CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-831/S-002

Trade Name: Foradil

Generic Name: Formoterol Fumarate

Sponsor: Novartis Pharmaceutical Corporation

Approval Date: September 25, 2001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-831/S-002

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-831/S-002

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-279
NDA 20-831/S-002

Novartis Pharmaceutical Corporation
59 Route 10
East Hanover, New Jersey 07936-1080

Attention: Kathleen Basmadjian, Ph.D.
Associate Director, Drug Regulatory Affairs

Dear Dr. Basmadjian:

Please refer to your new drug application (NDA) dated September 22, 2000, received September 25, 2000, and your supplemental new drug application dated September 24, 2001, received September 24, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Foradil (formoterol fumarate inhalation powder) Aerolizer.

We acknowledge receipt of your submissions dated November 15, 2000, January 31, May 4, June 18, July 5, 23 and 26 and September 12 and 24, 2001.

This new drug application provides for the use of Foradil (formoterol fumarate inhalation powder) Aerolizer for the long-term, twice daily (morning and evening) administration in the maintenance treatment of bronchoconstriction in patients with Chronic Obstructive Pulmonary Disease including chronic bronchitis and emphysema.

We have completed the review of these applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text and with the revisions shown in the enclosed labeling, and discussed during a telephone conversation between Dr. Craig Ostroff of this Division and yourself. Accordingly, these applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert) and submitted labeling (patient instructions for use submitted September 24, 2001). These revisions are terms of the NDA and supplemental NDA approvals. Marketing the product before making the revisions, exactly as requested, in the product's final printed labeling (FPL) may render the product misbranded and an unapproved new drug.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL to each NDA as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved NDA 21-279 and NDA 20-831/S-002." Approval of these submissions by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitments in your submission dated September 5, 2001 to NDA 21-279. These commitments are listed below.

1. Foradil Aerolizer: Holter Monitoring in Patients with COPD

Protocol Submission:	Within six months of the date of this letter
Study Start:	Within 12 months of the date of this letter
Final Report Submission:	Within 34 months of the date of this letter

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to NDA 20-831. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to NDA 20-831. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled **"Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."**

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We are waiving the pediatric study requirement for this indication.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements set forth under 21 CFR 314.80 and 314.81 for an approved NDA. To comply with these regulations, all 3-day and 15-day alert reports, periodic adverse drug experience reports, field alerts, annual reports, supplements, and other submissions should be addressed to the original NDA 20-831 for this drug product, not to NDA 21-279. This includes the quarterly periodic adverse drug experience reports required by this new NDA. In the future, no submissions should be made to NDA 21-279 except for the 20 copies of the final printed labeling, as requested above.

If you have any questions, call Dr. Craig Ostroff, Regulatory Management Officer, at 301-827-5585.

Sincerely,

{See appended electronic signature page}

Robert J. Meyer, M.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Meyer
9/25/01 06:19:51 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-831/S-002

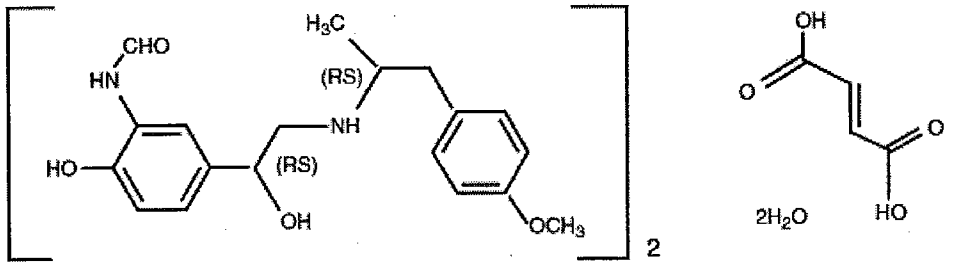
APPROVED LABELING

DESCRIPTION

FORADIL® AEROLIZER™ consists of a capsule dosage form containing a dry powder formulation of Foradil (formoterol fumarate) intended for oral inhalation only with the Aerolizer™ Inhaler.

Each clear, hard gelatin capsule contains a dry powder blend of 12 mcg of formoterol fumarate and 25 mg of lactose as a carrier.

The active component of Foradil is formoterol fumarate, a racemate. Formoterol fumarate is a selective beta$_2$-adrenergic bronchodilator. Its chemical name is (±)-2-hydroxy-5-[(1RS)-1-hydroxy-2-[[(1RS)-2-(4-methoxyphenyl)-1-methylethyl]-amino]ethyl]formanilide fumarate dihydrate; its structural formula is



Formoterol fumarate has a molecular weight of 840.9, and its empirical formula is $(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4 \cdot 2H_2O$. Formoterol fumarate is a white to yellowish crystalline powder, which is freely soluble in glacial acetic acid, soluble in methanol, sparingly soluble in ethanol and isopropanol, slightly soluble in water, and practically insoluble in acetone, ethyl acetate, and diethyl ether.

The Aerolizer Inhaler is a plastic device used for inhaling Foradil. The amount of drug delivered to the lung will depend on patient factors, such as inspiratory flow rate and inspiratory time. Under standardized in vitro testing at a fixed flow rate of 60 L/min for 2 seconds, the Aerolizer Inhaler delivered 10 mcg of formoterol fumarate from the mouthpiece. Peak inspiratory flow rates (PIFR) achievable through the Aerolizer Inhaler were evaluated in 33 adult and adolescent patients and 32 pediatric patients with mild-to-moderate asthma. Mean PIFR was 117.82 L/min (range 34-188 L/min) for adult and adolescent patients, and 99.66 L/min (range 43-187 L/min) for pediatric patients. Approximately ninety percent of each population studied generated a PIFR through the device exceeding 60 L/min.

To use the delivery system, a Foradil capsule is placed in the well of the Aerolizer Inhaler, and the capsule is pierced by pressing and releasing the buttons on the side of the device. The formoterol fumarate formulation is dispersed into the air stream when the patient inhales rapidly and deeply through the mouthpiece.

CLINICAL PHARMACOLOGY

Mechanism of Action

Formoterol fumarate is a long-acting selective beta$_2$-adrenergic receptor agonist (beta$_2$-agonist). Inhaled formoterol fumarate acts locally in the lung as a bronchodilator. In

vitro studies have shown that formoterol has more than 200-fold greater agonist activity at $beta_2$-receptors than at $beta_1$-receptors. Although $beta_2$-receptors are the predominant adrenergic receptors in bronchial smooth muscle and $beta_1$-receptors are the predominant receptors in the heart, there are also $beta_2$-receptors in the human heart comprising 10%-50% of the total beta-adrenergic receptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective $beta_2$-agonists may have cardiac effects.

The pharmacologic effects of $beta_2$-adrenoceptor agonist drugs, including formoterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3', 5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

In vitro tests show that formoterol is an inhibitor of the release of mast cell mediators, such as histamine and leukotrienes, from the human lung. Formoterol also inhibits histamine-induced plasma albumin extravasation in anesthetized guinea pigs and inhibits allergen-induced eosinophil influx in dogs with airway hyper-responsiveness. The relevance of these in vitro and animal findings to humans is unknown.

Animal Pharmacology

Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines are administered concurrently. The clinical significance of these findings is unknown.

Pharmacokinetics

Information on the pharmacokinetics of formoterol in plasma has been obtained in healthy subjects by oral inhalation of doses higher than the recommended range and in COPD patients after oral inhalation of doses at and above the therapeutic dose. Urinary excretion of unchanged formoterol was used as an indirect measure of systemic exposure. Plasma drug disposition data parallel urinary excretion, and the elimination half-lives calculated for urine and plasma are similar.

Absorption

Following inhalation of a single 120 mcg dose of formoterol fumarate by 12 healthy subjects, formoterol was rapidly absorbed into plasma, reaching a maximum drug concentration of 92 pg/mL within 5 minutes of dosing. In COPD patients treated for 12 weeks with formoterol fumarate 12 or 24 mcg b.i.d., the mean plasma concentrations of formoterol ranged between 4.0 and 8.8 pg/mL and 8.0 and 17.3 pg/mL, respectively, at 10 min, 2 h and 6 h post inhalation.

Following inhalation of 12 to 96 mcg of formoterol fumarate by 10 healthy males, urinary excretion of both (R,R)- and (S,S)-enantiomers of formoterol increased proportionally

to the dose. Thus, absorption of formoterol following inhalation appeared linear over the dose range studied.

In a study in patients with asthma, when formoterol 12 or 24 mcg twice daily was given by oral inhalation for 4 weeks or 12 weeks, the accumulation index, based on the urinary excretion of unchanged formoterol ranged from 1.63 to 2.08 in comparison with the first dose. For COPD patients, when formoterol 12 or 24 mcg twice daily was given by oral inhalation for 12 weeks, the accumulation index, based on the urinary excretion of unchanged formoterol was 1.19 - 1.38. This suggests some accumulation of formoterol in plasma with multiple dosing. The excreted amounts of formoterol at steady-state were close to those predicted based on single-dose kinetics. As with many drug products for oral inhalation, it is likely that the majority of the inhaled formoterol fumarate delivered is swallowed and then absorbed from the gastrointestinal tract.

Distribution

The binding of formoterol to human plasma proteins in vitro was 61%-64% at concentrations from 0.1 to 100 ng/mL. Binding to human serum albumin in vitro was 31%-38% over a range of 5 to 500 ng/mL. The concentrations of formoterol used to assess the plasma protein binding were higher than those achieved in plasma following inhalation of a single 120 mcg dose.

Metabolism

Formoterol is metabolized primarily by direct glucuronidation at either the phenolic or aliphatic hydroxyl group and O-demethylation followed by glucuronide conjugation at either phenolic hydroxyl groups. Minor pathways involve sulfate conjugation of formoterol and deformylation followed by sulfate conjugation. The most prominent pathway involves direct conjugation at the phenolic hydroxyl group. The second major pathway involves O-demethylation followed by conjugation at the phenolic 2'-hydroxyl group. Four cytochrome P450 isozymes (CYP2D6, CYP2C19, CYP2C9 and CYP2A6) are involved in the O-demethylation of formoterol. Formoterol did not inhibit CYP450 enzymes at therapeutically relevant concentrations. Some patients may be deficient in CYP 2D6 or 2C19 or both. Whether a deficiency in one or both of these isozymes results in elevated systemic exposure to formoterol or systemic adverse effects has not been adequately explored.

Excretion

Following oral administration of 80 mcg of radiolabeled formoterol fumarate to 2 healthy subjects, 59%-62% of the radioactivity was eliminated in the urine and 32%-34% in the feces over a period of 104 hours. Renal clearance of formoterol from blood in these subjects was about 150 mL/min. Following inhalation of a 12 mcg or 24 mcg dose by 16 patients with asthma, about 10% and 15%-18% of the total dose was excreted in the urine as unchanged formoterol and direct conjugates of formoterol, respectively. Following inhalation of 12 mcg or 24 mcg dose by 18 patients with COPD the corresponding values were 7% and 6-9% of the dose, respectively.

Based on plasma concentrations measured following inhalation of a single 120 mcg dose by 12 healthy subjects, the mean terminal elimination half-life was determined to be 10

hours. From urinary excretion rates measured in these subjects, the mean terminal elimination half-lives for the (R,R)- and (S,S)-enantiomers were determined to be 13.9 and 12.3 hours, respectively. The (R,R)- and (S,S)-enantiomers represented about 40% and 60% of unchanged drug excreted in the urine, respectively, following single inhaled doses between 12 and 120 mcg in healthy volunteers and single and repeated doses of 12 and 24 mcg in patients with asthma. Thus, the relative proportion of the two enantiomers remained constant over the dose range studied and there was no evidence of relative accumulation of one enantiomer over the other after repeated dosing.

Special Populations

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

Geriatric and Pediatric: The pharmacokinetics of formoterol have not been studied in the elderly population, and limited data are available in pediatric patients.

In a study of children with asthma who were 5 to 12 years of age, when formoterol fumarate 12 or 24 mcg was given twice daily by oral inhalation for 12 weeks, the accumulation index ranged from 1.18 to 1.84 based on urinary excretion of unchanged formoterol. Hence, the accumulation in children did not exceed that in adults, where the accumulation index ranged from 1.63 to 2.08 (see above). Approximately 6% and 6.5% to 9% of the dose was recovered in the urine of the children as unchanged and conjugated formoterol, respectively.

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

Pharmacodynamics

Systemic Safety and Pharmacokinetic/Pharmacodynamic Relationships

The major adverse effects of inhaled $beta_2$-agonists occur as a result of excessive activation of the systemic beta-adrenergic receptors. The most common adverse effects in adults and adolescents include skeletal muscle tremor and cramps, insomnia, tachycardia, decreases in plasma potassium, and increases in plasma glucose.

Pharmacokinetic/pharmacodynamic (PK/PD) relationships between heart rate, ECG parameters, and serum potassium levels and the urinary excretion of formoterol were evaluated in 10 healthy male volunteers (25 to 45 years of age) following inhalation of single doses containing 12, 24, 48, or 96 mcg of formoterol fumarate. There was a linear relationship between urinary formoterol excretion and decreases in serum potassium, increases in plasma glucose, and increases in heart rate.

In a second study, PK/PD relationships between plasma formoterol levels and pulse rate, ECG parameters, and plasma potassium levels were evaluated in 12 healthy volunteers following inhalation of a single 120 mcg dose of formoterol fumarate (10 times the

recommended clinical dose). Reductions of plasma potassium concentration were observed in all subjects. Maximum reductions from baseline ranged from 0.55 to 1.52 mmol/L with a median maximum reduction of 1.01 mmol/L. The formoterol plasma concentration was highly correlated with the reduction in plasma potassium concentration. Generally, the maximum effect on plasma potassium was noted 1 to 3 hours after peak formoterol plasma concentrations were achieved. A mean maximum increase of pulse rate of 26 bpm was observed 6 hours post dose. The maximum increase of mean corrected QT interval (QTc) was 25 msec when calculated using Bazett's correction and was 8 msec when calculated using Fredericia's correction. The QTc returned to baseline within 12-24 hours post-dose. Formoterol plasma concentrations were weakly correlated with pulse rate and increase of QTc duration. The effects on plasma potassium, pulse rate, and QTc interval are known pharmacological effects of this class of study drug and were not unexpected at the very high formoterol dose (120 mcg single dose, 10 times the recommended single dose) tested in this study. These effects were well-tolerated by the healthy volunteers.

The electrocardiographic and cardiovascular effects of FORADIL AEROLIZER were compared with those of albuterol and placebo in two pivotal 12-week double-blind studies of patients with asthma. A subset of patients underwent continuous electrocardiographic monitoring during three 24-hour periods. No important differences in ventricular or supraventricular ectopy between treatment groups were observed. In these two studies, the total number of patients with asthma exposed to any dose of FORADIL AEROLIZER who had continuous electrocardiographic monitoring was about 200.

Continuous electrocardiographic monitoring was not included in the clinical studies of FORADIL AEROLIZER that were performed in COPD patients. The electrocardiographic effects of FORADIL AEROLIZER were evaluated versus placebo in a 12-month pivotal double-blind study of patients with COPD. An analysis of ECG intervals was performed for patients who participated at study sites in the United States, including 46 patients treated with FORADIL AEROLIZER 12 mcg twice daily, and 50 patients treated with FORADIL AEROLIZER 24 mcg twice daily. ECGs were performed pre-dose, and at 5-15 minutes and 2 hours post-dose at study baseline and after 3, 6 and 12 months of treatment. The results showed that there was no clinically meaningful acute or chronic effect on ECG intervals, including QTc, resulting from treatment with FORADIL AEROLIZER.

Tachyphylaxis/Tolerance

In a clinical study in 19 adult patients with mild asthma, the bronchoprotective effect of formoterol, as assessed by methacholine challenge, was studied following an initial dose of 24 mcg (twice the recommended dose) and after 2 weeks of 24 mcg twice daily. Tolerance to the bronchoprotective effects of formoterol was observed as evidenced by a diminished bronchoprotective effect on FEV_1 after 2 weeks of dosing, with loss of protection at the end of the 12 hour dosing period.

Rebound bronchial hyper-responsiveness after cessation of chronic formoterol therapy has not been observed.

In three large clinical trials in patients with asthma, while efficacy of formoterol versus placebo was maintained, a slightly reduced bronchodilatory response (as measured by

12-hour FEV_1 AUC) was observed within the formoterol arms over time, particularly with the 24 mcg twice daily dose (twice the daily recommended dose). A similarly reduced FEV_1 AUC over time was also noted in the albuterol treatment arms (180 mcg four times daily by metered-dose inhaler).

CLINICAL TRIALS

Adolescent and Adult Asthma Trials

In a placebo-controlled, single-dose clinical trial, the onset of bronchodilation (defined as a 15% or greater increase from baseline in FEV_1) was similar for FORADIL AEROLIZER and albuterol 180 mcg by metered-dose inhaler.

In single-dose and multiple-dose clinical trials, the maximum improvement in FEV_1 for FORADIL AEROLIZER 12 mcg generally occurred within 1 to 3 hours, and an increase in FEV_1 above baseline was observed for 12 hours in most patients.

FORADIL AEROLIZER was compared to albuterol 180 mcg four times daily by metered-dose inhaler, and placebo in a total of 1095 adult and adolescent patients 12 years of age and above with mild-to-moderate asthma (defined as FEV_1 40%-80% of the patient's predicted normal value) who participated in two pivotal, 12-week, multi-center, randomized, double-blind, parallel group studies.

The results of both studies showed that FORADIL AEROLIZER 12 mcg twice daily resulted in significantly greater post-dose bronchodilation (as measured by serial FEV_1 for 12 hours post-dose) throughout the 12-week treatment period. Mean FEV_1 measurements from both studies are shown below for the first and last treatment days (see Figures 1 and 2).

Figures 1a and 1b: Mean FEV_1 from Clinical Trial A

Figure 1a
First Treatment Day

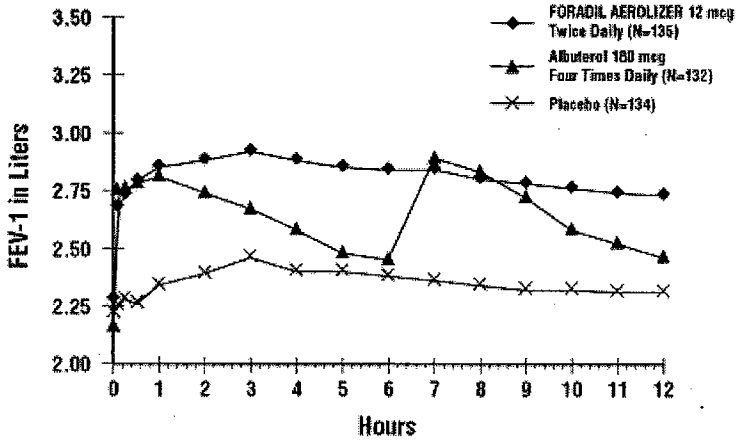
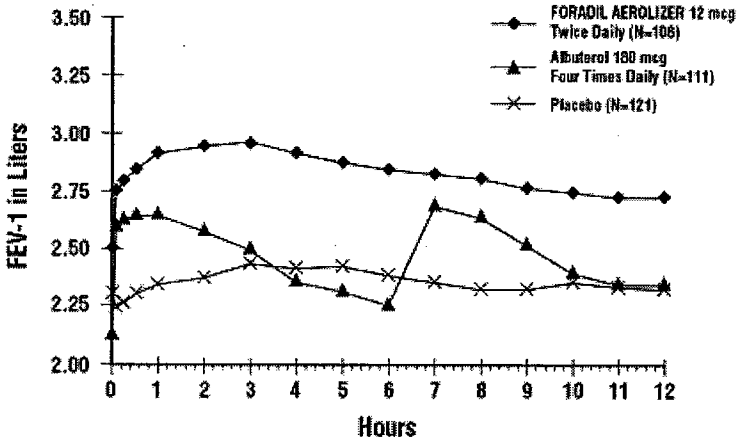


Figure 1b
Last Treatment Day



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218 Figures 2a and 2b: Mean FEV_1 from Clinical Trial B

Figure 2a
First Treatment Day

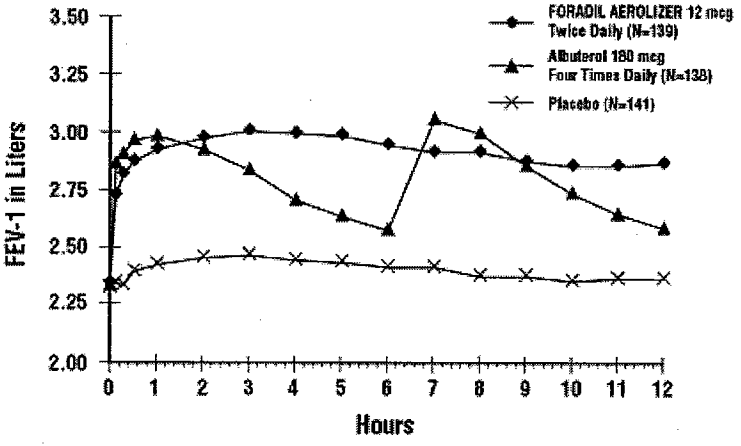

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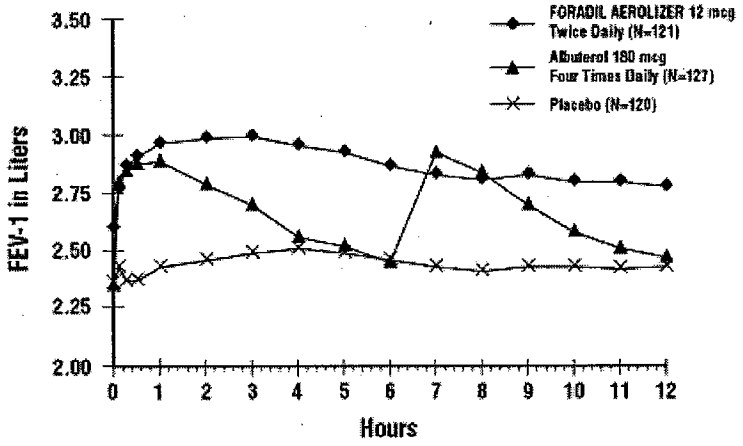
Figure 2b
Last Treatment Day



Compared with placebo and albuterol, patients treated with FORADIL AEROLIZER 12 mcg demonstrated improvement in many secondary efficacy endpoints, including improved combined and nocturnal asthma symptom scores, fewer nighttime awakenings, fewer nights in which patients used rescue medication, and higher morning and evening peak flow rates.

Pediatric Asthma Trial

A 12-month, multi-center, randomized, double-blind, parallel-group, study compared FORADIL AEROLIZER and placebo in a total of 518 children with asthma (ages 5-12 years) who required daily bronchodilators and anti-inflammatory treatment. Efficacy was evaluated on the first day of treatment, at Week 12, and at the end of treatment.

FORADIL AEROLIZER 12 mcg twice daily demonstrated a greater 12-hour FEV_1 AUC compared to placebo on the first day of treatment, after twelve weeks of treatment, and after one year of treatment.

Adolescent and Adult Exercise-Induced Bronchospasm Trials

The effect of FORADIL AEROLIZER on exercise-induced bronchospasm (defined as >20% fall in FEV_1) was examined in two randomized, single-dose, double-blind, crossover studies in a total of 38 patients 13 to 41 years of age with exercise-induced bronchospasm. Exercise challenge testing was conducted 15 minutes, and 4, 8, and 12 hours following administration of a single dose of study drug (FORADIL AEROLIZER 12 mcg, albuterol 180 mcg by metered-dose inhaler, or placebo) on separate test days. FORADIL AEROLIZER 12 mcg and albuterol 180 mcg were each superior to placebo for FEV_1 measurements obtained 15 minutes after study drug administration. FORADIL AEROLIZER 12 mcg maintained superiority over placebo at 4, 8, and 12 hours after administration. The efficacy of FORADIL AEROLIZER in the prevention of exercise-induced bronchospasm when dosed on a regular twice daily regimen has not been studied.

Adult COPD Trials

In multiple-dose clinical trials in patients with COPD, FORADIL AEROLIZER 12 mcg was shown to provide ~~rapid~~ onset of significant bronchodilation (defined as 15% or greater increase from baseline in FEV_1~~), reached~~ within 5 minutes of oral inhalation~~)~~ after the first dose. Bronchodilation was maintained for at least 12 hours.

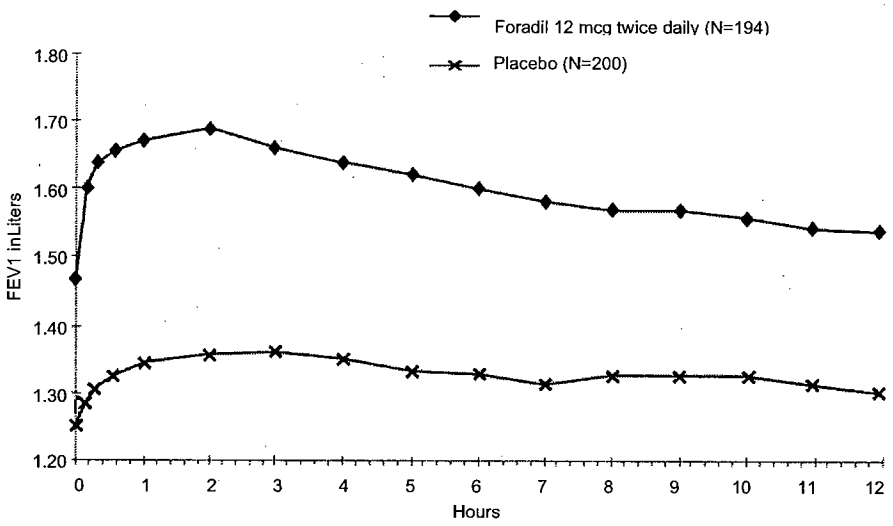
FORADIL AEROLIZER was studied in two pivotal, double-blind, placebo-controlled, randomized, multi-center, parallel-group trials in a total of 1634 adult patients (age range: 34-88 years; mean age: 63 years) with COPD who had a mean FEV_1 that was 46% of predicted. The diagnosis of COPD was based upon a prior clinical diagnosis of COPD, a smoking history (greater than 10 pack-years), age (at least 40 years), spirometry results (prebronchodilator baseline FEV_1 less than 70% of the predicted value, and at least 0.75 liters, with the FEV_1 /VC being less than 88% for men and less than 89% for women), and symptom score (greater than zero on at least four of the seven days prior to randomization). These studies included approximately equal numbers of patients with and without baseline brochodilator reversibility, defined as a 15% or greater increase FEV_1 after inhalation of 200 mcg of albuterol sulfate. A total of 405 patients received FORADIL AEROLIZER 12 mcg, administered twice daily. Each trial compared FORADIL AEROLIZER 12 mcg twice daily and FORADIL AEROLIZER 24 mcg twice daily with placebo and an active control drug. The active control drug was ipratropium bromide in COPD Trial A, and slow-release theophylline in COPD Trial B (the theophylline arm in this study was open-label). The treatment period was 12 weeks in COPD Trial A, and 12 months in COPD Trial B.

The results showed that FORADIL AEROLIZER 12 mcg twice daily resulted in significantly greater post-dose bronchodilation (as measured by serial FEV_1 for 12 hours post-dose; the primary efficacy analysis) compared to placebo when evaluated after 12 weeks of treatment in both trials, and after 12 months of treatment in the 12-month trial (COPD Trial B). Compared to FORADIL AEROLIZER 12 mcg twice daily, FORADIL AEROLIZER 24 mcg twice daily did not provide any additional benefit on a variety of endpoints including FEV_1.

Mean FEV_1 measurements after 12 weeks of treatment for one of the two major efficacy studies ~~is~~are shown in the figure below.

Figure 3

Mean FEV_1 after 12 Weeks of treatment from COPD Trial A



FORADIL AEROLIZER 12 mcg twice daily was statistically superior to placebo at all post-dose timepoints tested (from 5 minutes to 12 hours post-dose) throughout the 12-week (COPD Trial A) and 12-month (COPD Trial B) treatment periods.

In both pivotal trials compared with placebo, patients treated with FORADIL AEROLIZER 12 mcg demonstrated improved morning pre-medication peak expiratory flow rates and took fewer puffs of rescue albuterol.

INDICATIONS AND USAGE

FORADIL AEROLIZER is indicated for long-term, twice-daily (morning and evening) administration in the maintenance treatment of asthma and in the prevention of bronchospasm in adults and children 5 years of age and older with reversible obstructive airways disease, including patients with symptoms of nocturnal asthma, who require regular treatment with inhaled, short-acting, $beta_2$-agonists. It is not indicated for patients whose asthma can be managed by occasional use of inhaled, short-acting, $beta_2$-agonists.

FORADIL AEROLIZER is also indicated for the acute prevention of exercise-induced bronchospasm (EIB) in adults and children 12 years of age and older, when administered on an occasional, as needed basis.

FORADIL AEROLIZER can be used to treat asthma concomitantly with short-acting $beta_2$-agonists, inhaled or systemic corticosteroids, and theophylline therapy (see PRECAUTIONS, Drug Interactions). A satisfactory clinical response to FORADIL AEROLIZER does not eliminate the need for continued treatment with an anti-inflammatory agent.

FORADIL AEROLIZER is indicated for the long-term, twice daily (morning and evening) administration in the maintenance treatment of bronchoconstriction in patients with Chronic Obstructive Pulmonary Disease including chronic bronchitis and emphysema.

CONTRAINDICATIONS

Foradil (formoterol fumarate) is contraindicated in patients with a history of hypersensitivity to formoterol fumarate or to any components of this product.

WARNINGS

IMPORTANT INFORMATION: FORADIL AEROLIZER SHOULD NOT BE INITIATED IN PATIENTS WITH SIGNIFICANTLY WORSENING OR ACUTELY DETERIORATING ASTHMA, WHICH MAY BE A LIFE-THREATENING CONDITION. The use of FORADIL AEROLIZER in this setting is inappropriate.

FORADIL AEROLIZER IS NOT A SUBSTITUTE FOR INHALED OR ORAL CORTICOSTEROIDS. Corticosteroids should not be stopped or reduced at the time FORADIL AEROLIZER is initiated. (See PRECAUTIONS, Information for Patients and the accompanying Patient Instructions For Use.)

When beginning treatment with FORADIL AEROLIZER, patients who have been taking inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief of acute asthma symptoms (see PRECAUTIONS, Information for Patients).

Paradoxical Bronchospasm

As with other inhaled beta$_2$-agonists, formoterol can produce paradoxical bronchospasm, that may be life-threatening. If paradoxical bronchospasm occurs, FORADIL AEROLIZER should be discontinued immediately and alternative therapy instituted.

Deterioration of Asthma

Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the usual dose of FORADIL AEROLIZER no longer controls the symptoms of bronchoconstriction, and the patient's inhaled, short-acting beta$_2$-agonist becomes less effective or the patient needs more inhalation of short-acting beta$_2$-agonist than usual, these may be markers of deterioration of asthma. In this setting, a re-evaluation of the patient and the asthma treatment regimen should be undertaken at once, giving special consideration to the possible need for anti-inflammatory treatment, e.g., corticosteroids. Increasing the daily dosage of FORADIL AEROLIZER beyond the recommended dose in this situation is not appropriate. FORADIL AEROLIZER should not be used more frequently than twice daily (morning and evening) at the recommended dose.

Use of Anti-inflammatory Agents

The use of beta$_2$-agonists alone may not be adequate to control asthma in many patients. Early consideration should be given to adding anti-inflammatory agents, e.g., corticosteroids. There are no data demonstrating that Foradil has any clinical anti-inflammatory effect and therefore it cannot be expected to take the place of corticosteroids. Patients who already require oral or inhaled corticosteroids for treatment of asthma should be continued on this type of treatment even if they feel better as a result of initiating or increasing the dose of FORADIL AEROLIZER. Any change in corticosteroid dosage, in particular a reduction, should be made ONLY after clinical evaluation (see PRECAUTIONS, Information for Patients).

Cardiovascular Effects

Formoterol fumarate, like other beta$_2$-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of FORADIL AEROLIZER at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Therefore, formoterol fumarate, like other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension (see PRECAUTIONS, General).

Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions may occur after administration of FORADIL AEROLIZER, as demonstrated by cases of anaphylactic reactions, urticaria, angioedema, rash, and bronchospasm.

Do Not Exceed Recommended Dose

Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma. The exact cause of death is unknown, but cardiac arrest following an unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected.

PRECAUTIONS

General

FORADIL AEROLIZER should not be used to treat acute symptoms of asthma. FORADIL AEROLIZER has not been studied in the relief of acute asthma symptoms and extra doses should not be used for that purpose. When prescribing FORADIL AEROLIZER, the physician should also provide the patient with an inhaled, short-acting beta$_2$-agonist for treatment of symptoms that occur acutely, despite regular twice-daily (morning and evening) use of FORADIL AEROLIZER. Patients should also be cautioned that increasing inhaled

beta$_2$-agonist use is a signal of deteriorating asthma. (See Information for Patients and the accompanying Patient Instructions For Use.)

Formoterol fumarate, like other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders or thyrotoxicosis; and in patients who are unusually responsive to sympathomimetic amines. Clinically significant changes in systolic and/or diastolic blood pressure, pulse rate and electrocardiograms have been seen infrequently in individual patients in controlled clinical studies with formoterol. Doses of the related beta$_2$-agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

Beta-agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation.

Clinically significant changes in blood glucose and/or serum potassium were infrequent during clinical studies with long-term administration of FORADIL AEROLIZER at the recommended dose.

Foradil® capsules should ONLY be used with the Aerolizer™ Inhaler and SHOULD NOT be taken orally.

Foradil® capsules should always be stored in the blister, and only removed IMMEDIATELY before use.

Information for Patients

It is important that patients understand how to use the Aerolizer Inhaler appropriately and how it should be used in relation to other asthma medications they are taking (see the accompanying Patient Instructions For Use).

The active ingredient of Foradil (formoterol fumarate) is a long-acting, bronchodilator used for the treatment of asthma, including nocturnal asthma, and for the prevention of exercise-induced bronchospasm. FORADIL AEROLIZER provides bronchodilation for up to 12 hours. Patients should be advised not to increase the dose or frequency of FORADIL AEROLIZER without consulting the prescribing physician. Patients should be warned not to stop or reduce concomitant asthma therapy without medical advice.

FORADIL AEROLIZER is not indicated to relieve acute asthma symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting, beta$_2$-agonist (the health-care provider should prescribe the patient with such medication and instruct the patient in how it should be used). Patients should be instructed to seek medical attention if their symptoms worsen, if FORADIL AEROLIZER treatment becomes less effective, or if they need more inhalations of a short-acting beta$_2$-agonist than usual. Patients should not inhale more than the contents of the prescribed number of capsules at any one time. The daily dosage of FORADIL AEROLIZER should not exceed one capsule twice daily (24 mcg total daily dose).

When FORADIL AEROLIZER is used for the prevention of EIB, the contents of one capsule should be taken at least 15 minutes prior to exercise. Additional doses of FORADIL AEROLIZER should not be used for 12 hours. Prevention of EIB has not been studied in patients who are receiving chronic FORADIL AEROLIZER administration twice daily and these patients should not use additional FORADIL AEROLIZER for prevention of EIB.

FORADIL AEROLIZER should not be used as a substitute for oral or inhaled corticosteroids. The dosage of these medications should not be changed and they should not be stopped without consulting the physician, even if the patient feels better after initiating treatment with FORADIL AEROLIZER.

Patients should be informed that treatment with beta$_2$-agonists may lead to adverse events which include palpitations, chest pain, rapid heart rate, tremor or nervousness. Patients should be informed never to use FORADIL AEROLIZER with a spacer and never to exhale into the device.

Patients should avoid exposing the Foradil capsules to moisture and should handle the capsules with dry hands. The Aerolizer™ Inhaler should never be washed and should be kept dry. The patient should always use the new Aerolizer Inhaler that comes with each refill.

Women should be advised to contact their physician if they become pregnant or if they are nursing.

Patients should be told that in rare cases, the gelatin capsule might break into small pieces. These pieces should be retained by the screen built into the Aerolizer Inhaler. However, it remains possible that rarely, tiny pieces of gelatin might reach the mouth or throat after inhalation. The capsule is less likely to shatter when pierced if: storage conditions are strictly followed, capsules are removed from the blister immediately before use, and the capsules are only pierced once.

Drug Interactions

If additional adrenergic drugs are to be administered by any route, they should be used with caution because the pharmacologically predictable sympathetic effects of formoterol may be potentiated.

Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of adrenergic agonists.

The ECG changes and/or hypokalemia that may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the co-administration of beta-agonist with non-potassium sparing diuretics.

Formoterol, as with other beta$_2$-agonists, should be administered with extreme caution to patients being treated with monamine oxidase inhibitors, tricyclic antidepressants, or drugs 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 arrhythmias.

Beta-adrenergic receptor antagonists (beta-blockers) and formoterol may inhibit the effect of each other when administered concurrently. Beta-blockers not only block the therapeutic effects of beta-agonists, such as formoterol, but may produce severe bronchospasm in asthmatic patients. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-blockers in patients with asthma. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of formoterol fumarate has been evaluated in 2-year drinking water and dietary studies in both rats and mice. In rats, the incidence of ovarian leiomyomas was increased at doses of 15 mg/kg and above in the drinking water study and at 20 mg/kg in the dietary study, but not at dietary doses up to 5 mg/kg (AUC exposure approximately 450 times human exposure at the maximum recommended daily inhalation dose). In the dietary study, the incidence of benign ovarian theca-cell tumors was increased at doses of 0.5 mg/kg and above (AUC exposure at the low dose of 0.5 mg/kg was approximately 45 times human exposure at the maximum recommended daily inhalation dose). This finding was not observed in the drinking water study, nor was it seen in mice (see below).

In mice, the incidence of adrenal subcapsular adenomas and carcinomas was increased in males at doses of 69 mg/kg and above in the drinking water study, but not at doses up to 50 mg/kg (AUC exposure approximately 590 times human exposure at the maximum recommended daily inhalation dose) in the dietary study. The incidence of hepatocarcinomas was increased in the dietary study at doses of 20 and 50 mg/kg in females and 50 mg/kg in males, but not at doses up to 5 mg/kg in either males or females (AUC exposure approximately 60 times human exposure at the maximum recommended daily inhalation dose). Also in the dietary study, the incidence of uterine leiomyomas and leiomyosarcomas was increased at doses of 2 mg/kg and above (AUC exposure at the low dose of 2 mg/kg was approximately 25 times human exposure at the maximum recommended daily inhalation dose). Increases in leiomyomas of the rodent female genital tract have been similarly demonstrated with other beta-agonist drugs.

Formoterol fumarate was not mutagenic or clastogenic in the following tests: mutagenicity tests in bacterial and mammalian cells, chromosomal analyses in mammalian cells, unscheduled DNA synthesis repair tests in rat hepatocytes and human fibroblasts, transformation assay in mammalian fibroblasts and micronucleus tests in mice and rats.

Reproduction studies in rats revealed no impairment of fertility at oral doses up to 3 mg/kg (approximately 1000 times the maximum recommended daily inhalation dose in humans on a mg/m^2 basis).

Pregnancy, Teratogenic Effects, Pregnancy Category C

Formoterol fumarate has been shown to cause stillbirth and neonatal mortality at oral doses of 6 mg/kg (approximately 2000 times the maximum recommended daily inhalation dose in humans on a mg/m^2 basis) and above in rats receiving the drug during the late stage of

pregnancy. These effects, however, were not produced at a dose of 0.2 mg/kg (approximately 70 times the maximum recommended daily inhalation dose in humans on a mg/m^2 basis). When given to rats throughout organogenesis, oral doses of 0.2 mg/kg and above delayed ossification of the fetus, and doses of 6 mg/kg and above decreased fetal weight. Formoterol fumarate did not cause malformations in rats or rabbits following oral administration. Because there are no adequate and well-controlled studies in pregnant women, FORADIL AEROLIZER should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in Labor and Delivery

Formoterol fumarate has been shown to cause stillbirth and neonatal mortality at oral doses of 6 mg/kg (approximately 2000 times the maximum recommended daily inhalation dose in humans on a mg/m^2 basis) and above in rats receiving the drug for several days at the end of pregnancy. These effects were not produced at a dose of 0.2 mg/kg (approximately 70 times the maximum recommended daily inhalation dose in humans on a mg/m^2 basis). There are no adequate and well-controlled human studies that have investigated the effects of FORADIL AEROLIZER during labor and delivery.

Because beta-agonists may potentially interfere with uterine contractility, FORADIL AEROLIZER should be used during labor only if the potential benefit justifies the potential risk.

Nursing Mothers

In reproductive studies in rats, formoterol was excreted in the milk. It is not known whether formoterol is excreted in human milk, but because many drugs are excreted in human milk, caution should be exercised if FORADIL AEROLIZER is administered to nursing women. There are no well-controlled human studies of the use of FORADIL AEROLIZER in nursing mothers.

Pediatric Use

Asthma

A total of 776 children 5 years of age and older with asthma were studied in three multiple-dose controlled clinical trials. Of the 512 children who received formoterol, 508 were 5-12 years of age, and approximately one third were 5-8 years of age.

Exercise Induced Bronchoconstriction

A total of 20 adolescent patients, 12-16 years of age, were studied in three well-controlled single-dose clinical trials.

The safety and effectiveness of FORADIL AEROLIZER in pediatric patients below 5 years of age has not been established. (See CLINICAL TRIALS, Pediatric Asthma Trial, and ADVERSE REACTIONS, Experience in Pediatric, Adolescent and Adult Patients.)

Geriatric Use

Of the total number of patients who received FORADIL AEROLIZER in adolescent and adult chronic dosing asthma clinical trials, 318 were 65 years of age or older and 39 were 75 years of age and older. Of the 811 patients who received FORADIL AEROLIZER in two pivotal multiple-does controlled clinical studies in patients with COPD, 395 (48.7%) were 65 years of age or older while 62 (7.6%) were 75 years of age or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. A slightly higher frequency of chest infection was reported in the 39 asthma patients 75 years of age and older, although a causal relationship with Foradil has not been established. Other reported clinical experience has not identified differences in responses between the elderly and younger adult patients, but greater sensitivity of some older individuals cannot be ruled out. (See PRECAUTIONS, Drug Interactions.)

ADVERSE REACTIONS

Adverse reactions to Foradil are similar in nature to other selective $beta_2$-adrenoceptor agonists; e.g., angina, hypertension or hypotension, tachycardia, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, muscle cramps, nausea, dizziness, fatigue, malaise, hypokalemia, hyperglycemia, metabolic acidosis and insomnia.

Experience in Pediatric, Adolescent and Adult Patients with Asthma

Of the 5,824 patients in multiple-dose controlled clinical trials, 1,985 were treated with FORADIL AEROLIZER at the recommended dose of 12 mcg twice daily. The following table shows adverse events where the frequency was greater than or equal to 1% in the Foradil twice daily group and where the rates in the Foradil group exceeded placebo. Three adverse events showed dose ordering among tested doses of 6, 12 and 24 mcg administered twice daily; tremor, dizziness and dysphonia.

NUMBER AND FREQUENCY OF ADVERSE EXPERIENCES IN PATIENTS 5 YEARS OF AGE AND OLDER FROM MULTIPLE-DOSE CONTROLLED CLINICAL TRIALS

Adverse Event	Foradil Aerolizer 12 mcg twice daily		Placebo	
	n	(%)	n	(%)
Total Patients	1985	(100)	969	(100)
Infection viral	341	(17.2)	166	(17.1)
Bronchitis	92	(4.6)	42	(4.3)
Chest infection	54	(2.7)	4	(0.4)
Dyspnea	42	(2.1)	16	(1.7)
Chest pain	37	(1.9)	13	(1.3)
Tremor	37	(1.9)	4	(0.4)
Dizziness	31	(1.6)	15	(1.5)
Insomnia	29	(1.5)	8	(0.8)
Tonsilitis	23	(1.2)	7	(0.7)
Rash	22	(1.1)	7	(0.7)
Dysphonia	19	(1.0)	9	(0.9)

Experience in Children with Asthma

The safety of FORADIL AEROLIZER compared to placebo was investigated in one large, multicenter, randomized, double-blind clinical trial in 518 children with asthma (ages 5-12 years) in need of daily bronchodilators and anti-inflammatory treatment. The numbers and percent of patients who reported adverse events were comparable in the 12 mcg twice daily and placebo groups. In general, the pattern of the adverse events observed in children differed from the usual pattern seen in adults. The adverse events that were more frequent in the formoterol group than in the placebo group reflected infection/inflammation (viral infection, rhinitis, tonsilitis, gastroenteritis) or abdominal complaints (abdominal pain, nausea, dyspepsia).

Experience in Adult Patients with COPD

Of the 1634 patients in two pivotal multiple dose Chronic Obstructive Pulmonary Disease (COPD) controlled trials, 405 were treated with FORADIL AEROLIZER 12 mcg twice daily. The numbers and percent of patients who reported adverse events were comparable in the 12 mcg twice daily and placebo groups. Adverse events (AE's) experienced were similar to those seen in asthmatic patients, but with a higher incidence of COPD-related AE's in both placebo and formoterol treated patients.

The following table shows adverse events where the frequency was greater than or equal to 1% in the FORADIL AEROLIZER group and where the rates in the FORADIL AEROLIZER group exceeded placebo. The two clinical trials included doses of 12 mcg and 24 mcg, administered twice daily. Seven adverse events showed dose ordering among tested doses of 12 and 24 mcg administered twice daily; pharyngitis, fever, muscle cramps, increased sputum, dysphonia, myalgia, and tremor.

593

NUMBER AND FREQUENCY OF ADVERSE EXPERIENCES IN ADULT COPD PATIENTS TREATED IN MULTIPLE-DOSE CONTROLLED CLINICAL TRIALS		
Adverse event	FORADIL AEROLIZER 12mcg twice daily n (%)	Placebo n (%)
Total patients	405 (100)	420 (100)
Upper respiratory tract infection	30 (7.4)	24 (5.7)
Pain back	17 (4.2)	17 (4.0)
Pharyngitis	14 (3.5)	10 (2.4)
Pain chest	13 (3.2)	9 (2.1)
Sinusitis	11 (2.7)	7 (1.7)
Fever	9 (2.2)	6 (1.4)
Cramps leg	7 (1.7)	2 (0.5)
Cramps muscle	7 (1.7)	0
Anxiety	6 (1.5)	5 (1.2)
Pruritis	6 (1.5)	4 (1.0)
Sputum increased	6 (1.5)	5 (1.2)
Mouth dry	5 (1.2)	4 (1.0)
Trauma	5 (1.2)	0

594 Overall, the frequency of all cardiovascular adverse events in the two pivotal studies
595 was low and comparable to placebo (6.4% for FORADIL AEROLIZER 12 mcg twice daily,
596 and 6.0% for placebo). There were no frequently-occurring specific cardiovascular adverse
597 events for FORADIL AEROLIZER (frequency greater than or equal to 1% and greater than
598 placebo).

599 ## Post Marketing Experience

600 In extensive worldwide marketing experience with Foradil, serious exacerbations of asthma,
601 including some that have been fatal, have been reported. While most of these cases have been
602 in patients with severe or acutely deteriorating asthma (see WARNINGS), a few have
603 occurred in patients with less severe asthma. The contribution of Foradil to these cases could
604 not be determined.

605 Rare reports of anaphylactic reactions, including severe hypotension and angioedema,
606 have also been received in association with the use of formoterol fumarate inhalation powder.

607 # DRUG ABUSE AND DEPENDENCE

608 There was no evidence in clinical trials of drug dependence with the use of Foradil.

OVERDOSAGE

The expected signs and symptoms with overdosage of FORADIL AEROLIZER are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and symptoms listed under ADVERSE REACTIONS, e.g., angina, hypertension or hypotension, tachycardia, with rates up to 200 beats/min., arrhythmias, nervousness, headache, tremor, seizures, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, hypokalemia, hyperglycemia, and insomnia. Metabolic acidosis may also occur. As with all inhaled sympathomimetic medications, cardiac arrest and even death may be associated with an overdose of FORADIL AEROLIZER.

Treatment of overdosage consists of discontinuation of FORADIL AEROLIZER together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of FORADIL AEROLIZER. Cardiac monitoring is recommended in cases of overdosage.

The minimum acute lethal inhalation dose of formoterol fumarate in rats is 156 mg/kg~~,~~ (approximately 53,000 and 25,000 times the maximum recommended daily inhalation dose in adults and children, respectively, on a mg/m^2 basis). The median lethal oral doses in Chinese hamsters, rats, and mice provide even higher multiples of the maximum recommended daily inhalation dose in humans.

DOSAGE AND ADMINISTRATION

Foradil capsules should be administered only by the oral inhalation route (see the accompanying Patient Instructions for Use) and only using the Aerolizer Inhaler. Foradil capsules should not be ingested (i.e., swallowed) orally. Foradil capsules should always be stored in the blister, and only removed IMMEDIATELY BEFORE USE.

For Maintenance Treatment of Asthma

For adults and children 5 years of age and older, the usual dosage is the inhalation of the contents of one 12-mcg Foradil capsule 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 mcg 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 beta$_2$-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 and additional therapeutic options, such as inhaled or systemic corticosteroids, should be considered.

For Prevention of Exercise-Induced Bronchospasm (EIB)

For adults and adolescents 12 years of age or older, the usual dosage is the inhalation of the contents of one 12-mcg Foradil capsule at least 15 minutes before exercise administered on an occasional as-needed basis.

Additional doses of FORADIL AEROLIZER should not be used for 12 hours after the administration of this drug. Regular, twice-daily dosing has not been studied in preventing EIB. Patients who are receiving FORADIL AEROLIZER twice daily for maintenance treatment of their asthma should not use additional doses for prevention of EIB and may require a short-acting bronchodilator.

For Maintenance Treatment of Chronic Obstructive Pulmonary Disease (COPD)

The usual dosage is the inhalation of the contents of one 12 mcg Foradil capsule every 12 hours using the Aerolizer™ inhaler.

A total daily dose of greater than 24 mcg is not recommended.

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 COPD. Under these circumstances, the therapeutic regimen should be re-evaluated and additional therapeutic options should be considered.

HOW SUPPLIED

FORADIL® AEROLIZER™ contains: aluminum blister-packaged 12-mcg Foradil (formoterol fumarate) clear gelatin capsules with "CG" printed on one end and "FXF" printed on the opposite end; one Aerolizer™ Inhaler; and Patient Instructions for Use

Unit Dose (blister pack)

Box of 18 (strips of 6).....**NDC 0083-0167-11**

Unit Dose (blister pack)

Box of 60 (strips of 6).....**NDC 0083-0167-74.**

Foradil® capsules should be used with the Aerolizer™ Inhaler only. The Aerolizer™ Inhaler should not be used with any other capsules.

Prior to dispensing: Store in a refrigerator, 2°C-8°C (36°F-46°F)

After dispensing to patient: Store at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature]. Protect from heat and moisture. CAPSULES SHOULD ALWAYS BE STORED IN THE BLISTER AND ONLY REMOVED FROM THE BLISTER IMMEDIATELY BEFORE USE.

Always discard the Foradil® capsules and Aerolizer™ Inhaler by the "Use by" date and always use the new Aerolizer Inhaler provided with each new prescription.

Keep out of the reach of children.

SEPTEMBER 2001 Printed in U.S.A.

NOVARTIS

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, NJ 07936

89012502

FORADIL® AEROLIZER™

T2001-69
89012502

(formoterol fumarate inhalation powder)

FOR ORAL INHALATION ONLY

Patient Instructions for Use

NEVER PLACE A CAPSULE IN THE INHALER'S MOUTHPIECE

READ ALL INSTRUCTIONS BEFORE USE

FORADIL AEROLIZER consists of Foradil® capsules and Aerolizer™ inhaler. Both the capsules and the inhaler should be used by the "Use by" date written by your pharmacist on the sticker on the outside of the FORADIL AEROLIZER box. Upon receipt of FORADIL AEROLIZER from the pharmacy, remove the sticker with the "Use by" date from the outside of the box and place it on the Aerolizer inhaler cover. If the "Use by" date on the sticker is blank, you will need to count 4 months from the date of purchase and write this date on the sticker. Please check the product expiration date stamped on the box. If the product expiration date is less than 4 months from the purchase date, then you should write the expiration date on the sticker instead. Foradil capsules are provided in aluminum blisters wrapped in a foil pouch. You should open the pouch when you are ready to use Foradil Aerolizer.

This leaflet provides summary information about FORADIL AEROLIZER. Before you start to take FORADIL AEROLIZER, read this leaflet carefully and keep it for future use. You should read the leaflet that comes with your prescription every time you refill it because there may be new information. This leaflet does not contain the complete information about your medication.

For more information ask your health-care provider or pharmacist.

What you should know about FORADIL AEROLIZER

FORADIL AEROLIZER contains Foradil (formoterol fumarate), a medication that is provided as a powder inside a gelatin capsule, and an Aerolizer inhaler. Each gelatin capsule contains 12 mcg of active drug (formoterol fumarate) mixed with lactose, which is a sugar. The contents of the capsule (the powder) are inhaled, using the Aerolizer inhaler that is provided. THE CAPSULES SHOULD NOT BE SWALLOWED.

FORADIL AEROLIZER is used for the treatment of breathing problems experienced by people who have asthma, or chronic obstructive pulmonary disease (chronic bronchitis or emphysema). Foradil is a long-acting bronchodilator. It acts to help keep the airways open, making it easier to breathe, and reduces the symptoms of asthma, chronic bronchitis and emphysema. Symptoms of asthma and chronic obstructive pulmonary disease that are caused by airflow obstruction include shortness of breath, wheezing, chest tightness, and cough. A single dose of FORADIL AEROLIZER acts up to 12 hours, and therefore, should only be used twice daily.

Important Points to Remember About Using FORADIL AEROLIZER

1. **TELL YOUR HEALTH-CARE PROVIDER BEFORE STARTING TO TAKE THIS MEDICINE:**
- If you are pregnant or want to become pregnant,
- If you are breastfeeding a baby,
- If you are allergic to formoterol, or any other inhaled bronchodilator. In some circumstances, this medicine may not be right for you and your health-care provider may wish to give you a different medicine.

2. Make sure that your health-care provider knows what other medicines you are taking.

3. It is important that you inhale each dose as your health-care provider has advised. **Do not use FORADIL AEROLIZER more frequently than 2 times daily, morning and evening, approximately 12 hours apart, at the recommended dose.**

4. It is **IMPORTANT THAT YOU USE FORADIL AEROLIZER REGULARLY. DO NOT STOP TREATMENT EVEN IF YOU ARE FEELING BETTER** unless told to do so by your health-care provider.

5. If you miss a dose, just take your next scheduled dose when it is due. **DO NOT DOUBLE** the dose.

6. If you use FORADIL AEROLIZER more frequently than your health-care provider has prescribed, tell your health-care provider immediately. If you develop nausea and/or vomiting, shakiness, headache, fast or irregular heartbeat, or sleeplessness, tell your health-care provider immediately.

7. **DO NOT USE FORADIL AEROLIZER TO RELIEVE SUDDEN ASTHMA SYMPTOMS** (For example, sudden severe onset or worsening of wheezing, cough, chest tightness, and/or shortness of breath that has been diagnosed by your health-care provider as due to asthma). Sudden asthma symptoms should be treated with an inhaled, short-acting bronchodilator. If you do not have an inhaled, short-acting bronchodilator, contact your health-care provider to have one prescribed for you.

8. **Tell your health-care provider immediately if your asthma is getting worse, as indicated by any of the following situations** since you may need a re-evaluation of your treatment.
- The relief of your wheezing or chest tightness is not as good as usual or does not last for as long as usual.
- Your inhaled, short-acting bronchodilator becomes less effective.
- You need more inhalations than usual of your inhaled, short-acting bronchodilator.
- You have a significant decrease in your peak flow measurement as previously defined by your health-care provider.

9. Likewise, **tell your health-care provider immediately if your chronic obstructive pulmonary disease symptoms worsen, as indicated by any of the following situations** since you may need a re-evaluation of your treatment.
- The relief of your wheezing or chest tightness is not as good as usual or does not last for as long as usual, or your shortness of breath increases.
- Your inhaled, short-acting bronchodilator becomes less effective.
- You need more inhalations than usual of your inhaled, short-acting bronchodilator.
- You have a significant decrease in your peak flow measurement as previously defined by your health-care provider.
- Your sputum expectoration increases and becomes purulent.

10. Use other inhaled medicines only as directed by your health-care provider.

11. Do not use the Aerolizer inhaler with a spacer device.

How to use FORADIL AEROLIZER

Follow the instructions below. If you have any questions, ask your health-care provider or pharmacist.

Foradil capsules and the Aerolizer inhaler should be used by the "Use by" date written by your pharmacist on the sticker on the outside of the FORADIL AEROLIZER box. Upon receipt of FORADIL AEROLIZER from the pharmacy, remove the sticker with the "Use by" date from the outside of the box and place it on the Aerolizer inhaler cover. If the "Use by" date on the sticker is blank, you will need to count 4 months from the date of purchase and write this date on the sticker. Please check the product expiration date stamped on the box. If the product expiration date is less than 4 months from the purchase date, then you should write the expiration date on the sticker instead.

Your health-care provider will advise you how to use FORADIL AEROLIZER. Do not inhale more doses or use FORADIL AEROLIZER more often than your health-care provider advises.

USE ONLY AS DIRECTED BY YOUR HEALTH-CARE PROVIDER

For the long-term treatment of asthma, the recommended dose for adults and children 5 years of age and older is one Foradil capsule inhaled with the use of the Aerolizer inhaler (as described below) twice a day, approximately every 12 hours.

In patients 12 years of age and older, FORADIL AEROLIZER may be used to help prevent asthma attacks, brought on by physical activity or exercise. Inhale the contents of one capsule, as directed by your health-care provider, about 15 minutes before you start the activity or exercise.

Do not inhale more than the contents of one capsule at any one time. Additional doses of FORADIL AEROLIZER should not be used for 12 hours. If you are receiving FORADIL AEROLIZER twice daily for long-term treatment of asthma, you should not use additional doses of FORADIL AEROLIZER for prevention of asthma attacks brought on by physical activity or exercise. Instead you should use a short-acting bronchodilator that is prescribed for you by your health-care provider.

For the long-term treatment of chronic obstructive pulmonary disease (chronic bronchitis or emphysema), the recommended dose is one Foradil capsule inhaled with the use of the Aerolizer inhaler (as described below) twice a day, approximately every 12 hours.

How to use the Foradil capsules with your Aerolizer inhaler

Keep your Foradil and Aerolizer inhaler dry. Handle with DRY hands.

Foradil capsules are to be administered only with the Aerolizer inhaler provided. Do not use Foradil capsules with any other capsule inhaler, and do not use the Aerolizer inhaler to administer any other capsule medication. Do not use a spacer with the Aerolizer inhaler.

Check the "Use by" date on the Aerolizer inhaler cover. If the "Use by" date has passed, replace the product and Aerolizer inhaler. Remove the aluminum pouch covering the foil blister cards which contain the Foradil capsules.

1. Pull off the Aerolizer inhaler cover. (Figure 1)

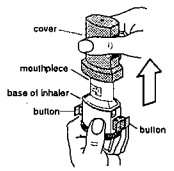


Figure 1

2. Hold the base of the Aerolizer inhaler firmly and twist the mouthpiece in the direction of the arrow to open. (Figure 2) Push the buttons in to make sure that the 4 pins are visible in the capsule well on each side.

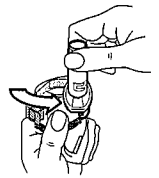


Figure 2

3. Remove capsule from foil blister IMMEDIATELY BEFORE USE.

4. Separate one blistered capsule by tearing at intersecting perforations. (Figure 3)

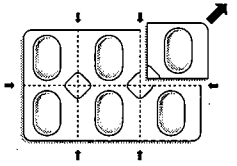


Figure 3

5. Peel paper backing from blister and push capsule through the remaining foil. (Figure 4)

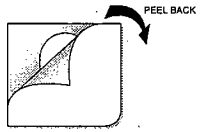


Figure 4

6. Place the capsule in the capsule-chamber in the base of the Aerolizer inhaler. NEVER PLACE A CAPSULE DIRECTLY INTO THE MOUTHPIECE. (Figure 5)

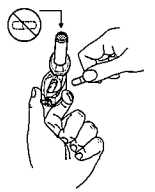


Figure 5

7. Twist the mouthpiece back to the closed position. (Figure 6)

Figure 6

8. With the mouthpiece of the Aerolizer inhaler upright, simultaneously press both buttons **ONCE**! You should hear a click as the capsule is being pierced. (Figure 7)

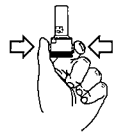


Figure 7

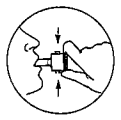
9. Release the buttons. If the buttons stick in the depressed position, grasp the wings on the buttons to retract them before the inhalation step. Do not depress the buttons a second time, since in rare cases, this may cause the capsule to shatter into small pieces. These pieces should be retained by the screen built into the Aerolizer inhaler. It remains possible that rarely, tiny pieces of gelatin capsule might reach your mouth or throat upon inhalation. Gelatin is not harmful if accidentally swallowed or inhaled. The capsule is less likely to shatter when pierced if capsules are removed from the foil blister IMMEDIATELY before use; storage conditions are strictly followed; and the capsule is only pierced ONCE.

10. Exhale fully. DO NOT EXHALE INTO THE MOUTHPIECE. (Figure 8)

Figure 8

11. Tilt your head back slightly. Keeping the Aerolizer inhaler horizontal, with the blue buttons to the left and right (NOT up and down), place the mouthpiece in your mouth, closing your lips around the mouthpiece. (Figure 9 and 10)

CORRECT
Figure 9



INCORRECT
Figure 10

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Foradil® Aerolizer™
(formoterol fumarate inhalation powder)

12. Breathe in rapidly but steadily, as deeply as you can (Figure 11). As the capsule spins around in the chamber dispensing the medication, you will experience a sweet taste and hear a whirring noise. If you have not heard the whirring noise, the capsule may be stuck. If this occurs, open the Aerolizer Inhaler and loosen the capsule allowing it to spin freely. DO NOT try to loosen the capsule by repeatedly pressing the buttons.

Figure 11

13. While removing the Aerolizer Inhaler from your mouth, continue to hold your breath as long as comfortably possible, then exhale.

14. Open the Aerolizer Inhaler to see if any powder is still in the capsule. If any powder remains in the capsule repeat steps 10 to 13. Most people are able to empty the capsule in one or two inhalations.

15. After use, open the Aerolizer Inhaler, remove and discard the empty capsule. Do not leave a used capsule in the chamber.

16. Close the mouthpiece and replace the cover.

REMEMBER:
- Never exhale into the Aerolizer Inhaler device.
- Never attempt to take the Aerolizer Inhaler apart.
- Never place a capsule directly into the mouthpiece of the Aerolizer Inhaler.
- Never leave a used capsule in the Aerolizer Inhaler chamber.
- Always use the Aerolizer Inhaler in a level, horizontal position.
- Never wash the Aerolizer Inhaler. KEEP IT DRY.
- Always keep the Aerolizer Inhaler and Foradil capsules in a dry place.
- Always use the new Aerolizer Inhaler that comes with your refill.

Side effects you may experience with FORADIL AEROLIZER

Along with its beneficial effects, a medicine may cause certain unwanted effects. FORADIL AEROLIZER may occasionally cause tremor, fast and irregular heart beat, or headache. Muscle cramps and pain, agitation, dizziness, nervousness or fatigue, difficulties with sleeping and irritation of the mouth or throat occur rarely. Some of these effects may go away as your body gets used to the medicine. Check with your doctor if any of these unwanted effects continues to bother you. Paradoxical bronchospasm, a narrowing of the airways, occurs very rarely, but may be serious. Report any increased difficulty in breathing after use of FORADIL AEROLIZER to your health-care provider immediately. You should also tell the health-care provider if you notice any other undesirable effects.

Expiration date
Use Foradil capsules before the "Use by" date on the Aerolizer Inhaler cover. The "Use by" date is either 4 months from the purchase date, or the product expiration date, whichever comes first.

Always discard the old Aerolizer Inhaler by the "Use by" date and use the new one provided with each new prescription.

Storing your FORADIL AEROLIZER
Once dispensed, store at controlled room temperature, 20°C to 25°C (68°F to 77°F). Protect from heat and moisture. CAPSULES SHOULD ALWAYS BE STORED IN THE BLISTER AND ONLY REMOVED FROM THE BLISTER IMMEDIATELY BEFORE USE.

Keep this and all drugs out of the reach of children.

REMEMBER: This medicine has been prescribed for you by your health-care provider. DO NOT give this medicine to anyone else.

Your health-care provider has determined that this product is likely to help your personal health. **USE THIS PRODUCT AS DIRECTED, UNLESS INSTRUCTED TO DO OTHERWISE BY YOUR HEALTH-CARE PROVIDER.** If you have any further questions about the use of FORADIL AEROLIZER, consult with your health-care provider or call 1-877-FORADIL (1-877-367-2345).

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SEPTEMBER 2001 Printed in U.S.A. 89012502

NOVARTIS

Distributed by
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

89012302

FORADIL® AEROLIZER™

T2001-70
89012302

(formoterol fumarate inhalation powder)

FOR ORAL INHALATION ONLY

Patient Instructions for Use

NEVER PLACE A CAPSULE IN THE INHALER'S MOUTHPIECE

READ ALL INSTRUCTIONS BEFORE USE

FORADIL AEROLIZER consists of Foradil® capsules and Aerolizer™ inhaler. Both the capsules and the inhaler should be used by the "Use by" date written by your pharmacist on the sticker on the outside of the FORADIL AEROLIZER box. Upon receipt of FORADIL AEROLIZER from the pharmacy, remove the sticker with the "Use by" date from the outside of the box and place it on the Aerolizer inhaler cover. If the "Use by" date on the sticker is blank, you will need to count 4 months from the date of purchase and write this date on the sticker. Please check the product expiration date stamped on the box. If the product expiration date is less than 4 months from the purchase date, then you should write the expiration date on the sticker instead. Foradil capsules are provided in aluminum blisters wrapped in a foil pouch. You should open the pouch when you are ready to use Foradil Aerolizer.

This leaflet provides summary information about FORADIL AEROLIZER. Before you start to take FORADIL AEROLIZER, read this leaflet carefully and keep it for future use. You should read the leaflet that comes with your prescription every time you refill it, because there may be new information. This leaflet does not contain the complete information about your medication.

For more information ask your health-care provider or pharmacist.

What you should know about FORADIL AEROLIZER

FORADIL AEROLIZER contains Foradil (formoterol fumarate), a medication that is provided as a powder inside a gelatin capsule, and an Aerolizer inhaler. Each gelatin capsule contains 12 mcg of active drug (formoterol fumarate) mixed with lactose, which is a sugar. The contents of the capsule (the powder) are inhaled, using the Aerolizer inhaler that is provided. THE CAPSULES SHOULD NOT BE SWALLOWED.

FORADIL AEROLIZER is used for the treatment of breathing problems experienced by people who have asthma, or chronic obstructive pulmonary disease (chronic bronchitis or emphysema). Foradil is a long-acting bronchodilator. It acts to help keep the airways open, making it easier to breathe, and reduces the symptoms of asthma, chronic bronchitis and emphysema. Symptoms of asthma and chronic obstructive pulmonary disease that are caused by airflow obstruction include shortness of breath, wheezing, chest tightness, and cough. A single dose of FORADIL AEROLIZER acts up to 12 hours, and therefore, should only be used twice daily.

Important Points to Remember About Using FORADIL AEROLIZER

1. **TELL YOUR HEALTH-CARE PROVIDER BEFORE STARTING TO TAKE THIS MEDICINE:**
   - If you are pregnant or want to become pregnant,
   - If you are breastfeeding a baby,
   - If you are allergic to formoterol, or any other inhaled bronchodilator. In some circumstances, this medicine may not be right for you and your health-care provider may wish to give you a different medicine.

2. Make sure that your health-care provider knows what other medicines you are taking.

3. It is important that you inhale each dose as your health-care provider has advised. **Do not use FORADIL AEROLIZER more frequently than 2 times daily, morning and evening, approximately 12 hours apart, at the recommended dose.**

4. It is **IMPORTANT THAT YOU USE FORADIL AEROLIZER REGULARLY. DO NOT STOP TREATMENT EVEN IF YOU ARE FEELING BETTER** unless told to do so by your health-care provider.

5. If you miss a dose, just take your next scheduled dose when it is due. **DO NOT DOUBLE** the dose.

6. If you use FORADIL AEROLIZER more frequently than your health-care provider has prescribed, tell your health-care provider immediately. If you develop nausea and/or vomiting, shakiness, headache, fast or irregular heartbeat, or sleeplessness, tell your health-care provider immediately.

7. **DO NOT USE FORADIL AEROLIZER TO RELIEVE SUDDEN ASTHMA SYMPTOMS** (For example, sudden severe onset or worsening of wheezing, cough, chest tightness, and/or shortness of breath that has been diagnosed by your health-care provider as due to asthma). Sudden asthma symptoms should be treated with an inhaled, short-acting bronchodilator. If you do not have an inhaled, short-acting bronchodilator, contact your health-care provider to have one prescribed for you.

8. **Tell your health-care provider immediately if your asthma is getting worse, as indicated by any of the following situations** since you may need a re-evaluation of your treatment.
   - The relief of your wheezing or chest tightness is not as good as usual or does not last for as long as usual.
   - Your inhaled, short-acting bronchodilator becomes less effective.
   - You need more inhalations than usual of your inhaled, short-acting bronchodilator.
   - You have a significant decrease in your peak flow measurement as previously defined by your health-care provider.

9. Likewise, **tell your health-care provider immediately if your chronic obstructive pulmonary disease symptoms worsen, as indicated by any of the following situations** since you may need a re-evaluation of your treatment.
   - The relief of your wheezing or chest tightness is not as good as usual or does not last for as long as usual, or your shortness of breath increases.
   - Your inhaled, short-acting bronchodilator becomes less effective.
   - You need more inhalations than usual of your inhaled, short-acting bronchodilator.
   - You have a significant decrease in your peak flow measurement as previously defined by your health-care provider.
   - Your sputum expectoration increases and becomes purulent.

10. Use other inhaled medicines only as directed by your health-care provider.

11. Do not use the Aerolizer inhaler with a spacer device.

How to use FORADIL AEROLIZER

Follow the instructions below. If you have any questions, ask your health-care provider or pharmacist.

Foradil capsules and the Aerolizer inhaler should be used by the "Use by" date written by your pharmacist on the sticker on the outside of the FORADIL AEROLIZER box. Upon receipt of FORADIL AEROLIZER from the pharmacy, remove the sticker with the "Use by" date from the outside of the box and place it on the Aerolizer inhaler cover. If the "Use by" date on the sticker is blank, you will need to count 4 months from the date of purchase and write this date on the sticker. Please check the product expiration date stamped on the box. If the product expiration date is less than 4 months from the purchase date, then you should write the expiration date on the sticker instead.

Your health-care provider will advise you how to use FORADIL AEROLIZER. Do not inhale more doses or use FORADIL AEROLIZER more often than your health-care provider advises.

USE ONLY AS DIRECTED BY YOUR HEALTH-CARE PROVIDER

For the long-term treatment of asthma, the recommended dose for adults and children 5 years of age and older is one Foradil capsule inhaled with the use of the Aerolizer inhaler (as described below) twice a day, approximately every 12 hours.

In patients 12 years of age and older, FORADIL AEROLIZER may be used to help prevent asthma attacks, brought on by physical activity or exercise. Inhale the contents of one capsule, as directed by your health-care provider, about 15 minutes before you start the activity or exercise.

Do not inhale more than the contents of one capsule at any one time. Additional doses of FORADIL AEROLIZER should not be used for 12 hours. If you are receiving FORADIL AEROLIZER twice daily for long-term treatment of asthma, you should not use additional doses of FORADIL AEROLIZER for prevention of asthma attacks brought on by physical activity or exercise, instead you should use a short-acting bronchodilator that is prescribed for you by your health-care provider.

For the long-term treatment of chronic obstructive pulmonary disease (chronic bronchitis or emphysema), the recommended dose is one Foradil capsule inhaled with the use of the Aerolizer inhaler (as described below) twice a day, approximately every 12 hours.

How to use the Foradil capsules with your Aerolizer inhaler

Keep your Foradil and Aerolizer inhaler dry. Handle with DRY hands.

Foradil capsules are to be administered only with the Aerolizer inhaler provided. Do not use Foradil capsules with any other capsule inhaler, and do not use the Aerolizer inhaler to administer any other capsule medication. Do not use a spacer with the Aerolizer inhaler.

Check the "Use by" date on the Aerolizer inhaler cover. If the "Use by" date has passed, replace the product and Aerolizer inhaler. Remove the aluminum pouch covering the foil blister cards which contain the Foradil capsules.

1. Pull off the Aerolizer inhaler cover. (Figure 1)

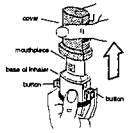

Figure 1

2. Hold the base of the Aerolizer inhaler firmly and twist the mouth piece in the direction of the arrow to open. (Figure 2) Push the buttons in to make sure that the 4 pins are visible in the capsule well on each side.

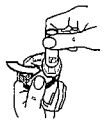

Figure 2

3. Remove capsule from foil blister IMMEDIATELY BEFORE USE.

4. Separate one blistered capsule by tearing at intersecting perforations.

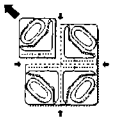

Figure 3

5. With foil-side up, fold back along perforation and flatten. (Figure 4)

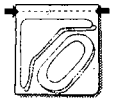

Figure 4

6. Starting at slit, tear off corner. (Figure 5)

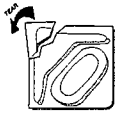

Figure 5

7. Separate/peel foil from paper backing and remove capsule. (Figure 6)

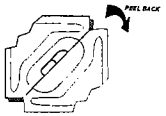

Figure 6

8. Place the capsule in the capsule-chamber in the base of the Aerolizer inhaler. NEVER PLACE A CAPSULE DIRECTLY INTO THE MOUTHPIECE. (Figure 7)

Figure 7

9. Twist the mouthpiece back to the closed position. (Figure 8)

Figure 8

10. With the mouthpiece of the Aerolizer inhaler upright, simultaneously press both buttons **ONCE!** You should hear a click as the capsule is being pierced. (Figure 9)

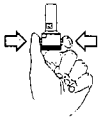

Figure 9

11. Release the buttons. If the buttons stick in the depressed position, grasp the wings on the buttons to retract them before the inhalation step. Do not depress the buttons a second time, since in rare cases, this may cause the capsule to shatter into small pieces. These pieces should be retained by the screen built into the Aerolizer inhaler. It remains possible that rarely, tiny pieces of gelatin capsule might reach your mouth or throat upon inhalation. Gelatin is not harmful if accidentally swallowed or inhaled. The capsule is less likely to shatter when pierced if capsules are removed from the foil blister IMMEDIATELY before use; storage conditions are strictly followed; and the capsule is only pierced ONCE.

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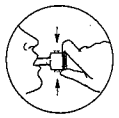
Foradil® Aerolizer™
(formoterol fumarate inhalation powder)

12. Exhale fully. DO NOT EXHALE INTO THE MOUTHPIECE. (Figure 10)

Figure 10

13. Tilt your head back slightly. Keeping the Aerolizer inhaler horizontal, with the blue buttons to the left and right (NOT up and down), place the mouthpiece in your mouth, closing your lips around the mouthpiece. (Figure 11 and 12)

CORRECT
Figure 11



INCORRECT
Figure 12

14. Breathe in rapidly but steadily, as deeply as you can (Figure 13). As the capsule spins around in the chamber dispensing the medication, you will experience a sweet taste and hear a whirring noise. If you have not heard the whirring noise, the capsule may be stuck. If this occurs, open the Aerolizer inhaler and loosen the capsule allowing it to spin freely. DO NOT try to loosen the capsule by repeatedly pressing the buttons.

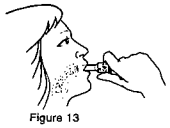


Figure 13

15. While removing the Aerolizer inhaler from your mouth, continue to hold your breath as long as comfortably possible, then exhale.

16. Open the Aerolizer inhaler to see if any powder is still in the capsule. If any powder remains in the capsule repeat steps 12 to 15. Most people are able to empty the capsule in one or two inhalations.

17. After use, open the Aerolizer inhaler, remove and discard the empty capsule. Do not leave a used capsule in the chamber.

18. Close the mouthpiece and replace the cover.

REMEMBER:
- Never exhale into the Aerolizer inhaler device.
- Never attempt to take the Aerolizer inhaler apart.
- Never place a capsule directly into the mouthpiece of the Aerolizer inhaler.
- Never leave a used capsule in the Aerolizer inhaler chamber.
- Always use the Aerolizer inhaler in a level, horizontal position.
- Never wash the Aerolizer inhaler. KEEP IT DRY.
- Always keep the Aerolizer inhaler and Foradil capsules in a dry place.
- Always use the new Aerolizer inhaler that comes with your refill.

Side effects you may experience with FORADIL AEROLIZER

Along with its beneficial effects, a medicine may cause certain unwanted effects. FORADIL AEROLIZER may occasionally cause tremor, fast and irregular heart beat, or headache. Muscle cramps and pain, agitation, dizziness, nervousness or fatigue, difficulties with sleeping and irritation of the mouth or throat occur rarely. Some of these effects may go away as your body gets used to the medicine. Check with your doctor if any of these unwanted effects continues to bother you. Paradoxical bronchospasm, a narrowing of the airways, occurs very rarely, but may be serious. Report any increased difficulty in breathing after use of FORADIL AEROLIZER to your health-care provider immediately. You should also tell the health-care provider if you notice any other undesirable effects.

Expiration date
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Always discard the old Aerolizer inhaler by the "Use by" date and use the new one provided with each new prescription.

Storing your FORADIL AEROLIZER
Once dispensed, store at controlled room temperature, 20°C to 25°C (68°F to 77°F). Protect from heat and moisture. CAPSULES SHOULD ALWAYS BE STORED IN THE BLISTER AND REMOVED FROM THE BLISTER IMMEDIATELY BEFORE USE.

Keep this and all drugs out of the reach of children.

REMEMBER: This medicine has been prescribed for you by your health-care provider. DO NOT give this medicine to anyone else.

Your health-care provider has determined that this product is likely to help your personal health. **USE THIS PRODUCT AS DIRECTED, UNLESS INSTRUCTED TO DO OTHERWISE BY YOUR HEALTH-CARE PROVIDER.** If you have any further questions about the use of FORADIL AEROLIZER, consult with your health-care provider or call 1-877-FORADIL (1-877-367-2345).

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Distributed by
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-831/S-002

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW #1

1. ORGANIZATION	2. NDA NUMBER
HFD-570 DPADP	20-831

3. NAME AND ADDRESS OF APPLICANT *(City and State)*
Novartis Pharmaceutical Corporation
59 Route 10
East Hanover, NJ 07936-1080

4. AF NUMBER

5. SUPPLEMENT(S)
NUMBER(S) DATES(S)
Y-002 21-APR-2003
(assigned 25-APR-2003)

6. NAME OF DRUG	7. NONPROPRIETARY NAME
Foradil® Aerolizer™ formoterol fumarate inhalation powder	formoterol fumarate inhalation powder

8. SUPPLEMENT PROVIDES FOR: The annual report Y-002 covers the period from 16-FEB-2002 to 15-FEB-2003.

9. AMENDMENT(S), REPORT(S), ETC.

10. PHARMACOLOGICAL CATEGORY	11. HOW DISPENSED
β_2-adrenergic bronchodilator for prevention and maintenance treatment of bronchoconstriction	RX X OTC __

12. RELATED IND/NDA/DMF

13. DOSAGE FORM(S)	14. POTENCY
inhalation powder	12 mcg/capsule; recommended dose one to two capsules every 12 hours; emitted dose 10 mcg when tested at 60L/min with 2 activations for 2 seconds each for one capsule

15. CHEMICAL NAME AND STRUCTURE
±2-Hydroxy-5-[(1RS)-1-hydroxy-2-[[(1RS)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]formanilide fumarate dihydrate

16. RECORDS AND REPORTS
CURRENT YES X NO__
REVIEWED YES__ NO X

17. COMMENTS: See review notes attached.
cc:
Orig. NDA 20-831
HFD-570/div. File
HFD-570/CBertha/2/19/04
HFD-570/RLostritto
HFD-570/AGreen
R/D Init. by:_____
F/T by: CBertha/2/19/04
doc # 03-04-21.rev.doc

18. CONCLUSIONS AND RECOMMENDATIONS: NAI

19. REVIEWER NAME:	SIGNATURE	DATE COMPLETED
Craig M. Bertha, Ph.D.		21-FEB-2004

2 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry- 20-831 S002

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/s/

Craig Bertha
3/8/04 06:42:47 AM
CHEMIST

Richard Lostritto
3/10/04 10:09:09 AM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-831/S-002

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

Project Manager's Labeling Review

NDA: 21-279 & NDA 20-831/S-002
Product: Foradil Aerolizer (formoterol fumarate inhalation powder)
Sponsor: Novartis
Submission dated: 9-24-01

These submissions contains the draft of the package insert (PI) and two patient instructions for use. This version was compared against the previous version submitted 9-12-01 to NDA 21-279.

Various documents were also considered. These include:

- Project Manager's Label Review of 9-12-01 version of PI
- Telecon dated 9-17-01
- Fax from applicant on 9-18-01

The 9-24-01 version of the two patient instructions for use are identical to the versions submitted 9-12-01 to NDA 21-279.

The 9-24-01 version of the package insert is identical to the 9-12-01 version submitted to NDA 21-279 except as follows:

1. All changes requested in the 9-17-01 correspondence and as recommended in the 9-25-01 Project Manager's Labeling review of the 9-12-01 version of the package insert were incorporated into the 9-24-01 version of the package insert.

OVERALL COMMENTS
This labeling submission is acceptable for division consideration with the noted comments.

Craig Ostroff, Pharm.D. Date
Project Manager

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/s/

Craig Ostroff
9/25/01 12:44:44 PM
CSO

Sandra Barnes
9/25/01 06:15:27 PM
CSO

MEMORANDUM OF TELECON

DATE: September 25, 2001

APPLICATION NUMBER: NDA 21-297, NDA 20-831/S-002
Foradil Aerolizer (formoterol fumarate inhalation powder)

BETWEEN:

Name: Kathy Basmadjian, Ph.D., Regulatory Affairs
Phone: 973-781-3666
Representing: Novartis Pharmaceuticals

AND

Name: Craig Ostroff, Pharm.D., Project Manager
Division of Pulmonary and Allergy Drug Products, HFD-570

SUBJECT: 1. Notification of Revision to 9-24-01 labeling
2. NDA Approval Confirmation of FAX Receipt

1. Labeling Revisions of the 9-24-01 labeling submitted to both the NDA and SNDA

The following three revisions were discussed:

a. Lines 247-250
The section should be revised as follows:

> In multiple-dose clinical trials in patients with COPD, FORADIL AEROLIZER 12 mcg was shown to provide ~~rapid~~ onset of significant bronchodilation (defined as 15% or greater increase from baseline in FEV_1), ~~reached~~ within 5 minutes of oral inhalation~~)~~ after the first dose. Bronchodilation was maintained for at least 12 hours.

b. Line 274
(1) Delete "is"; Insert "are" in its place

c. Line 625-626
The section should be revised as follows:

> ...(approximately 53,000 and 25,000 times the maximum recommended daily inhalation dose in adults and children, respectively, on a mg/m^2 basis)...

The applicant called back and confirmed that the changes as stated were acceptable.

2. Fax Receipt

The applicant has confirmed their receipt of the faxed approval letter.

Craig Ostroff, Pharm.D.
Project Manager

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/s/

Craig Ostroff
9/25/01 07:36:15 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-831

PRIOR APPROVAL SUPPLEMENT

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, New Jersey 07936-1080

Attention: Kathleen Basmadjian, PhD
Associate Director, Drug Regulatory Affairs

Dear Dr. Basmadjian:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Foradil ® Aerolizer ™ (formoterol fumarate inhalation powder)

NDA Number: 20-831

Supplement number: 002

Date of supplement: September 24, 2001

Date of receipt: September 24, 2001

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on November 23, 2001, in accordance with 21 CFR 314.101(a).

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Pulmonary and Allergy Drug Products, HFD-570
Attention: Division Document Room, 10B-03
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Division of Pulmonary and Drug Products, HFD-570
Attention: Document Room 10B-03
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Dr. Craig Ostroff, Regulatory Management Officer, at (301) 827-5585.

Sincerely yours,

Sandra L. Barnes
Chief, Project Management Staff
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Craig Ostroff
9/25/01 02:00:56 PM
For Sandy Barnes