

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-279**

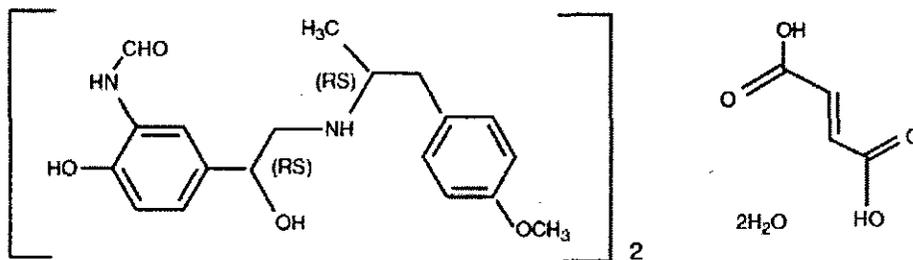
**APPROVED LABELING**

## DESCRIPTION

FORADIL<sup>®</sup> AEROLIZER<sup>™</sup> consists of a capsule dosage form containing a dry powder formulation of Foradil (formoterol fumarate) intended for oral inhalation only with the Aerolizer<sup>™</sup> 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<sub>2</sub>-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<sub>19</sub>H<sub>24</sub>N<sub>2</sub>O<sub>4</sub>)<sub>2</sub>•C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>•2H<sub>2</sub>O. 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<sub>2</sub>-adrenergic receptor agonist (beta<sub>2</sub>-agonist). Inhaled formoterol fumarate acts locally in the lung as a bronchodilator. In

35 vitro studies have shown that formoterol has more than 200-fold greater agonist activity at  
36 beta<sub>2</sub>-receptors than at beta<sub>1</sub>-receptors. Although beta<sub>2</sub>-receptors are the predominant  
37 adrenergic receptors in bronchial smooth muscle and beta<sub>1</sub>-receptors are the predominant  
38 receptors in the heart, there are also beta<sub>2</sub>-receptors in the human heart comprising 10%-50%  
39 of the total beta-adrenergic receptors. The precise function of these receptors has not been  
40 established, but they raise the possibility that even highly selective beta<sub>2</sub>-agonists may have  
41 cardiac effects.

42 The pharmacologic effects of beta<sub>2</sub>-adrenoceptor agonist drugs, including formoterol,  
43 are at least in part attributable to stimulation of intracellular adenylyl cyclase, the enzyme that  
44 catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3', 5'-adenosine  
45 monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial  
46 smooth muscle and inhibition of release of mediators of immediate hypersensitivity from  
47 cells, especially from mast cells.

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

### 53 **Animal Pharmacology**

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

### 58 **Pharmacokinetics**

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

### 65 **Absorption**

66 Following inhalation of a single 120 mcg dose of formoterol fumarate by 12 healthy subjects,  
67 formoterol was rapidly absorbed into plasma, reaching a maximum drug concentration of  
68 92 pg/mL within 5 minutes of dosing. In COPD patients treated for 12 weeks with formoterol  
69 fumarate 12 or 24 mcg b.i.d., the mean plasma concentrations of formoterol ranged between  
70 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  
71 inhalation.

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

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

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

### 86 ***Distribution***

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

### 91 ***Metabolism***

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

### 103 ***Excretion***

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

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

114 hours. From urinary excretion rates measured in these subjects, the mean terminal elimination  
115 half-lives for the (R,R)- and (S,S)-enantiomers were determined to be 13.9 and 12.3 hours,  
116 respectively. The (R,R)- and (S,S)-enantiomers represented about 40% and 60% of unchanged  
117 drug excreted in the urine, respectively, following single inhaled doses between 12 and  
118 120 mcg in healthy volunteers and single and repeated doses of 12 and 24 mcg in patients  
119 with asthma. Thus, the relative proportion of the two enantiomers remained constant over the  
120 dose range studied and there was no evidence of relative accumulation of one enantiomer over  
121 the other after repeated dosing.

## 122 **Special Populations**

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

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

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

134

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

## 137 **Pharmacodynamics**

### 138 **Systemic Safety and Pharmacokinetic/Pharmacodynamic Relationships**

139 The major adverse effects of inhaled beta<sub>2</sub>-agonists occur as a result of excessive activation of  
140 the systemic beta-adrenergic receptors. The most common adverse effects in adults and  
141 adolescents include skeletal muscle tremor and cramps, insomnia, tachycardia, decreases in  
142 plasma potassium, and increases in plasma glucose.

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

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

152 recommended clinical dose). Reductions of plasma potassium concentration were observed in  
153 all subjects. Maximum reductions from baseline ranged from 0.55 to 1.52 mmol/L with a  
154 median maximum reduction of 1.01 mmol/L. The formoterol plasma concentration was highly  
155 correlated with the reduction in plasma potassium concentration. Generally, the maximum  
156 effect on plasma potassium was noted 1 to 3 hours after peak formoterol plasma  
157 concentrations were achieved. A mean maximum increase of pulse rate of 26 bpm was  
158 observed 6 hours post dose. The maximum increase of mean corrected QT interval (QTc) was  
159 25 msec when calculated using Bazett's correction and was 8 msec when calculated using  
160 Fredericia's correction. The QTc returned to baseline within 12-24 hours post-dose.  
161 Formoterol plasma concentrations were weakly correlated with pulse rate and increase of QTc  
162 duration. The effects on plasma potassium, pulse rate, and QTc interval are known  
163 pharmacological effects of this class of study drug and were not unexpected at the very high  
164 formoterol dose (120 mcg single dose, 10 times the recommended single dose) tested in this  
165 study. These effects were well-tolerated by the healthy volunteers.

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

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

### 183 ***Tachyphylaxis/Tolerance***

184 In a clinical study in 19 adult patients with mild asthma, the bronchoprotective effect of  
185 formoterol, as assessed by methacholine challenge, was studied following an initial dose of  
186 24 mcg (twice the recommended dose) and after 2 weeks of 24 mcg twice daily. Tolerance to  
187 the bronchoprotective effects of formoterol was observed as evidenced by a diminished  
188 bronchoprotective effect on FEV<sub>1</sub> after 2 weeks of dosing, with loss of protection at the end of  
189 the 12 hour dosing period.

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

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

194 12-hour FEV<sub>1</sub> AUC) was observed within the formoterol arms over time, particularly with the  
195 24 mcg twice daily dose (twice the daily recommended dose). A similarly reduced FEV<sub>1</sub> AUC  
196 over time was also noted in the albuterol treatment arms (180 mcg four times daily by  
197 metered-dose inhaler).

## 198 CLINICAL TRIALS

### 199 Adolescent and Adult Asthma Trials

200 In a placebo-controlled, single-dose clinical trial, the onset of bronchodilation (defined as a  
201 15% or greater increase from baseline in FEV<sub>1</sub>) was similar for FORADIL AEROLIZER and  
202 albuterol 180 mcg by metered-dose inhaler.

203 In single-dose and multiple-dose clinical trials, the maximum improvement in FEV<sub>1</sub>  
204 for FORADIL AEROLIZER 12 mcg generally occurred within 1 to 3 hours, and an increase  
205 in FEV<sub>1</sub> above baseline was observed for 12 hours in most patients.

206 FORADIL AEROLIZER was compared to albuterol 180 mcg four times daily by  
207 metered-dose inhaler, and placebo in a total of 1095 adult and adolescent patients 12 years of  
208 age and above with mild-to-moderate asthma (defined as FEV<sub>1</sub> 40%-80% of the patient's  
209 predicted normal value) who participated in two pivotal, 12-week, multi-center, randomized,  
210 double-blind, parallel group studies.

211 The results of both studies showed that FORADIL AEROLIZER 12 mcg twice daily  
212 resulted in significantly greater post-dose bronchodilation (as measured by serial FEV<sub>1</sub> for  
213 12 hours post-dose) throughout the 12-week treatment period. Mean FEV<sub>1</sub> measurements  
214 from both studies are shown below for the first and last treatment days (see Figures 1 and 2).

215 Figures 1a and 1b: Mean FEV<sub>1</sub> from Clinical Trial A

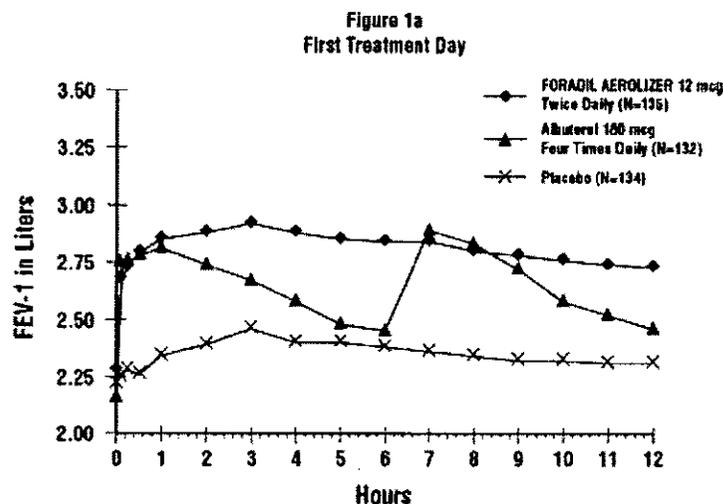
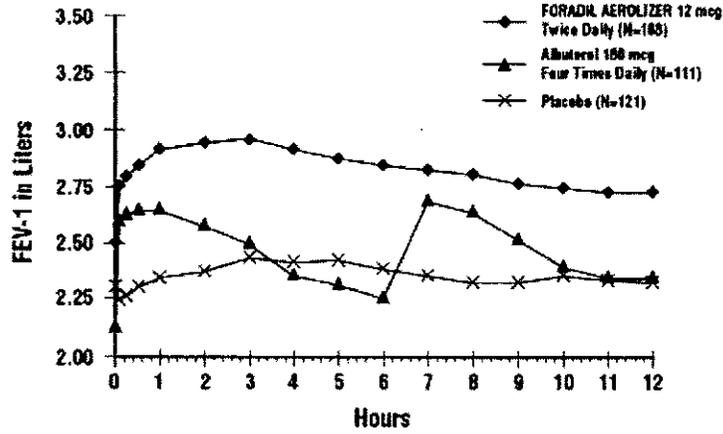


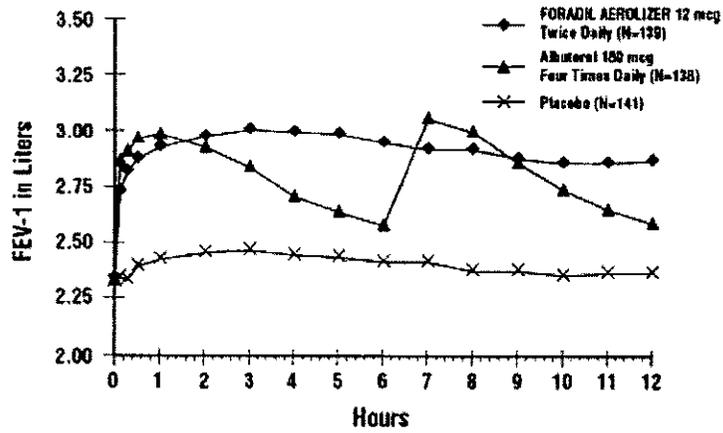
Figure 1b  
Last Treatment Day



217

218 Figures 2a and 2b: Mean FEV<sub>1</sub> from Clinical Trial B

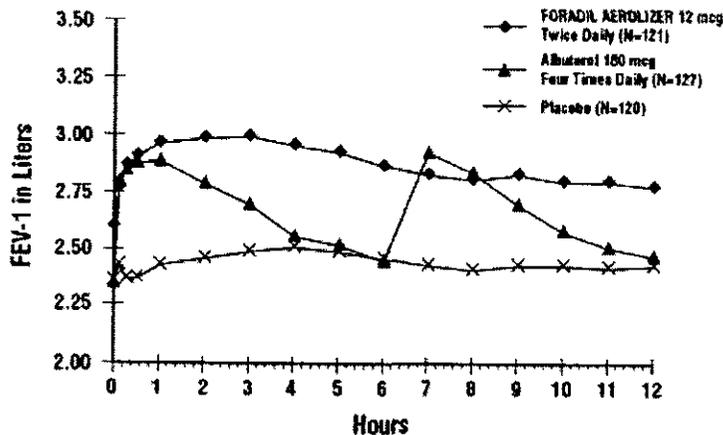
Figure 2a  
First Treatment Day



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Figure 2b  
Last Treatment Day



220

221 Compared with placebo and albuterol, patients treated with FORADIL AEROLIZER  
222 12 mcg demonstrated improvement in many secondary efficacy endpoints, including  
223 improved combined and nocturnal asthma symptom scores, fewer nighttime awakenings,  
224 fewer nights in which patients used rescue medication, and higher morning and evening peak  
225 flow rates.

### 226 Pediatric Asthma Trial

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

231 FORADIL AEROLIZER 12 mcg twice daily demonstrated a greater 12-hour FEV<sub>1</sub>  
232 AUC compared to placebo on the first day of treatment, after twelve weeks of treatment, and  
233 after one year of treatment.

### 234 Adolescent and Adult Exercise-Induced Bronchospasm Trials

235 The effect of FORADIL AEROLIZER on exercise-induced bronchospasm (defined as >20%  
236 fall in FEV<sub>1</sub>) was examined in two randomized, single-dose, double-blind, crossover studies  
237 in a total of 38 patients 13 to 41 years of age with exercise-induced bronchospasm. Exercise  
238 challenge testing was conducted 15 minutes, and 4, 8, and 12 hours following administration  
239 of a single dose of study drug (FORADIL AEROLIZER 12 mcg, albuterol 180 mcg by  
240 metered-dose inhaler, or placebo) on separate test days. FORADIL AEROLIZER 12 mcg and  
241 albuterol 180 mcg were each superior to placebo for FEV<sub>1</sub> measurements obtained 15 minutes  
242 after study drug administration. FORADIL AEROLIZER 12 mcg maintained superiority over  
243 placebo at 4, 8, and 12 hours after administration. The efficacy of FORADIL AEROLIZER in  
244 the prevention of exercise-induced bronchospasm when dosed on a regular twice daily  
245 regimen has not been studied.

246 **Adult COPD Trials**

247 In multiple-dose clinical trials in patients with COPD, FORADIL AEROLIZER 12 mcg was  
248 shown to provide — onset of significant bronchodilation (defined as 15% or greater  
249 increase from baseline in FEV<sub>1</sub>; — within 5 minutes of oral inhalation) after the first  
250 dose. Bronchodilation was maintained for at least 12 hours.

251 FORADIL AEROLIZER was studied in two pivotal, double-blind, placebo-controlled,  
252 randomized, multi-center, parallel-group trials in a total of 1634 adult patients (age range: 34-  
253 88 years; mean age: 63 years) with COPD who had a mean FEV<sub>1</sub> that was 46% of predicted.  
254 The diagnosis of COPD was based upon a prior clinical diagnosis of COPD, a smoking  
255 history (greater than 10 pack-years), age (at least 40 years), spirometry results  
256 (prebronchodilator baseline FEV<sub>1</sub> less than 70% of the predicted value, and at least 0.75 liters,  
257 with the FEV<sub>1</sub>/VC being less than 88% for men and less than 89% for women), and symptom  
258 score (greater than zero on at least four of the seven days prior to randomization). These  
259 studies included approximately equal numbers of patients with and without baseline  
260 bronchodilator reversibility, defined as a 15% or greater increase FEV<sub>1</sub> after inhalation of 200  
261 mcg of albuterol sulfate. A total of 405 patients received FORADIL AEROLIZER 12 mcg,  
262 administered twice daily. Each trial compared FORADIL AEROLIZER 12 mcg twice daily  
263 and FORADIL AEROLIZER 24 mcg twice daily with placebo and an active control drug.  
264 The active control drug was ipratropium bromide in COPD Trial A, and slow-release  
265 theophylline in COPD Trial B (the theophylline arm in this study was open-label). The  
266 treatment period was 12 weeks in COPD Trial A, and 12 months in COPD Trial B.

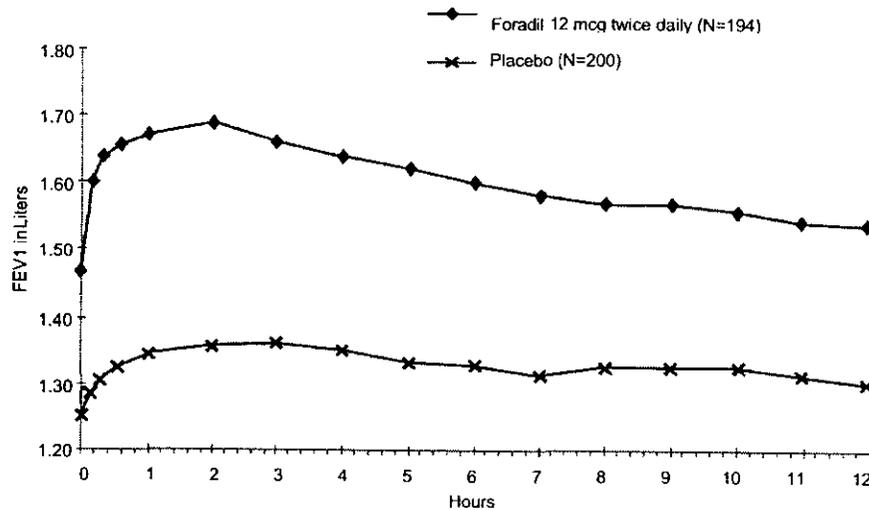
267 The results showed that FORADIL AEROLIZER 12 mcg twice daily resulted in significantly  
268 greater post-dose bronchodilation (as measured by serial FEV<sub>1</sub> for 12 hours post-dose; the  
269 primary efficacy analysis) compared to placebo when evaluated after 12 weeks of treatment in  
270 both trials, and after 12 months of treatment in the 12-month trial (COPD Trial B). Compared  
271 to FORADIL AEROLIZER 12 mcg twice daily, FORADIL AEROLIZER 24 mcg twice daily  
272 did not provide any additional benefit on a variety of endpoints including FEV<sub>1</sub>.

273 Mean FEV<sub>1</sub> measurements after 12 weeks of treatment for one of the two major efficacy  
274 studies are shown in the figure below.

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275 Figure 3

276 Mean FEV<sub>1</sub> after 12 Weeks of treatment from COPD Trial A



277

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

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

## 284 INDICATIONS AND USAGE

285 FORADIL AEROLIZER is indicated for long-term, twice-daily (morning and evening)  
286 administration in the maintenance treatment of asthma and in the prevention of bronchospasm  
287 in adults and children 5 years of age and older with reversible obstructive airways disease,  
288 including patients with symptoms of nocturnal asthma, who require regular treatment with  
289 inhaled, short-acting, beta<sub>2</sub>-agonists. It is not indicated for patients whose asthma can be  
290 managed by occasional use of inhaled, short-acting, beta<sub>2</sub>-agonists.

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

294 FORADIL AEROLIZER can be used to treat asthma concomitantly with short-acting  
295 beta<sub>2</sub>-agonists, inhaled or systemic corticosteroids, and theophylline therapy (see  
296 PRECAUTIONS, Drug Interactions). A satisfactory clinical response to FORADIL  
297 AEROLIZER does not eliminate the need for continued treatment with an anti-inflammatory  
298 agent.

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

## 302 **CONTRAINDICATIONS**

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

## 305 **WARNINGS**

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

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

314 **When beginning treatment with FORADIL AEROLIZER, patients who have**  
315 **been taking inhaled, short-acting beta<sub>2</sub>-agonists on a regular basis (e.g., four times a day)**  
316 **should be instructed to discontinue the regular use of these drugs and use them only for**  
317 **symptomatic relief of acute asthma symptoms (see PRECAUTIONS, Information for**  
318 **Patients).**

### 319 **Paradoxical Bronchospasm**

320 As with other inhaled beta<sub>2</sub>-agonists, formoterol can produce paradoxical bronchospasm, that  
321 may be life-threatening. If paradoxical bronchospasm occurs, FORADIL AEROLIZER should  
322 be discontinued immediately and alternative therapy instituted.

### 323 **Deterioration of Asthma**

324 Asthma may deteriorate acutely over a period of hours or chronically over several days or  
325 longer. If the usual dose of FORADIL AEROLIZER no longer controls the symptoms of  
326 bronchoconstriction, and the patient's inhaled, short-acting beta<sub>2</sub>-agonist becomes less  
327 effective or the patient needs more inhalation of short-acting beta<sub>2</sub>-agonist than usual, these  
328 may be markers of deterioration of asthma. In this setting, a re-evaluation of the patient and  
329 the asthma treatment regimen should be undertaken at once, giving special consideration to  
330 the possible need for anti-inflammatory treatment, e.g., corticosteroids. Increasing the daily  
331 dosage of FORADIL AEROLIZER beyond the recommended dose in this situation is not  
332 appropriate. FORADIL AEROLIZER should not be used more frequently than twice daily  
333 (morning and evening) at the recommended dose.

334 **Use of Anti-inflammatory Agents**

335 The use of beta<sub>2</sub>-agonists alone may not be adequate to control asthma in many patients. Early  
336 consideration should be given to adding anti-inflammatory agents, e.g., corticosteroids. There  
337 are no data demonstrating that Foradil has any clinical anti-inflammatory effect and therefore  
338 it cannot be expected to take the place of corticosteroids. Patients who already require oral or  
339 inhaled corticosteroids for treatment of asthma should be continued on this type of treatment  
340 even if they feel better as a result of initiating or increasing the dose of FORADIL  
341 AEROLIZER. Any change in corticosteroid dosage, in particular a reduction, should be made  
342 ONLY after clinical evaluation (see PRECAUTIONS, Information for Patients).

343 **Cardiovascular Effects**

344 Formoterol fumarate, like other beta<sub>2</sub>-agonists, can produce a clinically significant  
345 cardiovascular effect in some patients as measured by increases in pulse rate, blood pressure,  
346 and/or symptoms. Although such effects are uncommon after administration of FORADIL  
347 AEROLIZER at recommended doses, if they occur, the drug may need to be discontinued. In  
348 addition, beta-agonists have been reported to produce ECG changes, such as flattening of the  
349 T wave, prolongation of the QTc interval, and ST segment depression. The clinical  
350 significance of these findings is unknown. Therefore, formoterol fumarate, like other  
351 sympathomimetic amines, should be used with caution in patients with cardiovascular  
352 disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension  
353 (see PRECAUTIONS, General).

354 **Immediate Hypersensitivity Reactions**

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

358 **Do Not Exceed Recommended Dose**

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

363 **PRECAUTIONS**

364 **General**

365 FORADIL AEROLIZER should not be used to treat acute symptoms of asthma. FORADIL  
366 AEROLIZER has not been studied in the relief of acute asthma symptoms and extra doses  
367 should not be used for that purpose. When prescribing FORADIL AEROLIZER, the  
368 physician should also provide the patient with an inhaled, short-acting beta<sub>2</sub>-agonist for  
369 treatment of symptoms that occur acutely, despite regular twice-daily (morning and evening)  
370 use of FORADIL AEROLIZER. Patients should also be cautioned that increasing inhaled

371 beta<sub>2</sub>-agonist use is a signal of deteriorating asthma. (See Information for Patients and the  
372 accompanying Patient Instructions For Use.)

373 Formoterol fumarate, like other sympathomimetic amines, should be used with caution  
374 in patients with cardiovascular disorders, especially coronary insufficiency, cardiac  
375 arrhythmias, and hypertension; in patients with convulsive disorders or thyrotoxicosis; and in  
376 patients who are unusually responsive to sympathomimetic amines. Clinically significant  
377 changes in systolic and/or diastolic blood pressure, pulse rate and electrocardiograms have  
378 been seen infrequently in individual patients in controlled clinical studies with formoterol.  
379 Doses of the related beta<sub>2</sub>-agonist albuterol, when administered intravenously, have been  
380 reported to aggravate preexisting diabetes mellitus and ketoacidosis.

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

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

388 Foradil<sup>®</sup> capsules should ONLY be used with the Aerolizer<sup>™</sup> Inhaler and SHOULD  
389 NOT be taken orally.

390 Foradil<sup>®</sup> capsules should always be stored in the blister, and only removed  
391 IMMEDIATELY before use.

## 392 **Information for Patients**

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

396 The active ingredient of Foradil (formoterol fumarate) is a long-acting, bronchodilator  
397 used for the treatment of asthma, including nocturnal asthma, and for the prevention of  
398 exercise-induced bronchospasm. FORADIL AEROLIZER provides bronchodilation for up to  
399 12 hours. Patients should be advised not to increase the dose or frequency of FORADIL  
400 AEROLIZER without consulting the prescribing physician. Patients should be warned not to  
401 stop or reduce concomitant asthma therapy without medical advice.

402 FORADIL AEROLIZER is not indicated to relieve acute asthma symptoms and extra  
403 doses should not be used for that purpose. Acute symptoms should be treated with an inhaled,  
404 short-acting, beta<sub>2</sub>-agonist (the health-care provider should prescribe the patient with such  
405 medication and instruct the patient in how it should be used). Patients should be instructed to  
406 seek medical attention if their symptoms worsen, if FORADIL AEROLIZER treatment  
407 becomes less effective, or if they need more inhalations of a short-acting beta<sub>2</sub>-agonist than  
408 usual. Patients should not inhale more than the contents of the prescribed number of capsules  
409 at any one time. The daily dosage of FORADIL AEROLIZER should not exceed one capsule  
410 twice daily (24 mcg total daily dose).

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

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

420 Patients should be informed that treatment with beta<sub>2</sub>-agonists may lead to adverse  
421 events which include palpitations, chest pain, rapid heart rate, tremor or nervousness. Patients  
422 should be informed never to use FORADIL AEROLIZER with a spacer and never to exhale  
423 into the device.

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

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

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

### 435 **Drug Interactions**

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

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

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

446 Formoterol, as with other beta<sub>2</sub>-agonists, should be administered with extreme caution  
447 to patients being treated with monamine oxidase inhibitors, tricyclic antidepressants, or drugs  
448 known to prolong the QTc interval because the action of adrenergic agonists on the  
449 cardiovascular system may be potentiated by these agents. Drugs that are known to prolong  
450 the QTc interval have an increased risk of ventricular arrhythmias.

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

### 459 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

469 In mice, the incidence of adrenal subcapsular adenomas and carcinomas was increased  
470 in males at doses of 69 mg/kg and above in the drinking water study, but not at doses up to  
471 50 mg/kg (AUC exposure approximately 590 times human exposure at the maximum  
472 recommended daily inhalation dose) in the dietary study. The incidence of hepatocarcinomas  
473 was increased in the dietary study at doses of 20 and 50 mg/kg in females and 50 mg/kg in  
474 males, but not at doses up to 5 mg/kg in either males or females (AUC exposure  
475 approximately 60 times human exposure at the maximum recommended daily inhalation  
476 dose). Also in the dietary study, the incidence of uterine leiomyomas and leiomyosarcomas  
477 was increased at doses of 2 mg/kg and above (AUC exposure at the low dose of 2 mg/kg was  
478 approximately 25 times human exposure at the maximum recommended daily inhalation  
479 dose). Increases in leiomyomas of the rodent female genital tract have been similarly  
480 demonstrated with other beta-agonist drugs.

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

485 Reproduction studies in rats revealed no impairment of fertility at oral doses up to  
486 3 mg/kg (approximately 1000 times the maximum recommended daily inhalation dose in  
487 humans on a mg/m<sup>2</sup> basis).

### 488 **Pregnancy, Teratogenic Effects, Pregnancy Category C**

489 Formoterol fumarate has been shown to cause stillbirth and neonatal mortality at oral doses of  
490 6 mg/kg (approximately 2000 times the maximum recommended daily inhalation dose in  
491 humans on a mg/m<sup>2</sup> basis) and above in rats receiving the drug during the late stage of

492 pregnancy. These effects, however, were not produced at a dose of 0.2 mg/kg (approximately  
493 70 times the maximum recommended daily inhalation dose in humans on a mg/m<sup>2</sup> basis).  
494 When given to rats throughout organogenesis, oral doses of 0.2 mg/kg and above delayed  
495 ossification of the fetus, and doses of 6 mg/kg and above decreased fetal weight. Formoterol  
496 fumarate did not cause malformations in rats or rabbits following oral administration. Because  
497 there are no adequate and well-controlled studies in pregnant women, FORADIL  
498 AEROLIZER should be used during pregnancy only if the potential benefit justifies the  
499 potential risk to the fetus.

### 500 **Use in Labor and Delivery**

501 Formoterol fumarate has been shown to cause stillbirth and neonatal mortality at oral doses of  
502 6 mg/kg (approximately 2000 times the maximum recommended daily inhalation dose in  
503 humans on a mg/m<sup>2</sup> basis) and above in rats receiving the drug for several days at the end of  
504 pregnancy. These effects were not produced at a dose of 0.2 mg/kg (approximately 70 times  
505 the maximum recommended daily inhalation dose in humans on a mg/m<sup>2</sup> basis). There are no  
506 adequate and well-controlled human studies that have investigated the effects of FORADIL  
507 AEROLIZER during labor and delivery.

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

### 511 **Nursing Mothers**

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

### 517 **Pediatric Use**

#### 518 ***Asthma***

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

#### 522 ***Exercise Induced Bronchoconstriction***

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

525 The safety and effectiveness of FORADIL AEROLIZER in pediatric patients below  
526 5 years of age has not been established. (See CLINICAL TRIALS, Pediatric Asthma Trial,  
527 and ADVERSE REACTIONS, Experience in Pediatric, Adolescent and Adult Patients.)

528 **Geriatric Use**

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

540 **ADVERSE REACTIONS**

541 Adverse reactions to Foradil are similar in nature to other selective beta<sub>2</sub>-adrenoceptor  
542 agonists; e.g., angina, hypertension or hypotension, tachycardia, arrhythmias, nervousness,  
543 headache, tremor, dry mouth, palpitation, muscle cramps, nausea, dizziness, fatigue, malaise,  
544 hypokalemia, hyperglycemia, metabolic acidosis and insomnia.

545 **Experience in Pediatric, Adolescent and Adult Patients with Asthma**

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

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

555 Adverse Event	556 Foradil Aerolizer		557 Placebo	
	12 mcg twice daily			
	n	(%)	n	(%)
558 Total Patients	1985	(100)	969	(100)
559 Infection viral	341	(17.2)	166	(17.1)
560 Bronchitis	92	(4.6)	42	(4.3)
561 Chest infection	54	(2.7)	4	(0.4)
562 Dyspnea	42	(2.1)	16	(1.7)
563 Chest pain	37	(1.9)	13	(1.3)
564 Tremor	37	(1.9)	4	(0.4)
565 Dizziness	31	(1.6)	15	(1.5)
566 Insomnia	29	(1.5)	8	(0.8)
567 Tonsillitis	23	(1.2)	7	(0.7)
568 Rash	22	(1.1)	7	(0.7)
569 Dysphonia	19	(1.0)	9	(0.9)

570 **Experience in Children with Asthma**

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

580 **Experience in Adult Patients with COPD**

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

587 The following table shows adverse events where the frequency was greater than or  
588 equal to 1% in the FORADIL AEROLIZER group and where the rates in the FORADIL  
589 AEROLIZER group exceeded placebo. The two clinical trials included doses of 12 mcg and  
590 24 mcg, administered twice daily. Seven adverse events showed dose ordering among tested  
591 doses of 12 and 24 mcg administered twice daily; pharyngitis, fever, muscle cramps,  
592 increased sputum, dysphonia, myalgia, and tremor.

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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.

609 **OVERDOSAGE**

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

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

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

629 **DOSAGE AND ADMINISTRATION**

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

634 **For Maintenance Treatment of Asthma**

635 For adults and children 5 years of age and older, the usual dosage is the inhalation of the  
636 contents of one 12-mcg Foradil capsule every 12 hours using the Aerolizer™ Inhaler. The  
637 patient must not exhale into the device. The total daily dose of Foradil should not exceed one  
638 capsule twice daily (24 mcg total daily dose). More frequent administration or administration  
639 of a larger number of inhalations is not recommended. If symptoms arise between doses, an  
640 inhaled short-acting beta<sub>2</sub>-agonist should be taken for immediate relief.

641 If a previously effective dosage regimen fails to provide the usual response, medical  
642 advice should be sought immediately as this is often a sign of destabilization of asthma. Under  
643 these circumstances, the therapeutic regimen should be reevaluated and additional therapeutic  
644 options, such as inhaled or systemic corticosteroids, should be considered.

645 **For Prevention of Exercise-Induced Bronchospasm (EIB)**

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

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

654 **For Maintenance Treatment of Chronic Obstructive Pulmonary Disease**  
655 **(COPD)**

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

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

659 If a previously effective dosage regimen fails to provide the usual response, medical  
660 advice should be sought immediately as this is often a sign of destabilization of COPD. Under  
661 these circumstances, the therapeutic regimen should be re-evaluated and additional therapeutic  
662 options should be considered.

663 **HOW SUPPLIED**

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

667 Unit Dose (blister pack)

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

669 Unit Dose (blister pack)

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

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

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

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

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

680 Keep out of the reach of children.

681

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# FORADIL® AEROLIZER™

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## 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)

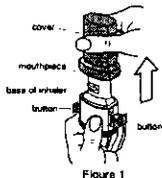


Figure 1

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.

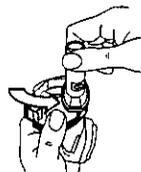


Figure 2

3. Remove capsule from foil blister IMMEDIATELY BEFORE USE.

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

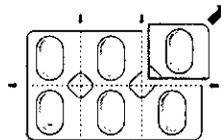


Figure 3

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

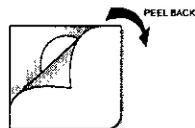


Figure 4

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)

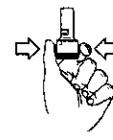


Figure 7

9. Release the buttons. If the buttons stick in the depressed position, grasp the wings on the buttons to retract them before the inhalation site. 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)

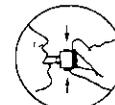


Figure 8

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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 NOVARTIS

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East Hanover, New Jersey 07936



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**FORADIL® AEROLIZER™** T2001-70  
(formoterol fumarate inhalation powder) 89012302

**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)

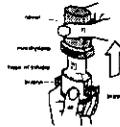


Figure 1

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.

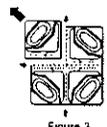


Figure 3

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

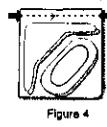


Figure 4

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



Figure 5

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

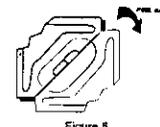


Figure 6

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)

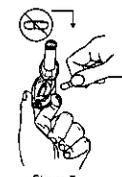


Figure 7

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)

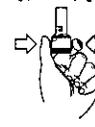


Figure 9

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)

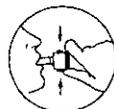


Figure 10

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**

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.

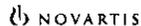
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Once dispensed, store at controlled room temperature, 20°C to 25°C (68°F to 77°F). Protect from heat and moisture. CAPSULES SHOULD ALWAYS BE STORED IN THE BLISTER AND REMOVED FROM THE BLISTER IMMEDIATELY BEFORE USE.

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

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/s/

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