

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Foradil Aerolizer 12 microgram inhalation powder, hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 12 micrograms formoterol fumarate dihydrate.

Excipient(s) with known effect

Each capsule contains 25 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Inhalation powder, hard capsule.

Colourless and transparent with the markings "CG" on one part and "FXF" on the other part of the capsule.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

- Prophylaxis and treatment of bronchoconstriction in patients with asthma as an add-on to inhaled corticosteroid (ICS) treatment (see section 4.4 Special warnings and precautions for use).
- Prophylaxis of bronchospasm induced by inhaled allergens, cold air, or exercise.
- Prophylaxis and treatment of bronchoconstriction in patients with reversible or irreversible chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema.

4.2 Posology and method of administration

Posology

For inhalation use in adults and in children 6 years of age and older.

Adults

Asthma

For regular maintenance therapy, 1 to 2 inhalation capsules (equivalent to 12 to 24 micrograms formoterol) twice daily, in the morning and the evening. Foradil should only be prescribed as an add-on to an inhaled corticosteroid.

The maximum recommended maintenance dose is 48 micrograms per day.

If required, an additional 1 to 2 capsules per day may be used for the relief of ordinary symptoms provided the recommended maximum daily dose of 48 micrograms per day is not exceeded. However, if the need for additional doses is more than occasional (e.g. more frequent than 2 days per week) medical advice should be sought and therapy reassessed, as this may indicate a worsening of the underlying condition. Foradil should not be used to relieve the acute symptoms of an asthma attack. In the event of an acute attack, a short-acting beta2-agonist should be used (see section 4.4 Special warnings and precautions for use).

Prophylaxis against exercise-induced bronchospasm or before exposure to a known unavoidable allergen

The content of 1 inhalation capsule (12 microgram) should be inhaled at least 15 minutes prior to exercise or exposure. In patients with a history of severe bronchospasm, 2 inhalation capsules (24 microgram) may be necessary as prophylaxis. In patients with persistent asthma, use of Foradil for the prevention of exercise-induced bronchospasm or before exposure to a known unavoidable allergen may be clinically indicated, but the treatment of asthma should also include an ICS.

Chronic obstructive pulmonary disease

For regular maintenance therapy, 1 to 2 inhalation capsules (12 to 24 microgram) twice daily, in the morning and in the evening.

Paediatric population (Children aged 6 years or older)

Asthma

For regular maintenance therapy, 1 inhalation capsule (12 microgram) twice daily, in the morning and in the evening. Foradil should only be prescribed as an add-on to an inhaled corticosteroid.

For children 6-12 years of age, treatment with a combination product containing an inhaled corticosteroid and long-acting beta2-agonist (LABA) is recommended, except in cases where a separate inhaled corticosteroid and long-acting beta2-agonist are required (see section 4.4 Special warnings and precautions for use and section 4.8 Undesirable effects).

The maximum recommended dose is 24 microgram per day.

Foradil should not be used to relieve the acute symptoms of an asthma attack. In the event of an acute attack, a short-acting beta2-agonist should be used (see section 4.4 Special warnings and precautions for use).

Prophylaxis against exercise-induced bronchospasm or before exposure to a known unavoidable allergen

The content of 1 inhalation capsule (12 micrograms) should be inhaled at least 15 minutes prior to exercise or exposure.

In patients with persistent asthma, use of Foradil for the prevention of exercise-induced bronchospasm or before exposure to a known unavoidable allergen may be clinically indicated, but the treatment of asthma should also include an ICS.

Adults and children aged 6 years or older:

The bronchodilator effect of Foradil is still significant 12 hours after inhalation. Therefore, in most cases, twice-daily maintenance therapy will control the bronchoconstriction associated with chronic conditions, both during the day and at night.

Children under 6 years

Children up to the age of 6 years should not be treated with Foradil.

Special populations

Renal impairment

Formoterol has not been studied in patients with renal impairment (see section 5.2 Pharmacokinetic properties).

Hepatic impairment

Formoterol has not been studied in patients with hepatic impairment (see section 5.2 Pharmacokinetic properties).

Elderly population

The pharmacokinetics of formoterol has not been studied in the elderly population (See section 5.2 Pharmacokinetic properties). The available data from clinical trials performed in elderly patients do not suggest that the dosage should be different than in other adults (see section 5.2 Pharmacokinetic properties).

Method of Administration

Foradil inhalation powder capsules should be used only with the Aerolizer inhaler provided in the Foradil pack.

To ensure proper administration of the drug, a physician or other health professional should:

- Show the patient how to use the inhaler.
- Dispense the capsule only together with the inhaler.
- Instruct the patient that the capsules are only for inhalation use and not to be swallowed (see section 4.4 Special warnings and precautions for use).

Detailed handling instructions are included in the package leaflet.

The capsules should be removed from the blister pack **only immediately** before use.

4.3 Contraindications

Hypersensitivity to formoterol fumarate or to lactose (which contains small amounts of milk proteins). Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.4 Special warnings and precautions for use

Recommended dose

The dose of Foradil should be individualized to the patient's needs and should be at the lowest possible dose to fulfill the therapeutic objective. It should not be increased beyond the maximum recommended dose (see section 4.2 Posology and method of administration). Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Need for concomitant anti-inflammatory therapy in asthma

When treating patients with asthma, use Foradil, a long-acting beta2-agonist (LABA), only as an add-on to an inhaled corticosteroid (ICS) for patients who are not adequately controlled on an ICS alone or whose disease severity clearly warrants initiation of treatment with both an ICS and a LABA.

Formoterol should not be used (and is not sufficient) as the first treatment for asthma.

Asthmatic patients who require therapy with long-acting β_2 -agonists, should also receive optimal maintenance anti-inflammatory therapy with corticosteroids. Patients must be advised to continue taking their anti-inflammatory therapy after the introduction of Foradil even when symptoms decrease. Should symptoms persist or treatment with β_2 -agonists need to be increased, this indicates a worsening of the underlying condition and warrants a reassessment of the maintenance therapy.

Although Foradil may be introduced as add-on therapy when inhaled corticosteroids do not provide adequate control of asthma symptoms, patients should not be initiated on Foradil during an acute severe asthma exacerbation or if they have significantly worsening or acutely deteriorating asthma. Serious asthma-related adverse events and exacerbations may occur during treatment with Foradil. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation on Foradil. Once asthma symptoms are controlled, consideration may be given to gradually reducing the dose of Foradil. Regular review of patients as treatment is stepped down is important. The lowest effective dose of Foradil should be used.

The maximum daily dose should not be exceeded. The long term safety of regular treatment at higher doses than 36 micrograms per day in adults with asthma, 18 micrograms per day in children with asthma and 18 micrograms per day in patients with COPD has not been established. Children up to the age of 6 years should not be treated with Formoterol, as no sufficient experience is available for this group.

Foradil should not be used in conjunction with another LABA.

Whenever Foradil is prescribed, patients should be evaluated for the adequacy of the anti-inflammatory therapy they receive. Patients must be advised to continue anti-inflammatory therapy unchanged after the introduction of Foradil, even if the symptoms improve.

Once asthma symptoms are controlled, consideration may be given to gradually reducing the dose of Foradil. Regular monitoring of patients as treatment is stepped down is important. The lowest effective dose of Foradil should be used.

Asthma exacerbations

Clinical studies with Foradil suggested a higher incidence of serious asthma exacerbations in children (5-12 years) who received Foradil than in those who received placebo, particularly in patients 5-12 years of age (see section 4.8 Undesirable effects). These studies do not allow precise quantification of the differences in serious asthma exacerbation rates between treatment groups.

A physician should reassess asthma therapy if symptoms persist, or if the number of doses of Foradil required to control symptoms increase, because this usually indicates a worsening of the underlying condition.

Foradil must not be initiated or the dose increased during an asthma exacerbation.

Foradil must not be used to relieve acute asthma symptoms. In the event of an acute attack, a short-acting beta2-agonist should be used. Patients must be informed of the need to seek medical treatment immediately if their asthma deteriorates suddenly.

Frequent need of medication (i.e. prophylactic treatment e.g. corticosteroids and long-acting beta 2-agonists) for the prevention of exercise-induced bronchoconstriction several times every week, despite an adequate maintenance treatment, can be a sign of suboptimal asthma control, and warrants a reassessment of the asthma therapy and an evaluation of the compliance.

Concomitant conditions

Special care and supervision, with particular emphasis on dosage limits, is required when Foradil is given in patients with the following conditions: Ischaemic heart disease, cardiac arrhythmias (especially third-degree atrioventricular block), severe cardiac decompensation, idiopathic subvalvular aortic stenosis, severe hypertension, aneurysm, phaeochromocytoma, hypertrophic obstructive cardiomyopathy, thyrotoxicosis, tachyarrhythmias or severe heart failure, known or suspected prolongation of the QT interval ($QT_c > 0.44$ sec.; see section 4.5 Interactions with other medicinal products and other forms of interaction).

Due to the hyperglycaemic effect of beta2-stimulants, including Foradil, additional blood glucose monitoring is recommended in diabetic patients.

Hypokalaemia

Potentially serious hypokalaemia may result from beta2-agonist therapy, including Foradil. Hypokalaemia may increase susceptibility to cardiac arrhythmias. Particular caution is advised in patients with severe asthma as hypokalaemia may be potentiated by hypoxia and concomitant treatment (see section 4.5 Interactions with other medicinal product and other forms of interaction). It is recommended that serum potassium levels be monitored in such situations.

Paradoxical bronchospasm

As with other inhalation therapy, the potential for paradoxical bronchospasm should be kept in mind. If it occurs, the preparation should be discontinued immediately and alternative therapy substituted.

Incorrect route of administration

There have been reports of patients who have mistakenly swallowed Foradil capsules instead of placing the capsules in the Aerolizer inhalation device. The majority of these ingestions were not associated with side effects. Healthcare providers should discuss with the patient how to correctly use Foradil Aerolizer (see section 4.2 Posology and method of administration). If a patient who is prescribed Foradil Aerolizer does not experience breathing improvement, the healthcare provider should ask how the patient is using Foradil Aerolizer.

Excipients

Formoterol contains lactose monohydrate (less than 500 micrograms per delivered dose). This amount does not normally cause problems in lactose intolerant people. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interactions

Beta-adrenergic blockers may weaken or antagonise the effect of Foradil. Therefore Foradil should not be given together with beta-adrenergic blockers (including eye drops) unless there are compelling reasons for their use.

Foradil should be administered with caution to patients being treated with drugs such as quinidine, disopyramide, procainamide, phenothiazines, antihistamines e.g. terfenadine, astemizole and mizolastine, monoamine oxidase inhibitors, macrolides and tricyclic antidepressants or any drug known to prolong the QTc interval, because the action of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc-interval have an increased risk of ventricular arrhythmia (see section 4.4 Special warnings and precautions for use).

Concomitant treatment with other sympathomimetic substances such as β_2 -agonists or ephedrine may potentiate the undesirable effects of Foradil and may require titration of the dose.

Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate the possible hypokalaemic effect of beta2-agonists (See section 4.4 Special warnings and precautions for use). Hypokalaemia may increase susceptibility to cardiac arrhythmias in patients treated with digitalis glycosides. There is an elevated risk of cardiac arrhythmias in patients receiving concomitant anaesthesia with halogenated hydrocarbons.

The bronchodilating effects of formoterol can be enhanced by anticholinergic drugs.

4.6 Fertility, pregnancy and lactationPregnancy

There are no or limited amount of data from the use of formoterol in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Like other beta₂-adrenergic agonists, formoterol may inhibit labour due to a relaxant effect on uterine smooth muscle. This medicinal product should only be used during pregnancy if the expected benefit to the patient justifies the potential risk to the foetus.

Breast-feeding

It is not known whether formoterol is transferred into human breast milk. However, formoterol is transferred into the milk of lactating rats after oral administration (see section 5.3). A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There is no data on the effect of formoterol on human fertility. Studies in rats have shown formoterol racemate has no effects on fertility. Formoterol enantiomer showed adverse effects on fertility only at dose levels higher than the maximum human exposure to formoterol (see section 5.3).

4.7 Effects on ability to drive and use machines

Patients experiencing dizziness or other similar side effects should be advised to refrain from driving or using machines.

4.8 Undesirable effects

The most commonly reported adverse events of β_2 -agonist therapy, such as tremor and palpitations, tend to be mild and disappear within a few days of treatment.

Adverse reactions (Table 1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common ($\geq 1/10$); common ($\geq 1/100 < 1/10$); uncommon ($\geq 1/1,000, < 1/100$); rare ($\geq 1/10,000, < 1/1,000$); very rare ($< 1/10,000$); not known (cannot be estimated from the available data) including isolated reports.

Table 1

Immune system disorders		
	Rare:	Hypersensitivity (including bronchospasm, hypotension, urticaria, angioedema, pruritus, rash)
Metabolism and nutrition disorders		
	Not known:	Hypokalaemia**, hyperglycemia**
Psychiatric disorders		
	Uncommon:	Agitation, anxiety, nervousness, restlessness, sleep disturbances
Nervous system disorders		
	Common:	Headache, tremor
	Uncommon:	Dizziness,
	Very rare:	Dysgeusia
Cardiac disorders		
	Common:	Palpitations
	Uncommon:	Tachycardia
	Not known:	Cardiac arrhythmias**, e.g. atrial fibrillation, supraventricular tachycardia, extrasystoles. Angina pectoris**, electrocardiogram QT prolonged**
	Very rare:	Peripheral oedema
Respiratory, thoracic and mediastinal disorders		
	Uncommon:	Bronchospasm, including paradoxical bronchospasm, throat irritation
	Common:	Serious asthma exacerbations in children aged 5-12 years*
	Not known:	Cough**
Gastrointestinal disorders		
	Uncommon:	Dry mouth
	Rare:	Nausea
Skin and subcutaneous tissue disorders		
	Not known:	Rash**
Musculoskeletal and connective tissue disorders		
	Uncommon:	Muscle spasms, myalgia
Investigations		
	Not known:	Increased blood pressure (including hypertension)**
Vascular disorders:		
	Very Rare:	Variations in blood pressure

*An analyses of patients aged 5–12 years enrolled in Foradil asthma clinical studies demonstrated an increased risk of serious asthma exacerbations for children treated with formoterol. The rate of serious asthma exacerbations was 5.4 events per 100 patient years for children treated with formoterol compared with 0.6 events per 100 patient years for children receiving placebo.

**These adverse events were reported in patients treated with Foradil during the post-marketing phase.

As with all inhalation therapy, paradoxical bronchospasm may occur in very rare cases (see section 4.4). Treatment with β_2 -agonists may result in an increase in blood levels of insulin, free fatty acids, glycerol and ketone bodies. The excipient lactose contains small amounts of milk proteins. These may cause allergic reactions.

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, website: www.hpra.ie.

4.9 Overdose

Symptoms:

An overdose of Foradil is likely to lead to effects that are typical of beta2-adrenergic stimulants: nausea, vomiting, headache, tremor, drowsiness, palpitations, tachycardia, ventricular arrhythmias, metabolic acidosis, hypokalaemia, hyperglycaemia, prolonged QTc-interval, hypertension.

Treatment:

Supportive and symptomatic treatment is indicated. In serious cases, patients should be hospitalised.

Use of cardioselective beta-blockers may be considered, but only under the supervision of a physician and with extreme caution since the use of beta-adrenergic blocker medication may provoke bronchospasm. Serum potassium levels should be monitored.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective beta2-adrenergic agonist, ATC code: R03AC13

Formoterol is a potent selective beta2-adrenergic stimulant. It exerts a bronchodilator effect in patients with reversible airways obstruction. The effect sets in rapidly (within 1—to 3 minutes) and is still significant 12 hours after inhalation. At therapeutic doses, cardiovascular effects are minor and occur only occasionally.

Formoterol inhibits the release of histamine and leucotrienes from passively sensitised human lung. Some anti-inflammatory properties, such as inhibition of oedema and inflammatory cell accumulation, have been observed in animal experiments.

In vitro studies on guinea pig trachea have indicated that racemic formoterol and its (R,R)- and (S,S)-enantiomers are highly selective beta2-adrenoceptor agonists. The (S,S)-enantiomer was 800 to 1000 times less potent than the (R,R)-enantiomer and did not affect the activity of the (R,R)-enantiomer on tracheal smooth muscle. No pharmacological basis for the use of one of the two enantiomers in preference to the racemic mixture was demonstrated.

In man, Foradil has been shown to be effective in preventing bronchospasm induced by inhaled allergens, exercise, cold air, histamine, or methacholine.

Foradil administered by the Aerolizer inhaler at doses of 12 micrograms b.i.d. and 24 micrograms b.i.d. was shown objectively to provide rapid onset of bronchodilation in patients with stable COPD that was maintained over at least 12 hours.

Asthma

Twenty-seven internal clinical trials in a wide range of ages included pediatric, adult and elderly population. Well controlled clinical trials demonstrated the superiority of formoterol over placebo and salbutamol in the treatment of asthma with a treatment duration range of 1 day (single-dose) to 12 weeks. Moreover, 4 open-label, follow-up clinical trials including the pediatric, adult and elderly populations of these previous studies, were conducted demonstrating an acceptable efficacy and

safety profile of Foradil for an additional 12 months of treatment. Below are described 3 of the major trials that have supported the indication for formoterol in asthma in children, adults and elderly respectively.

Study DP/PD2 was a double-blind, 12-week, parallel-group, multicentre trial that assessed formoterol dry powder 12 microgram and 24 microgram daily vs. salbutamol dry powder 1200 microgram daily in 219 (age 5 – 13) children with asthma. The study concluded that formoterol dry powder 12 microgram b.i.d. administered as dry powder capsules by inhalation through the Aerolizer® device has superior bronchodilator effect when compared with salbutamol 400 microgram t.i.d. dry powder after 12 weeks of therapy as assessed by PEFR. Regarding the safety, formoterol 12 microgram b.i.d. was slightly better tolerated than salbutamol 400 microgram t.i.d. of formoterol 6 microgram b.i.d. during 3 months of treatment.

Study DP/RD1 was a placebo-controlled, multi-centre, double-blind, between-patient trial that compared multiple doses of 12 microgram formoterol dry powder with multiple doses of 400 microgram salbutamol dry powder in 304 patients (age 19–72) with asthma during a 12-week active treatment period. The study concluded that formoterol 12 microgram b.i.d. is statistically superior, both to salbutamol 400 microgram q.i.d. and placebo with regard to the primary outcome variable (morning PEFR before inhalation). Regarding the safety, formoterol 12 microgram b.i.d. was equally well tolerated as salbutamol 400 microgram q.i.d. or placebo during 3 months of treatment.

Study DP/RD3 was a multi-centre, double-blind, parallel-group trial that compared the 3-month efficacy and tolerability of inhaled formoterol 12 microgram and 24 microgram b.i.d. dry powder and salbutamol 400 microgram q.i.d. dry powder in 262 (age 64–82) elderly patients suffering from asthma. The study concluded that formoterol 12 microgram and 24 microgram b.i.d. are statistically superior to salbutamol 400 microgram q.i.d. with regard to the primary outcome variable (morning PEFR before inhalation) over 3 months. Regarding the safety, formoterol was slightly better tolerated than salbutamol.

Prophylaxis of bronchospasm induced by inhaled allergens, cold air, or exercise

Four clinical studies were performed with formoterol in patients treated for the prophylaxis of bronchospasm induced by exercise and 2 studies were performed in patients for the prophylaxis of bronchospasm induced by inhaled allergen. Three major studies supporting the Foradil indication in the prophylaxis of bronchospasm induced by inhaled allergens, cold air or exercise are described below.

Prophylaxis of exercise-induced bronchoconstriction

A single-dose, randomized, double-blind, double-dummy, 4-way crossover trial compared 12 microgram and 24 microgram of formoterol dry powder capsules, 180 microgram albuterol metered-dose inhaler versus placebo in 17 patients (age 13–50) for the prevention of exercise-induced bronchoconstriction. The study concluded that a single dose of formoterol 12 microgram or 24 microgram provides significantly greater protection against exercise-induced bronchoconstriction as assessed by FEV₁ compared with placebo at 15 minutes and 4, 8 and 12 hours after dosing. Both doses of formoterol provided significantly greater protection than albuterol at 4, 8 and 12 hours post-dose. No significant difference in efficacy was identified between formoterol 12 microgram and 24 microgram. There were less adverse events reported with formoterol 24 microgram.

Prophylaxis of allergen-induced bronchoconstriction

A randomized, placebo-controlled, within-patient, multicentre clinical trial assessed the efficacy and tolerability of a single dose of inhaled formoterol 24 microgram in protecting 24 patients (age 17–40) with asthma against allergen-induced bronchoconstriction evaluated between 3 and 32 hours after the inhalation of the trial medication. The study concluded that formoterol led to a significant and long-lasting protection against allergen-induced bronchoconstriction as assessed by FEV₁. Regarding the safety, formoterol had an excellent tolerability profile.

Prophylaxis of cold-air-induced bronchoconstriction

In a controlled study, the duration of the effect of inhaled formoterol (24 microgram) was compared with that of a placebo and that of inhaled albuterol (200 microgram) in 12 adult asthmatic subjects who underwent hyperventilation tests with cold dry air (-20 °C) on 4 study days. On the control day, they were subjected to four hyperventilation tests to ensure functional stability. On the 3 remaining days, after a first hyperventilation test, they inhaled placebo, albuterol, or formoterol in randomized, double-blind fashion. The hyperventilation test was repeated 1, 4, and 8 h and, if the blocking effect was still present, 12 and 24 h after the drug had been administered. The study concluded that the protection against bronchoconstriction, as assessed by FEV₁, induced by hyperventilation of unconditioned air in asthmatic subjects is significantly more prolonged after formoterol than after albuterol.

COPD

Two large multinational, multicenter, randomized, double-blind, parallel group, controlled trials have been carried out in the target population of patients with COPD (studies 25827 02 056 and 25827 02 058). Both were placebo-controlled and included an active comparator arm. The primary objective in both trials was to assess the efficacy of formoterol 12 µg and 24 µg twice daily by Aerolizer® device compared with placebo. In both trials further analysis was made of patients classified as "reversible" or "irreversible" at baseline based on a cut-off of 15% increase in FEV₁ 30 minutes after inhalation of 200 µg salbutamol. Approximately 50% of patients had reversible COPD in both trials.

Study 25827 02 056 was a randomized, double-blind, between-patient trial that compared two doses of inhaled formoterol fumarate dry powder (12 and 24 microgram b.i.d.) with placebo and ipratropium bromide MDI (40 microgram q.i.d.) for 12 weeks in 698 patients (age 40–87) with COPD. The study concluded that formoterol fumarate (12 and 24 microgram b.i.d.) produced statistically and clinically significant improvements in lung function, as measured by FEV₁ area under the curve, when compared to placebo after 12 weeks of treatment. Formoterol fumarate also improved the quality of life of patients and was more effective than ipratropium bromide (40 microgram q.i.d.) with similar satisfactory tolerability.

Study 25827 02 058 was a randomized, between-patient trial that compared two doses of inhaled formoterol fumarate dry powder (12 microgram b.i.d. and 24 microgram b.i.d.) with placebo (double-blind) and with oral slow release theophylline (200–400 mg) at individual doses based on serum levels (open-label), each administered twice daily for one year in 725 patients (age 34–88) with COPD. The study concluded that formoterol fumarate at both 24 microgram and 12 microgram b.i.d. produced statistically and clinically significant improvements in lung function, as measured by FEV₁, area under the curve, when compared to placebo after 12 weeks of treatment. Formoterol fumarate also improved the quality of life of patients and was more effective than theophylline with superior tolerability.

5.2 Pharmacokinetic properties

Foradil has a therapeutic dose range of 12 to 24 micrograms bid. Data on the plasma pharmacokinetics of formoterol was collected in healthy volunteers after inhalation of doses higher than the recommended range and in COPD patients after inhalation of therapeutic doses. Urinary excretion of unchanged formoterol, used as an indirect measure of systemic exposure, correlates with plasma drug disposition data. The elimination half-lives calculated for urine and plasma are similar.

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 266 pmol/L within 5 min of inhalation. In COPD patients treated for 12 weeks with 12 or 24 micrograms formoterol fumarate b.i.d., the mean plasma concentrations of formoterol ranged between 11.5 and 25.7 pmol/L and 23.3 and 50.3 pmol/L, respectively, 10 min, 2 hours and 6 hours after inhalation.

Studies investigating the cumulative urinary excretion of formoterol and/or its (R,R)- and (S,S)-enantiomers showed the amount of formoterol available in the circulation to increase in proportion to the inhaled dose (12 to 96 micrograms).

After inhalation of 12 microgram or 24 micrograms formoterol fumarate b.i.d for 12 weeks, urinary excretion of unchanged formoterol increased by between 63 and 73% (last vs. first dose) in patients with asthma and by between 19 and 38% in COPD patients. This suggests some limited accumulation of formoterol in plasma with multiple dosing. There was no relative accumulation of one enantiomer over the other after repeated dosing.

As reported for other inhaled drugs, it is likely that most of the formoterol administered from an inhaler will be swallowed and then absorbed from the gastrointestinal tract. When 80 microgram of ³H-labeled formoterol fumarate were orally administered to two healthy volunteers, at least 65% of the drug was absorbed

Distribution:

The plasma protein binding of formoterol was 61-64%, and binding to human serum albumin was 34%. There is no saturation of binding sites in the concentration range reached with therapeutic doses.

Biotransformation/metabolism:

Formoterol is eliminated primarily by metabolism, with direct glucuronidation being the major pathway of biotransformation. O-demethylation followed by glucuronidation is another pathway. Minor pathways involve sulphate conjugation of formoterol and deformylation followed by sulphate conjugation. Multiple isozymes catalyse the glucuronidation (UGT1A1, 1A3, 1A6, 1A7, 1A8, 1A9, 1A10, 2B7 and 2B15) and O-demethylation (CYP2D6, 2C19, 2C9 and 2A6) of formoterol, suggesting a low potential for drug-drug interactions though inhibition of a specific isozyme involved in formoterol metabolism. Formoterol did not inhibit cytochrome P450 isozymes at therapeutically relevant concentrations.

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. The (R,R) and (S,S)-enantiomers accounted, respectively, for 40% and 60% of urinary recovery of unchanged formoterol, after single doses (12 to 120 microgram) in healthy volunteers, and after single and repeated doses in asthma patients.

The drug and its metabolites were completely eliminated from the body with about two-thirds of an oral dose being excreted in the urine and one-third in the faeces. Renal clearance of formoterol is 150 mL/min.

In healthy volunteers, the terminal elimination half-life of formoterol in plasma after inhalation of a single 120 microgram dose of formoterol fumarate was 10 hours and the terminal elimination half-lives of the (R,R)- and (S,S)-enantiomers, as derived from the urinary excretion rates, were 13.9 and 12.3 hours, respectively.

Special populations

Effects of gender: After correction for body weight, formoterol pharmacokinetics did not differ significantly between males and females.

Elderly patients: The pharmacokinetics of formoterol have not been studied in the elderly population.

Paediatrics: In a study in 5- to 12-year-old children with asthma who were given 12 or 24 micrograms formoterol fumarate twice daily by inhalation for 12 weeks, urinary excretion of unchanged formoterol increased by between 18 and 84% as compared to the amounts measured after the first dose. Accumulation in children did not exceed that in adults, where the increase was between 63 and 73% (see above). In the children studied, about 6% of the dose was recovered in the urine as unchanged formoterol.

Patients with hepatic/renal Impairment: The pharmacokinetics of formoterol have not been studied in patients with hepatic or renal impairment.

5.3 Preclinical safety data

Non-clinical data reveal no specific hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity or genotoxicity.

In carcinogenicity studies, there was an increase in the incidence of uterine leiomyomas in rats and smooth muscle tumours in the female genital tract, and of liver tumours in mice of both sexes treated with formoterol racemate; smooth muscle tumours are considered to be a class effect in rodents after long-term exposure to high doses of β_2 -adrenoreceptor agonists. In addition, male mice also showed a slightly higher incidence of benign adrenal subcapsular cell tumours. Based on the totality of the nonclinical data, therapeutic use of formoterol fumarate in accordance with the indicated posology is unlikely to be associated with a carcinogenic risk in humans.

In nonclinical reproductive toxicology studies, fetotoxicity findings are reported in rats following oral administration of formoterol fumarate racemate to rats at doses 30-fold higher than the maximum recommended inhalation human dose (MRHID) based on BSA, while in rabbits no fetotoxicity was observed at 20000 times the MRHID based on BSA. Formoterol (R,R)-enantiomer was teratogenic in both rats (umbilical hernia and brachygnathia) and rabbits (liver subcapsular cysts) following oral administration of at doses 500 and 20000-fold higher than the MRHID respectively (based on body surface area).

[BSA]). The formoterol (R,R)-enantiomer was not teratogenic following administration by inhalation at doses 15-fold higher than the MRHID based on BSA.

Oral administration of formoterol (R,R)-enantiomer caused a decrease in pregnancy rate at 15 mg/kg/day (corresponding to 2500 times the MRHID based on BSA) and was attributed to impairment of male fertility. No impairment of fertility was observed with formoterol racemate when administered orally up to 60 mg/kg/day (corresponding to 10000 times the MRHID based on BSA) in studies performed in male and female rats.

Formoterol was associated with a decrease in body weight in offspring exposed either in utero, or postnatally via lactation.

Juvenile toxicity study

In a rat juvenile toxicity study, formoterol ((R,R)-enantiomer) caused testicular tubular atrophy, spermatid debris, oligospermia in epididymides in males at 3 mg/kg/day (corresponding to 500 times, the MRHID based on BSA).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Gelatine

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Cartons of 10 and 60 capsules in AL/AL blister packs, together with the inhaler device.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Novartis Ireland Limited
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Elm Park
Merrion Road, Ballsbridge
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8 MARKETING AUTHORISATION NUMBER

PA0896/013/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 January 1996

Date of last renewal: 26 January 2006

10 DATE OF REVISION OF THE TEXT

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