NOVARTIS

Foradil®

Formoterol (Selective beta2-adrenergic agonist)

DESCRIPTION AND COMPOSITION

Pharmaceutical Form

Foradil inhalation powder, hard capsules.

White free flowing powder in a clear hard gelation capsule, marked 'CG' on the cap and 'FXF' on the body or 'CG' on the body and 'FXF' on the cap in black ink, size 3.

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

Active substance

One capsule contains 12 micrograms of formoterol fumerate dihydrate (INN: formoterol)

Active Moiety

Formoterol

Excipients

Lactose monohydrate (25 mg/ capsule, which contains milk proteins), gelatin.

Pharmaceutical formulations may vary between countries.

Box of 30 capsules, 10 capsules per blister pack.

Information might differ in some countries

INDICATIONS

- Prophylaxis and treatment of bronchoconstriction in patients with asthma as an add-on to inhaled corticosteroid (ICS) treatment (see section WARNINGS AND PRECAUTIONS).
- 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. Foradil has been shown to improve quality of life in COPD patients.

DOSAGE AND ADMINISTRATION

Method of administration

For inhalation use in adults and in children 5 years of age and older.

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 WARNINGS AND PRECAUTIONS).

Detailed handling instructions are included in the package leaflet.

It is important for the patient to understand that the gelatin capsule might fragment and small pieces of gelatin might reach the mouth or throat after inhalation. The tendency for this to happen is minimised by not piercing the capsule more than once. The capsule made of edible gelatin is not harmful if ingested.

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

Dosage

Adults

Asthma

For regular maintenance therapy, 1 to 2 inhalation capsules (equivalent to 12 to 24 micrograms formoterol) twice daily. 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 daily maximum 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 WARNINGS AND PRECAUTIONS).

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 a history of severe bronchospasm, 2 inhalation capsules (24 micrograms) 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 micrograms) twice daily.

Pediatrics (Children aged 5 years or older)

Asthma

Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. For patients with asthma less than 18 years of age who require addition of a LABA to an inhaled corticosteroid, a fixed-dose combination product containing both an inhaled corticosteroid and LABA should ordinarily be used to ensure adherence with both drugs. In cases where use of a separate long-term asthma control medication (e.g. inhaled corticosteroid) and LABA is clinically indicated, appropriate steps must be taken to ensure adherence with both treatment components. If adherence cannot be assured, a fixed-dose combination product containing both an inhaled corticosteroid and LABA is recommended.

For regular maintenance therapy, the usual dosage is the inhalation of the contents of 1 Foradil capsule (12 micrograms) every 12 hours using the Aerolizer Inhaler. The patient must not exhale into the device. The total daily dose of Foradil should not exceed one capsule twice daily (24 micrograms total daily dose). More frequent administration or administration of a larger number of inhalations is not recommended. If symptoms arise between doses, an inhaled short-acting beta2-agonist should be taken for immediate relief.

If a previously effective dosage regimen fails to provide the usual response, medical advice should be sought immediately as this is often a sign of destabilization of asthma. Under these circumstances, the therapeutic regimen should be reevaluated.

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. Foradil is not recommended in children under 5 years of age.

Adults and children aged 5 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.

Special populations

Renal impairment

Formoterol has not been studied in patients with renal impairment (see section CLINICAL PHARMACOLOGY).

Hepatic impairment

Formoterol has not been studied in patients with hepatic impairment (see section CLINICAL PHARMACOLOGY).

Geriatrics (older than 65 years)

The pharmacokinetics of formoterol has not been studied in the elderly population (See section CLINICAL PHARMACOLOGY). 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 CLINICAL STUDIES).

CONTRAINDICATIONS

Known hypersensitivity to formoterol or to any of the excipients.

WARNINGS AND PRECAUTIONS

Asthma-related death

Formoterol, the active ingredient of Foradil, belongs to the class of long-acting beta2-adrenergic agonists. In a study with salmeterol, a different long-acting beta2-agonist, a higher rate of death due to asthma was observed in the patients treated with salmeterol (13/13,176) than in the placebo group (3/13179). No study adequate to determine whether the rate of asthma-related death is increased with Foradil has been conducted.

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 DOSAGE AND ADMINISTRATION).

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 aloneor whose disease severity clearly warrants initiation of treatment with both an ICS and a LABA

For children 5-12 years of age, treatment with a combination product containing an ICS and LABA is recommended, except in case where a separate ICS and LABA are required (see Section DOSAGE AND ADMINISTRATION and section ADVERSE DRUG REACTIONS).

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 patients who received Foradil than in those who received placebo, particularly in patients 5-12 years of age (see section ADVERSE DRUG REACTIONS). These studies do not allow precise quantification of the differences in serious asthma exacerbation rates between treatment groups.

The physician should reassess asthma therapy if symptoms persist, or if the number of doses of Foradil required to control symptoms increases, because this usually indicates that the underlying condition has deteriorated.

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.

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, known or suspected prolongation of the QT interval (QTc >0.44 sec.; see section INTERACTIONS).

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

Hypokalaemia

Potentially serious hypokalaemia may occur as a result of 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 INTERACTIONS). 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 DOSAGE AND ADMINISTRATION subsection 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.

INTERACTIONS

Beta-adrenergic blockers may weaken or antagonize 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, as other beta2-agonists, should be administered with caution to patients being treated with drugs such as quinidine, disopyramide, procainamide, phenothiazines, antihistamines, macrolides, monoamine oxidase inhibitors 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 WARNINGS AND PRECAUTIONS).

Concomitant administration of other sympathomimetic agents may potentiate the undesirable effects of Foradil.

Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate the possible hypokalemic effect of beta2-agonists (see section WARNINGS AND PRECAUTIONS).

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

PREGNANCY, BREAST-FEEDING AND FERTILITY

Pregnancy

There is limited data regarding the use of Foradil in pregnant women. Its use during pregnancy should be avoided unless there is no safer alternative. Like other beta2-adrenergic stimulants, formoterol may inhibit labour due to a relaxant effect on uterine smooth muscle.

Breast-feeding

There is limited data regarding the use of Foradil during breast-feeding. It is not known whether formoterol passes into human breast milk. The substance has been detected in the milk of lactating rats (see section NON-CLINICAL SAFETY DATA). Because many drugs are excreted in human milk, mothers taking Foradil should not breast-feed.

Fertility

There is no available data on the effect of formoterol on human fertility. No impairment of fertility was observed in studies performed in male and female rats (see section NON-CLINICAL SAFETY DATA).

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.

ADVERSE DRUG REACTIONS

Serious asthma exacerbations

Placebo-controlled clinical studies of at least 4 weeks treatment duration with Foradil suggested a higher incidence of serious asthma exacerbations in patients who received Foradil (0.9% for 10 to12 micrograms twice daily, 1.9% for 24 micrograms twice daily) than in those who received placebo (0.3%), particularly in patients 5-12 years of age.

Experience in adolescent and adult patients with asthma

In two pivotal 12-week controlled trials conducted for US registration with combined enrollment of 1,095 patients 12 years of age and older, serious asthma exacerbations (acute worsening of asthma resulting in hospitalization) occurred more commonly with Foradil 24 micrograms twice daily (9/271, 3.3%) than with Foradil 12 micrograms twice daily (1/275, 0.4%), placebo (2/277, 0.7%), or albuterol (2/272, 0.7%).

A subsequent clinical trial to address this observation enrolled 2,085 patients to compare asthma-related serious adverse events in the higher and lower dose groups. The results from this 16-week trial did not show an apparent dose-relationship for Foradil. The percent of patients with serious asthma exacerbations in this study was somewhat higher for Foradil than for placebo (for the three double-blind treatment groups: Foradil 24 micrograms twice daily (2/527, 0.4%), Foradil 12 micrograms twice daily (3/527, 0.6%), and placebo (1/514, 0.2%) and for the open-label treatment group: Foradil 12 micrograms twice daily plus up to two additional doses per day (1/517, 0.2%).

Experience in children aged 5-12 years with asthma

The safety of Foradil 12 micrograms twice daily compared to Foradil 24 micrograms twice daily and placebo was investigated in one large, multicenter, randomized, double-blind, 52-week clinical trial in 518 children with asthma (ages 5 to 12 years) in need of daily bronchodilators and anti-inflammatory treatment. More children who received Foradil 24 micrograms twice daily (11/171, 6.4%) or Foradil 12 micrograms twice daily (8/171, 4.7%) than children who received placebo (0/176, 0.0%) experienced serious asthma exacerbations.

For treatment recommendation see Section DOSAGE AND ADMINISTRATION and section WARNINGS AND PRECAUTION.

Tabulated summary of adverse drug reactions

Adverse reactions (Table 1) are listed by MedDRA system organ class. MedDRA version used is 15.1. 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 (≥ 1/10); common (≥ 1/100 < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000), including isolated reports.

Table 1 Adverse drug reactions from clinical trials and other sources

Immune system disorders		
	Very rare:	Hypersensitivity (including hypotension, urticaria, angio edema, pruritus, rash)
Psychiatric disorders		
	Uncommon:	Agitation, anxiety, nervousness, insomnia
Nervous system disorders		
	Common:	Headache, tremor
	Uncommon:	Dizziness
	Very rare:	Dysgeusia
Cardiac disorders		
	Common:	Palpitations
	Uncommon:	Tachycardia
	Very rare:	Edema peripheral
Respiratory, thoracic and mediastinal disorders		
	Uncommon	Bronchospasm, including bronchospasm paradoxical, throat irritation
Gastrointestinal disorders		
	Uncommon:	Dry mouth
	Very rare:	Nausea
Musculoskeletal and connective tissue disorders		
	Uncommon	Muscle spasms, myalgia

Adverse drug reactions from post-marketing experience (frequency not known)

The following undesirable effects have been observed with other Foradil formulations: cough and rash.

The following post-marketing adverse drug reactions have been derived from post-marking experience in patients treated with Foradil. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. MedDRA version used is 15.1. Within each system organ class, ADRs are presented below in Table 2 in order of decreasing seriousness:

Table 2 Adverse drug reactions from spontaneous and literature reports (frequency not known)

Metabolism and nutrition disorders:
Hypokalaemia, hyperglycaemia.
Investigations:
Electrocardiogram QT prolonged, blood pressure increased (including hypertension)
Respiratory, thoracic and mediastinal disorders:

Cough

Skin and subcutaneous tissue disorders:

Rash

Cardiac disorders:

Angina pectoris, cardiac arrhythmias e.g. atrial fibrillation, ventricular extrasystoles, tachyarrhythmia

OVERDOSAGE

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, 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.

CLINICAL PHARMACOLOGY

Mechanism of action (MOA) and Pharmcodynamics (PD)

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 leukotrienes 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.

Formoterol 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, and which was

accompanied by subjective improvement in Quality of Life using the Saint George's Respiratory Questionnaire.

Pharmacokinetics (PK)

Foradil has a therapeutic dose range of 12 to 24 micrograms b.i.d. 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 micrograms 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 micrograms of ^{3}H-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 to 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 micrograms) 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 from the blood was 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.

CLINICAL STUDIES

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 µg and 24 µg of formoterol dry powder capsules, 180 µg 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 µg or 24 µg provides significantly greater protection against exercise-induced bronchoconstriction as assessed by FEV_1 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 µg and 24 µg. There were less adverse events reported with formoterol 24 µg.

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 µg 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 FEV_1. 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 µg) was compared with that of a placebo and that of inhaled albuterol (200 µg) 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 FEV_1, 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 FEV_1 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 µg b.i.d.) with placebo and ipratropium bromide MDI (40 µg q.i.d.) for 12 weeks in 698 patients (age 40–87) with COPD. The study concluded that formoterol fumarate (12 and 24 µg b.i.d.) produced

statistically and clinically significant improvements in lung function, as measured by FEV_1 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 µg 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 µg b.i.d. and 24 µg 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 µg and 12 µg b.i.d. produced statistically and clinically significant improvements in lung function, as measured by FEV, 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.

NON-CLINICAL SAFETY DATA

Mutagenicity

Mutagenicity tests covering a broad range of experimental endpoints have been conducted. No genotoxic effects were found in any of the *in vitro* or *in vivo* tests performed.

Carcinogenicity

Two-year studies in rats and mice did not show any carcinogenic potential.

Male mice treated at very high dose levels showed a slightly higher incidence of benign adrenal subcapsular cell tumours. However, this finding was not seen in a second mouse feeding study, in which pathological changes at high doses consisted of an increased incidence both of benign smooth muscle tumours in the female genital tract, and of liver tumours in both sexes. Smooth muscle tumours are a known effect of beta-agonists given at high doses in rodents.

Two studies in rats, covering different dose ranges, showed an increase in mesovarial leiomyomas. These benign neoplasms are typically associated with long-term treatment of rats at high doses of beta 2-adrenergic drugs. Increased incidences of ovarian cysts and benign granulosa/thecal cell tumours were also seen; beta-agonists are known to have effects on the ovary in rats which are very likely specific to rodents. A few other tumour types noted in the first study using the higher doses were within the incidences of the historical control population, and were not seen in the lower-dose experiment.

None of the tumour incidences were increased to a statistically significant extent at the lowest dose of the second rat study, a dose leading to a systemic exposure 10 times higher than that expected from the maximum recommended dose of formoterol in humans.

On the basis of these findings and the absence of a mutagenic potential, it is concluded that use of formoterol at therapeutic doses does not present a carcinogenic risk.

Reproduction toxicity

Animal tests have shown no teratogenic effects. Formoterol was evaluated for its effects on fertility and general reproductive performance in sexually mature male and female rats. No impairment of fertility or effect on early embryonic development was observed at doses up to 60 mg/kg/day administered orally to rats (approximately 12,000 times the maximum recommended daily inhalation powder dose in human on a mg/m^2 basis). After oral administration, formoterol was excreted in the milk of lactating rats.

INCOMPATIBILITIES

None known.

STORAGE

See folding box.

Store in the original package (blister packs) together with the inhaler. Protect from moisture.

Information might differ in some countries.

Foradil should not be used after the date marked "EXP" on the pack.

Foradil must be kept out of the reach and sight of children.

Manufacturer:

Novartis Pharma Stein AG, Switzerland

Package Leaflet

Information issued: December 2012.SIN

® = registered trademark

Novartis Pharma AG, Basel, Switzerland

INFORMATION FOR PATIENTS

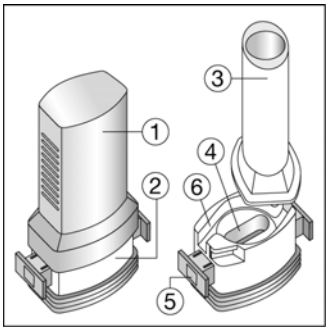
How to use the Foradil capsules with your inhaler

Follow the illustrated instructions to learn how to use Foradil capsules with the Aerolizer inhaler.

Use the Foradil capsules **only with the inhaler** provided in the pack. This Aerolizer has been specially developed for use with Foradil capsules.

Remove the capsule from the foil pack just before use. Make sure your fingers are completely dry so that the capsule does not get wet.

Do not swallow the capsule. The powder in the capsule is to be used for inhalation only.



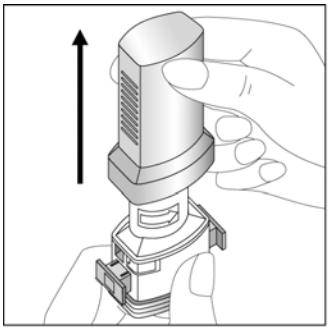
The Aerolizer consists of the following parts:

1. A blue cap to protect the mouthpiece of the base
2. A base that allows the proper release of medicine from the capsule

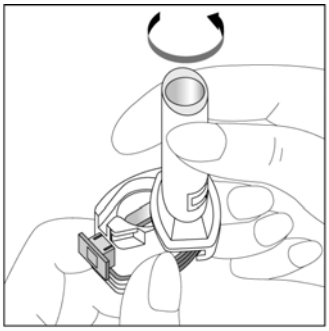
The base consists of:

3. A mouth piece
4. A capsule chamber
5. A blue button with “winglets” (projecting side pieces) and pins on each side
6. An air inlet channel.

Instructions for correct use



1. Pull off the cap.

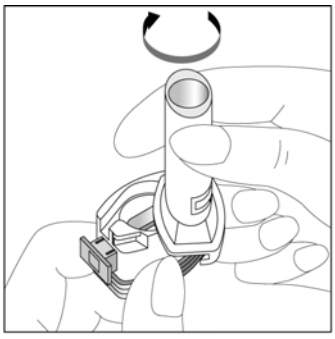


2. Open the capsule chamber.

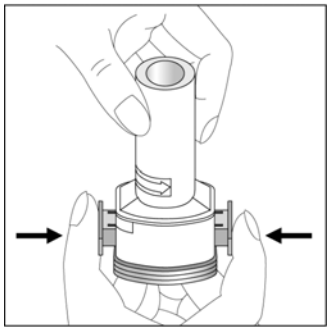
Hold the base firmly and turn the mouthpiece in the direction of the arrow.

3. Make sure your fingers are completely dry. Remove one capsule from the foil pack just before use and place it flat on the bottom of the capsule chamber.

IMPORTANT: Do not put the capsule into the mouthpiece!



4. Close the capsule chamber by turning the mouthpiece back until you hear the 'click'.



5. To release the powder from the capsule:
   - Hold the Aerolizer in the upright position with the mouthpiece upward.
   - Pierce the capsule by firmly pressing together both blue buttons at the same time. Then release the buttons. Do this only once.

   Please note: the capsule might splinter at this step and small gelatin fragments might get into your mouth or throat. However, gelatin is edible and therefore not harmful.

6. Breathe out fully.

7. To inhale your medicine deeply into your airways:

- Place the mouthpiece in your mouth and tilt your head slightly backwards.
- Close your lips firmly around the mouthpiece.
- Breathe in rapidly but steadily and as deeply as you can.

Note: You should hear a whirring noise as the capsule spins around in the space above the capsule chamber. If you do not hear this noise, open the capsule chamber and check that the capsule lies loose in the capsule chamber. Then repeat step 7. DO NOT try to loosen the capsule by pressing the buttons repeatedly.

8. After breathing in through the Aerolizer, hold your breath for as long as you comfortably can while removing the Aerolizer from your mouth. Then breathe out through your nose. Open the capsule chamber to see if there is any powder left in the capsule. If there is, repeat steps 6 to 8.

9. After you have used up all the powder, open the capsule chamber (see step 2). Remove the empty capsule and use a dry tissue or a soft brush to remove any powder left inside. Note: DO NOT USE WATER to clean the Aerolizer.

10. Close the mouthpiece and replace the cap.