pressurised aluminium coated container sealed with a metering valve and fitted into a polypropylene plastic actuator which incorporates a dose counter (120 doses pack) or a dose indicator (180 doses pack), and a mouthpiece and is provided with a polypropylene plastic cap.

Each pack contains:
1 pressurised container which provides 120 actuations or
2 pressurised containers which provide 120 actuations each or
1 pressurised container which provides 180 actuations

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For pharmacies:
Enter the date of dispensing to the patient on the pack.
Ensure that there is a period of at least 3 months between the date of dispensing and the expiry date printed on the pack.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Chiesi Farmaceutici S.p.A.
26A via Palermo
43122 Parma
Italy

8 MARKETING AUTHORISATION NUMBER

PA0584/008/003

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10 DATE OF REVISION OF THE TEXT

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