

Drug Regulatory Affairs

**FORADIL<sup>®</sup> AEROLIZER<sup>®</sup>**  
**(formoterol)**

12 microgram inhalation powder, hard capsules

**Basic Prescribing Information**

**NOTICE**

The Basic Prescribing Information (BPI) is the Novartis Core Data Sheet. It displays the company's current position on important characteristics of the product, including the Core Safety Information according to ICH E2C.

National Prescribing Information is based on the BPI. However, because regulatory requirements and medical practices vary between countries, National Prescribing Information (incl. US Package Insert or European SPCs) may differ in several respects, including but not limited to the characterisation of risks and benefits.

Author(s): Dawn Little, Bruno Duverger

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## **1 Name of the medicinal product**

FORADIL<sup>®</sup> AEROLIZER<sup>®</sup> 12 microgram inhalation powder, hard capsules.

## **2 Qualitative and quantitative composition**

One capsule contains 12 micrograms formoterol fumarate dihydrate (INN : formoterol).

For a full list of excipients, see Section 6.1 List of excipients.

## **3 Pharmaceutical form**

Inhalation powder, hard capsules.

Information might differ in some countries.

## **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) [125].
- Prophylaxis of bronchospasm induced by inhaled allergens, cold air, or exercise [44,79,105,106].
- Prophylaxis and treatment of bronchoconstriction in patients with reversible or irreversible chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema. Foradil<sup>®</sup> has been shown to improve quality of life in COPD patients [105,106].

### **4.2 Posology and method of administration**

For inhalation use in adults and in children 5 years of age and older [4,44,59-61,63,79,86-90,105,106].

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

#### **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 [117].

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 [126]. 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) [117].

### **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 [9,11].

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.

### **Children aged 5 years or older**

#### **Asthma**

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

For children 5-12 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) [130].

The maximum recommended dose is 24 microgram per day [117].

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) [117].

### **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 [101,114].

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 [44].

### **4.3 Contraindications**

Known hypersensitivity to formoterol or to any of the excipients.

### **4.4 Special warnings and precautions for use**

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 (3/13,179). No study adequate to determine whether the rate of asthma-related death is increased with Foradil has been conducted [116,117].

### **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) [92,117-119].

### **Anti-inflammatory therapy**

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 [67,117,120].

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 4.2 Posology and method of administration and section 4.8 Undesirable effects) [130].

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 [127].

### **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 4.8 Undesirable effects). 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 [117,120].

### **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 [64]), severe cardiac decompensation, idiopathic subvalvular aortic stenosis, hypertrophic obstructive cardiomyopathy, thyrotoxicosis, known or suspected prolongation of the QT interval (QTc >0.44 sec.; see Section 4.5 Interactions with other medicinal products and other forms of interaction) [62,65,66].

Due to the hyperglycaemic effect of beta2-stimulants, including Foradil, additional blood glucose monitoring is recommended in diabetic patients [128].

### **Hypokalaemia**

Potentially serious hypokalaemia may occur as a result of beta2-agonist therapy, including Foradil. Hypokalaemia may increase susceptibility to cardiac arrhythmias [117,128]. 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 products 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.

## **4.5 Interaction with other medicinal products and other forms of interaction**

Foradil, as other beta2-agonists, should be administered with caution to patients being treated with drugs such as quinidine, disopyramide, procainamide, phenothiazines, antihistamines, 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 4.4 Special warnings and precautions for use) [68-71].

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 hypokalaemic effect of beta2-agonists (see Section 4.4 Special warnings and precautions for use).

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 [72,73]) unless there are compelling reasons for their use.

## **4.6 Pregnancy and lactation**

### **Pregnancy**

The safety of Foradil during pregnancy and lactation has not yet been established. 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.

### **Lactation**

It is not known whether formoterol passes into human breast milk. The substance has been detected in the milk of lactating rats [80]. Mothers taking Foradil should not breast-feed.

## **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**

### **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 to 12 microgram twice daily, 1.9% for 24 microgram twice daily) than in those who received placebo (0.3%), particularly in patients 5-12 years of age [117].

### **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 microgram twice daily (9/271, 3.3%) than with Foradil 12 microgram twice daily (1/275, 0.4%), placebo (2/277, 0.7%), or albuterol (2/272, 0.7%) [117-119].

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 microgram twice daily (2/527, 0.4%), Foradil 12 microgram 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%) [117,122].

### **Experience in children aged 5-12 years with asthma**

The safety of Foradil 12 microgram twice daily compared to Foradil 24 microgram 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 microgram twice daily (11/171, 6.4%) or Foradil 12 microgram twice daily (8/171, 4.7%) than children who received placebo (0/176, 0.0%) experienced serious asthma exacerbations [117,92].

For treatment recommendation see Section 4.2 Posology and method of administration and section 4.4 Special warnings and precaution for use [130].

### Other undesirable effects

Adverse reactions (Table 1) are ranked in descending order of frequency, as follow: 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 ( $< 1/10,000$ ), including isolated reports [115]. Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

**Table 1**

<b>Immune system disorders</b>	
Very rare:	Hypersensitivity (including hypotension, urticaria, angioneurotic oedema, pruritus, exanthem) [91]
<b>Psychiatric disorders</b>	
Uncommon:	Agitation, anxiety, nervousness, insomnia
<b>Nervous system disorders</b>	
Common:	Headache, tremor
Uncommon:	Dizziness
Very rare	Dysgeusia [121]
<b>Cardiac disorders</b>	
Common:	Palpitations
Uncommon:	Tachycardia
Very rare	Oedema peripheral [121]
<b>Respiratory, thoracic and mediastinal disorders</b>	
Uncommon	Bronchospasm, including bronchospasm paradoxical [128], throat irritation
<b>Gastrointestinal disorders</b>	
Very rare:	Nausea
<b>Musculoskeletal and connective tissue disorders</b>	
Uncommon	Muscle cramps, myalgia

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

The following post-marketing events have been reported in patients treated with Foradil [128]:

Metabolism and nutrition disorders: Hypokalaemia, hyperglycaemia

Investigations: Electrocardiogram QT prolonged

## 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.

### 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.

## 5 Pharmacological properties

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective beta2-adrenergic agonist, ATC code: R03AC13 [129].

Formoterol is a potent selective beta2-adrenergic stimulant. It exerts a bronchodilator effect in patients with reversible airways obstruction [1,2,40,41]. The effect sets in rapidly (within 1 to 3 minutes) [3,4,42,43] and is still significant 12 hours after inhalation [4,5,44]. At therapeutic doses cardiovascular effects are minor and occur only occasionally [44].

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 [46,47,48].

*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 1,000 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 [103,104].

In man, Foradil has been shown to be effective in preventing bronchospasm induced by inhaled allergens, exercise, cold air, histamine, or methacholine [9-12,49,50].

Formoterol administered by the Aerolizer inhaler at doses of 12 microgram b.i.d. and 24 microgram 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 [105,106,113].

### 5.2 Pharmacokinetic properties

Foradil has a therapeutic dose range of 12 to 24 microgram 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 [94,107]. In COPD patients treated for 12 weeks with 12 or 24 microgram 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 [123].

Studies investigating the cumulative urinary excretion of formoterol [81-83,93,124] and/or its (R,R)- and (S,S)-enantiomers [97,98] showed the amount of formoterol available in the circulation to increase in proportion to the inhaled dose (12 to 96 microgram).

After inhalation of 12 microgram or 24 microgram 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 [93] and by between 19 and 38% in COPD patients [123]. 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 [97].

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 [14,15]. When 80 microgram of <sup>3</sup>H-labeled formoterol fumarate were orally administered to two healthy volunteers, at least 65% of the drug was absorbed [16].

## Distribution

The plasma protein binding of formoterol was 61 to 64 % [19], and binding to human serum albumin was 34 % [84]).

There is no saturation of binding sites in the concentration range reached with therapeutic doses.

## Biotransformation

Formoterol is eliminated primarily by metabolism, with direct glucuronidation being the major pathway of biotransformation. O-demethylation followed by glucuronidation is another pathway [16,18,82,85,95]. Minor pathways involve sulphate conjugation of formoterol and deformylation followed by sulphate conjugation [109]. 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 [99,110], 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 [100].

## Elimination

In asthmatic [93] and COPD patients [123] treated for 12 weeks with 12 or 24 microgram 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 [96,98,107], and after single and repeated doses in asthma patients [97].

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 [16]. Renal clearance of formoterol from the blood was 150 mL/min [16].

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 [94] 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 [96,107].

### Special populations

**Gender:** After correction for body weight, formoterol pharmacokinetics did not differ significantly between males and females [94].

**Geriatric:** The pharmacokinetics of formoterol have not been studied in the elderly population.

**Paediatric:** In a study in 5- to 12-year-old children with asthma who were given 12 or 24 microgram 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 [124]. 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 [124].

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

## 5.3 Preclinical 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 [22-30,55,56].

### 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 [33]. However, this finding was not seen in a second mouse feeding study [102], 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 [31].

Two studies in rats, covering different dose ranges, showed an increase in mesovarial leiomyomas [32,77]. These benign neoplasms are typically associated with long-term treatment of rats at high doses of adrenergic drugs [31]. 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 [74-76]. 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 [77], 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 [32,33,57,76,77,102].beta 2-

## **Reproduction toxicity**

Animal tests have shown no teratogenic effects [34-38]. After oral administration, formoterol was excreted in the milk of lactating rats [39].

## **6 Pharmaceutical particulars**

### **6.1 List of excipients**

Lactose monohydrate (which contains milk proteins), gelatin.

Information might differ in some countries.

### **6.2 Incompatibilities**

None known.

### **6.3 Shelf life**

Country specific.

Information might differ in some countries.

### **6.4 Special precautions for storage**

Do not store above 25°C.

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

Information might differ in some countries.

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

### **6.5 Nature and content of container**

Alu/alu blister packs.

### **6.6 Instructions for use and handling**

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.
- Warn the patient that the capsules are only for inhalation use and not to be swallowed.

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. However, the capsule is made of edible gelatin, which is not harmful.**

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

This is a non-referenced document.