NOVARTIS

Foradil®

inhalation powder in capsules
Foradil is also available in the form of a metered-dose aerosol (see corresponding prescribing information).

Composition

Active substance: Formoterol fumarate dihydrate (phenylethanolamine derivative)
Excipients: Lactose monohydrate (25 mg / capsule, which contains milk proteins), gelatin.
Information might differ in some countries

Pharmaceutical form and quantity of active substance per unit
Capsules of inhalation powder containing 12 µg formoterol fumarate dihydrate.

Indications / Potential uses

Adults (including elderly patients)
Prophylaxis and treatment of bronchoconstriction in patients with asthma, as an add-on to inhaled corticosteroid (ICS) treatment (see "Warnings and precautions").
Prophylaxis of acute attacks of bronchoconstriction, including those triggered by allergens, exercise or cold air.
Treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD), such as chronic bronchitis and emphysema.
Children from 6 years of age
Prophylaxis and treatment of bronchoconstriction in patients with asthma.
Prophylaxis of acute attacks of bronchoconstriction, including those triggered by allergens, exercise or cold air.

Dosage / Administration

Dosage
Asthma indication
In asthmatic patients, long-term bronchodilator therapy with long-acting beta$_2$-adrenergic agents should only be prescribed in combination with anti-inflammatory therapy (e.g. inhaled corticosteroids; see "Warnings and precautions"). Anti-inflammatory therapy should therefore be initiated together with Foradil in patients not yet receiving such treatment.
Long-term therapy (as adjunct to a corticosteroid)
Adults (including elderly patients)
The usual dose is one capsule (12 µg) of inhalation powder twice daily. Foradil should only be prescribed as an add-on to an inhaled corticosteroid. It is best to administer the dose in the morning and in the evening. If required for relief of the usual symptoms, a further 1-2 capsules (12-24 µg) daily may be given, but the maximum recommended daily dose of 48 µg must not be exceeded. Treatment should be reassessed, however, if the need for additional doses is more than occasional (i.e. more often than two days per week), as this might indicate a worsening of the underlying condition.
In severe cases, the dose may be increased to two capsules (24 µg) twice daily, the second capsule being inhaled approx. 2 minutes after the first.
The maximum recommended maintenance dose is 48 µg per day.

Children from 6 years of age
The usual dose is one capsule (12 µg) of inhalation powder twice daily (mornings and evenings). Foradil should only be prescribed as an add-on to an ICS.
The maximum recommended maintenance dose is 24 µg 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 beta$_2$-agonist should be used (see "Warnings and precautions").

Prophylaxis of bronchospasm in exercise-induced asthma
Adults (including elderly patients)
The contents of one capsule (12 µg) should be inhaled at least 15 minutes before exercise or exposure. In patients with a history of severe bronchospasm, two capsules (24 µg) may be necessary for prophylaxis, the second being inhaled approx. 2 minutes after the first.
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 treatment of asthma should also include an ICS.

Children from 6 years of age
Prophylaxis: The contents of one capsule (12 µg) should be inhaled at least 15 minutes before 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 treatment of asthma should also include an ICS.
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 a long-acting beta$_2$-agonist (LABA) is recommended, except in cases where an inhaled corticosteroid and a long-acting beta$_2$-agonist must be used separately (see "Warnings and precautions" and "Adverse effects").

COPD indication
Maintenance therapy: 1-2 capsules of inhalation powder (12-24 µg) twice daily.

Administration
Foradil inhalation powder in capsules should only be used with the Aerolizer supplied in the pack.
The capsules must not be removed from the pack until immediately before use.
Patients should be informed that the gelatin capsules may break, causing small pieces of gelatin to enter the mouth or throat.
In order to ensure correct administration, the patient should be shown how to use the Foradil Aerolizer inhaler by a doctor or other healthcare professional.

Elderly patients (over 65 years of age)
The pharmacokinetics of formoterol have not been studied in the elderly population (see "Properties / Actions", *Clinical efficacy*). The available data from clinical trials performed in elderly patients do not suggest that the dosage should be different than in other adults.

Contraindications

Known hypersensitivity to formoterol, to any of the other ingredients of Foradil or to other beta$_2$-stimulants.
Tachyarrhythmia, third degree atrioventricular block, idiopathic subvalvular aortic stenosis, hypertrophic obstructive cardiomyopathy, thyrotoxicosis.
Use of beta-agonists at doses higher than those recommended has been shown to prolong the QT interval in the ECG, thus increasing the risk of ventricular arrhythmia. Foradil should therefore not be used in patients with known or suspected prolongation of the QT interval (QTc >0.44 seconds, see"Interactions").

Warnings and precautions

Asthma-related deaths
Formoterol, the active substance of Foradil, belongs to the class of long-acting beta$_2$-agonists.
In a study with salmeterol, another long-acting beta$_2$-agonist, a higher rate of deaths due to asthma was observed in patients treated with salmeterol than in the placebo group (13/13 176 [0.10%] vs. 3/13 179 [0.02%]). There have been no studies to determine the frequency of deaths due to asthma in patients treated with formoterol. However, it is possible that the increased risk of death due to asthma observed with salmeterol may represent a class effect of the long-acting beta$_2$-agonists, including formoterol.
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 "Adverse effects"). However, these studies do not allow precise quantification of the differences in the frequency of serious asthma attacks within the treatment groups.
The doctor should reassess asthma therapy if symptoms continue or if the number of doses of Foradil needed to suppress symptoms increases, as this usually indicates 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 beta$_2$ agonist should be used.
Patients must be informed of the need to seek medical treatment immediately if their asthma deteriorates suddenly.

Anti-inflammatory therapy
In the indication of bronchial asthma, Foradil – a long-acting beta$_2$-agonist (LABA) – may be used as long-term therapy only as an add-on to an inhaled corticosteroid (ICS), and only in patients who do not achieve adequate control of asthma on an ICS alone, or whose disease severity clearly warrants initiation of treatment with both an ICS and a LABA.
For children 6-12 years of age, treatment with a combination product containing an ICS and a LABA is recommended, except in cases where an ICS and a LABA must be used separately (see "Dosage / Administration" and "Adverse effects").
Foradil should not be used in conjunction with another LABA.
Whenever Foradil is prescribed, patients should be evaluated for the adequacy of the basic anti-inflammatory therapy they receive.
If patients are already receiving such therapy, it should continue unchanged after introduction of Foradil, even if symptoms improve.
Symptoms of asthma may be masked in children treated with long-acting beta-agonists, resulting in the risk that anti-inflammatory medication may be underdosed, and early symptoms concealed during asthma exacerbations. In one study in children receiving standard anti-inflammatory treatment, serious asthma exacerbations leading to hospitalization were more frequent with formoterol than with salbutamol taken as needed.
Once asthma symptoms are controlled, consideration may be given to gradually reducing the dose of Foradil. Regular monitoring of patients is important as treatment is stepped down. The lowest effective dose of Foradil should be used.

Recommended dose
The dose of Foradil, which should be tailored to the needs of the individual patient, should be titrated to the lowest possible level consistent with achieving the therapeutic objective. It should not exceed the maximum recommended dose (see "Dosage / Administration").
Experience with Foradil inhalation powder in children under 6 years of age is limited and use is therefore not recommended in such patients.

Concomitant conditions
Special care and monitoring, with particular emphasis on dosage limits, is required in patients receiving Foradil who have any of the following conditions (see "Contraindications"):
- Ischaemic heart disease
- Myocardial infarction
- Severe hypertension
- Arrhythmias, in particular with atrioventricular block
- Severe heart failure
- Aneurysm
- Phaeochromocytoma
- Epilepsy
- Hepatic impairment: Accumulation may occur because formoterol is principally eliminated via the liver.

Due to the hyperglycaemic effect of beta$_2$-stimulants, including Foradil, additional blood glucose monitoring is recommended in diabetic patients.

Hypokalaemia
Treatment with beta$_2$-agonists, including Foradil, may cause potentially severe hypokalaemia. Hypokalaemia may increase susceptibility to arrhythmias in patients treated with digitalis. Particular caution is indicated in patients with severe asthma, as hypokalaemia may be potentiated by hypoxia or by concomitant treatment with other medicinal products (see "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 borne in mind. If it occurs, the medicinal product should be withdrawn immediately and alternative therapy started.
Patients should be instructed to go to their doctor or nearest hospital immediately if additional inhalations do not adequately improve acute or rapidly worsening dyspnoea.

Incorrect route of administration
There have been reports of patients who have mistakenly swallowed Foradil capsules instead of placing the capsules in the Foradil Aerolizer. The majority of these ingestions were not associated with side effects. Healthcare providers who dispense the drug should discuss with the patient how to correctly use Foradil Aerolizer (see "Dosage / Administration"). If a patient who is prescribed Foradil Aerolizer does not experience breathing improvement, the patient should be asked how he or she is using Foradil Aerolizer.

Interactions

As with other beta$_2$-agonists, Foradil should be used with caution in patients receiving quinidine, disopyramide, procainamide, phenothiazine, antihistamines, macrolide antibiotics, tricyclic antidepressants, MAO inhibitors or other substances known to prolong the QT interval. The adrenergic effect on the cardiovascular system might be increased by these substances. The additional administration of substances known to prolong the QT interval increases the risk of ventricular arrhythmias (see "Warnings and precautions").
Concomitant administration of other sympathomimetic agents may potentiate the adverse effects of Foradil.
Concomitant treatment with xanthine derivatives, steroids or diuretics may potentiate the possible hypokalaemic effect of beta$_2$-agonists (see "Warnings and precautions").
L-dopa, L-thyroxine and oxytocin may potentiate the cardiovascular adverse effects of beta$_2$-agonists, and therefore also those of Foradil.
There is an elevated risk of arrhythmias in patients receiving concomitant anaesthesia with halogenated hydrocarbons.
Beta-blockers may weaken or even antagonize the effect of Foradil. Foradil should therefore not be given concomitantly with beta-blockers (including eye drops) unless there are compelling circumstances.

Pregnancy / Breastfeeding
Reproductive toxicity studies in animals have shown no evidence of risk to the fetus. Animal studies have not revealed any teratogenic effects. No controlled studies have been performed in pregnant women.

Pregnancy
The safety of Foradil during pregnancy and breastfeeding has not yet been established. Its use during pregnancy should be avoided unless there is no safer alternative. Like other beta$_2$-adrenergic stimulants, formoterol may inhibit labour due to a relaxant effect on uterine smooth muscle.

Breastfeeding
It is not known whether formoterol enters the breast milk. Foradil should therefore not be used by breastfeeding women. Formoterol has been detected in the milk of rats.

Effects on ability to drive and use machines
Patients who experience dizziness or similar adverse effects must not use machines or drive vehicles. If adverse effects – such as tremor or agitation – occur, they may impair the patient's ability to drive or use machines.

Adverse effects

Serious asthma exacerbations
Placebo-controlled clinical studies of at least 4 weeks' treatment duration with Foradil showed a higher incidence of serious asthma exacerbations in patients who received Foradil (0.9% for 10 to 12 µg twice daily, 1.9% for 24 µg 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 controlled, pivotal, 12 week studies involving the use of Foradil Aerolizer in a total of 1095 patients aged 12 years and older, serious asthma exacerbations (acute worsening of asthma resulting in hospitalization) occurred more commonly with 24 µg Foradil twice daily (9/271, 3.3%) than with 12 µg Foradil twice daily (1/275, 0.4%), placebo (2/277, 0.7%) or salbutamol (2/272, 0.7%).
2085 patients were enrolled in a subsequent clinical study to address this observation and further evaluate asthma-related serious adverse effects. In this study, the percentage of patients with serious asthma exacerbations was as follows for the three double-blind treatment groups: 24 µg Foradil twice daily (2/527, 0.4%), 12 µg Foradil twice daily (3/527, 0.6%) and placebo (1/514, 0.2%). Figures for the open-label treatment group were: 12 µg Foradil twice daily plus up to two additional doses per day (1/517, 0.2%). The frequency of asthma exacerbations in this study was lower than had been assumed for the calculation, and the study is therefore not adequately powered to discover possible dose-dependent differences in the frequency of asthma exacerbations.

Experience in children, 5-12 years of age, with asthma
The safety of 12 µg Foradil twice daily, compared with 24 µg Foradil twice daily and placebo, was investigated in a large-scale, randomized, double-blind, 52-week, multicentre clinical study in 518 children (5 to 12 years of age) with asthma in need of daily bronchodilator and anti-inflammatory treatment. Children given 24 µg Foradil twice daily (11/171, 6.4%) or 12 µg Foradil twice daily (8/171, 4.7%) developed serious asthma exacerbations more frequently than did children who received placebo (0/176, 0.0%).
For treatment recommendations, see "Dosage / Administration" and "Warnings and precautions".

Other adverse effects
Frequencies were defined as follows: *Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000).*
Adverse effects are ranked in order of decreasing seriousness within each frequency grouping.

Immune system disorders
Very rare: Hypersensitivity including hypotension, urticaria, angioedema, pruritus, rash.

Metabolism and nutrition disorders
Rare: Hypokalaemia.
Very rare: Hyperglycaemia.

Psychiatric disorders
Uncommon: Agitation, anxiety, nervousness, insomnia.

Nervous system disorders
Common: Headache, tremor.
Uncommon: Dizziness, dysgeusia.

Cardiac disorders
Common: Palpitations.
Uncommon: Tachycardia, peripheral oedema.
Respiratory disorders
Uncommon: Bronchospasm, including paradoxical bronchospasm, sore throat.

Gastrointestinal disorders
Very rare: Nausea.
Cases of dry mouth have been observed.

Musculoskeletal disorders
Uncommon: Muscle spasms, myalgia.
The following post-marketing events have been reported in patients treated with Foradil: Because these effects were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency. Within each system organ class, adverse effects are presented in order of decreasing seriousness.

Metabolism and nutrition disorders: Hypokalaemia, hyperglycaemia.

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

Respiratory disorders: Cough.

Skin and subcutaneous tissue disorders: Rash.

Investigations: QT prolonged in electrocardiogram, elevated blood pressure.

Overdose

Signs and symptoms
An overdose of Foradil can lead to effects that are typical of beta$_2$-stimulants: nausea, vomiting, headache, tremor, drowsiness, palpitations, tachycardia, ventricular arrhythmias, hypotension, hypertension, metabolic acidosis, hypokalaemia, hyperglycaemia.

Treatment
Supportive and symptomatic treatment (if necessary including sedatives, antiarrhythmics, etc.) is indicated in Foradil overdosage. In serious cases, patients should be hospitalized.
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-blockers may provoke bronchospasm.
In cases of accidental oral ingestion, activated charcoal (0.5 g/kg body weight) should be given if this can be done within 4 hours of ingestion, and if there are no contraindications. If intoxication is severe, the electrolyte and acid-base balance should be monitored and corrected.

Properties / Actions

ATC code: R03AC13
Formoterol is a potent, selective beta$_2$-adrenergic stimulant. It exerts a bronchodilator effect in patients with reversible or irreversible airway obstruction. The effect sets in rapidly (within 1 to 3 minutes) and is still significant 12 hours after inhalation. Twice-daily administration of Foradil is therefore sufficient in most cases. On account of the pronounced selectivity for beta$_2$ receptors, cardiovascular effects are minor, and occur only occasionally, at therapeutic doses.
Formoterol inhibits the release of histamine and leukotrienes from the passively sensitized human lung. Some anti-inflammatory properties, such as inhibition of oedema and of inflammatory cell accumulation, have been observed in animal experiments.

In vitro studies using guinea pig trachea have shown that racemic formoterol and its (R,R)- and (S,S)-enantiomers are highly selective beta$_2$-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 the tracheal smooth muscle.
No pharmacological basis for the use of one of the two enantiomers in preference to the racemic mixture was demonstrated.
Foradil has been shown to be effective in the prevention and treatment of bronchospasm induced by allergens, exercise, cold air or the histamine or methacholine provocation tests.
(-> In patients with chronic obstructive pulmonary disease, Foradil [12 or 24 µg twice daily] brought about rapid bronchodilation that persisted for over 12 hours. This treatment was shown to bring about an improvement in quality of life in these patients [St. George's Respiratory Questionnaire]).

Pharmacokinetics
Data on the plasma pharmacokinetics of formoterol were collected in healthy volunteers following administration of one dose in excess of the recommended range and in COPD patients following inhalation of a therapeutic dose. Urinary excretion of unchanged formoterol, as an indirect measure of systemic exposure, correlates with plasma concentrations. The calculated elimination half-lives for urine and plasma are similar.

Absorption
As is the case with other inhaled medicinal products, most of the formoterol administered is likely to be swallowed and then absorbed from the gastrointestinal tract. When 80 µg of ^{3}H-labelled formoterol fumarate was administered orally to two healthy volunteers, at least 65% of the substance was absorbed.
Foradil has a therapeutic range of 12-24 µg twice daily. Following inhalation of a single 120 µg dose of formoterol fumarate in healthy volunteers, formoterol was rapidly absorbed into plasma, reaching a maximum concentration of 266 pmol/litre within 5 minutes of inhalation. In COPD patients treated for 12 weeks with 12 or 24 µg formoterol fumarate twice daily, mean plasma concentrations of formoterol ranged from 11.5 to 25.7 pmol/litre and 23.3 to 50.3 pmol/litre, respectively, 10 minutes, 2 hours and 6 hours after inhalation.
Studies investigating cumulative renal excretion of formoterol and/or of the (R,R)- and (S,S)-enantiomers showed that the amount of formoterol available systemically increases in proportion to the dose inhaled (12-96 µg).
Following inhalation of 12 or 24 µg formoterol fumarate twice daily for 12 weeks, urinary excretion of unchanged formoterol increased by between 63 and 73% (as compared with the first dose) in asthmatic patients and between 19 and 38% in patients with COPD. These results indicate limited accumulation of formoterol in the plasma with multiple dosing. No relative accumulation of one enantiomer, as compared with the other, was observed with repeated administration.

Distribution
Formoterol is 61-64% bound to plasma proteins, with 34% being bound to human serum albumin. There is no saturation of binding sites in the concentration range reached with therapeutic doses.

Metabolism
Formoterol is eliminated primarily by metabolism, for the most part by direct glucuronidation. Another pathway is O-demethylation followed by glucuronidation.
Less frequent pathways are sulphate conjugation of formoterol and deformylation followed by sulphate conjugation. Many isoenzymes 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 associated with inhibition of specific isoenzymes (involved in formoterol metabolism). At therapeutically relevant concentrations, formoterol does not inhibit cytochrome P450 isoenzymes.

Elimination
Following twice daily inhalation of 12 or 24 mg formoterol fumarate for 12 weeks in asthma or COPD patients, approximately 10% and 7% of the dose, respectively, was 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, both following a single dose (12 to 120 mg) in healthy volunteers and following single and repeated doses in asthma patients.
The active substance and its metabolites were completely eliminated from the body; approx. two-thirds of an oral dose was found in the urine and one-third in the faeces. Renal clearance of formoterol from the blood was 150 ml/minute.
In healthy volunteers the terminal elimination half-life of formoterol in the plasma following inhalation of a single dose of 120 µg formoterol fumarate was 10 hours and the terminal elimination half-lives of the (R,R)- and (S,S)-enantiomers were 13.9 and 12.3 hours, respectively, as derived from urinary excretion rates.
Pharmacokinetics in special patient populations

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

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

Children: The data available are limited. In a study involving asthmatic children aged 5-12 years, twice daily inhalation of 12 or 24 mg formoterol fumarate for 12 weeks resulted in an increase in renal excretion of unchanged formoterol by between 18 and 84% as compared with the value determined after the first dose. Accumulation in children did not exceed the amount in adults, in whom the increase was between 63 and 73%. In the children studied, approximately 6% of the dose was excreted in the urine as unchanged formoterol.

Hepatic and renal impairment: The pharmacokinetics of formoterol have not been studied in patients with hepatic or renal impairment.

Preclinical data

Two-year studies with formoterol in mice and rats did not show any carcinogenic potential. Very high doses led to a slight increase in the incidence of adenomas in male mice. This was not confirmed in a second study, which in turn showed a slight increase in the incidence of leiomyomas in females and of hepatic adenomas in both sexes. In two rat studies there was a slight increase in leiomyomas, ovarian cysts and benign tumours of ovarian granulosa and theca cells. All these tumours are a known effect of long-term administration of beta-agonists in rodents. The lowest doses administered in these studies, which corresponded to 22 to 35 times the therapeutic exposure in humans, did not result in an increased incidence of tumours above control values. On the basis of these findings and the absence of mutagenic potential, it may be concluded that the use of formoterol at therapeutic doses does not present a carcinogenic risk.

Other information

Shelf life
Do not use after the expiry date (= EXP) printed on the pack.
Special precautions for storage
See folding box.
Keep out of the reach and sight of children.

Instructions for use and handling
In order to ensure correct use, a doctor or other healthcare professional should:
- show the patient how to use the inhaler.
- only dispense the capsules together with the inhaler.
- tell the patient that the capsules are only for inhalation and not to be swallowed.

Detailed instructions for use are included in the patient information. It is important that the patient understands that the gelatin capsules may break, causing small pieces of gelatin to enter the mouth or throat following inhalation. This risk is minimized if the capsule is not pierced more than once. However, the capsules are made of edible gelatin which is not harmful.

Pack sizes
Country specific pack sizes

Manufacturer
See folding box.

Information last revised
July 2013

® = registered trademark
Novartis Pharma AG, Basle, Switzerland

This is a medicament

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

Keep medicaments out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists

1144388-A21-R02