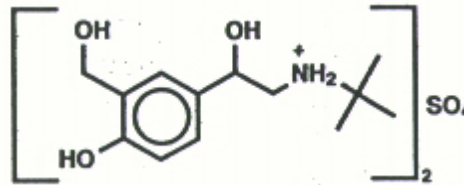


1 **PROAIR™ HFA (ALBUTEROL SULFATE)**
2 **INHALATION AEROSOL**
3 For Oral Inhalation Only

4 **PRESCRIBING INFORMATION**

5 **DESCRIPTION**

6 The active ingredient of ProAir HFA (albuterol sulfate) Inhalation Aerosol is
7 albuterol sulfate, a racemic salt, of albuterol. Albuterol sulfate is a relatively
8 selective beta₂-adrenergic agonist (see **CLINICAL PHARMACOLOGY**).
9 Albuterol sulfate has the chemical name α¹-[(*tert*-butylamino) methyl]-4-
10 hydroxy-*m*-xylene-α,α'-diol sulfate (2:1) (salt), and has the following chemical
11 structure:



12
13 The molecular weight of albuterol sulfate is 576.7, and the empirical formula is
14 (C₁₃H₂₁NO₃)₂•H₂SO₄. Albuterol sulfate is a white to off-white crystalline
15 powder. It is soluble in water and slightly soluble in ethanol. Albuterol sulfate is
16 the official generic name in the United States, and salbutamol is the World Health
17 Organization recommended generic name. ProAir HFA Inhalation Aerosol is a
18 pressurized metered-dose aerosol unit for oral inhalation. It contains a
19 microcrystalline suspension of albuterol sulfate in propellant HFA-134a (1, 1, 1,
20 2-tetrafluoroethane) and ethanol.

21 Prime the inhaler before using for the first time and in cases where the inhaler has
22 not been used for more than 2 weeks by releasing three “test sprays” into the air,
23 away from the face. After priming, each actuation delivers 108 mcg albuterol
24 sulfate, from the actuator mouthpiece (equivalent to 90 mcg of albuterol base).
25 Each canister provides 200 actuations (inhalations).

26
27 This product does not contain chlorofluorocarbons (CFCs) as the propellant.

28
29 **CLINICAL PHARMACOLOGY**

30
31 **Mechanism of Action**

32 Activation of beta₂-adrenergic receptors on airway smooth muscle leads to the
33 activation of adenylyl cyclase and to an increase in the intracellular concentration of
34 cyclic-3', 5'-adenosine monophosphate (cyclic AMP). This increase of cyclic
35 AMP is associated with the activation of protein kinase A, which in turn inhibits
36 the phosphorylation of myosin and lowers intracellular ionic calcium
37 concentrations, resulting in muscle relaxation. Albuterol relaxes the smooth
38 muscle of all airways, from the trachea to the terminal bronchioles. Increased

39 cyclic AMP concentrations are also associated with the inhibition of release of
40 mediators from mast cells in the airway. Albuterol acts as a functional antagonist
41 to relax the airway irrespective of the spasmogen involved, thus protecting against
42 all bronchoconstrictor challenges. While it is recognized that beta₂-adrenergic
43 receptors are the predominant receptors on bronchial smooth muscle, data
44 indicate that there are beta-receptors in the human heart, 10% to 50% of which
45 are cardiac beta₂-adrenergic receptors. The precise function of these receptors has
46 not been established (**See WARNINGS: Cardiovascular Effects**).

47

48 However, all beta-adrenergic agonist drugs can produce a significant
49 cardiovascular effect in some patients, as measured by pulse rate, blood pressure,
50 symptoms, and/or electrocardiographic changes.

51

52 **Preclinical**

53

54 Intravenous studies in rats with albuterol sulfate have demonstrated that albuterol
55 crosses the blood-brain barrier and reaches brain concentrations amounting to
56 approximately 5% of the plasma concentrations. In structures outside the blood-
57 brain barrier (pineal and pituitary glands), albuterol concentrations were found to
58 be 100 times those in the whole brain.

59

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

64

65 Propellant HFA-134a is devoid of pharmacological activity except at very high
66 doses in animals (380 - 1300 times the maximum human exposure based on
67 comparisons of AUC values), primarily producing ataxia, tremors, dyspnea, or
68 salivation. These are similar to effects produced by the structurally related
69 chlorofluorocarbons (CFCs), which have been used extensively in metered-dose
70 inhalers.

71

72 In animals and humans, propellant HFA-134a was found to be rapidly absorbed
73 and rapidly eliminated, with an elimination half-life of 3 - 27 minutes in animals
74 and 5 - 7 minutes in humans. Time to maximum plasma concentration (T_{max}) and
75 mean residence time are both extremely short leading to a transient appearance of
76 HFA-134a in the blood with no evidence of accumulation.

77

78 **Pharmacokinetics**

79

80 The systemic levels of albuterol are low after inhalation of recommended doses.
81 In a crossover study conducted in healthy male and female volunteers, high
82 cumulative doses of ProAir HFA Inhalation Aerosol (1,080 mcg of albuterol base
83 administered over one hour) yielded mean peak plasma concentrations (C_{max}) and
84 systemic exposure (AUC_{inf}) of approximately 4,100 pg/mL and 28,426 pg•hr/mL,
85 respectively compared to approximately 3,900 pg/mL and 28,395 pg•hr/mL,
86 respectively following the same dose of an active HFA-134a albuterol inhaler

87 comparator. The terminal plasma half-life of albuterol delivered by ProAir HFA
88 Inhalation Aerosol was approximately 6 hours. Comparison of the
89 pharmacokinetic parameters demonstrated no differences between the products.
90

91 No pharmacokinetic studies for ProAir HFA Inhalation Aerosol have been
92 conducted in neonates, children, or elderly subjects.
93

94 **Metabolism and Elimination**

95
96 Information available in the published literature suggests that the primary enzyme
97 responsible for the metabolism of albuterol in humans is SULT1A3
98 (sulfotransferase). When racemic albuterol was administered either intravenously
99 or via inhalation after oral charcoal administration, there was a 3- to 4-fold
100 difference in the area under the concentration-time curves between the (R)- and
101 (S)-albuterol enantiomers, with (S)-albuterol concentrations being consistently
102 higher. However, without charcoal pretreatment, after either oral or inhalation
103 administration the differences were 8- to 24-fold, suggesting that the (R)-albuterol
104 is preferentially metabolized in the gastrointestinal tract, presumably by
105 SULT1A3.
106

107 The primary route of elimination of albuterol is through renal excretion (80% to
108 100%) of either the parent compound or the primary metabolite. Less than 20%
109 of the drug is detected in the feces. Following intravenous administration of
110 racemic albuterol, between 25% and 46% of the (R)-albuterol fraction of the dose
111 was excreted as unchanged (R)-albuterol in the urine.
112

113 **Special Populations**

114
115 **Hepatic Impairment:** The effect of hepatic impairment on the pharmacokinetics
116 of ProAir HFA Inhalation Aerosol has not been evaluated.
117

118 **Renal Impairment:** The effect of renal impairment on the pharmacokinetics of
119 albuterol was evaluated in 5 subjects with creatinine clearance of 7 to 53 mL/min,
120 and the results were compared with those from healthy volunteers. Renal disease
121 had not effect on the half-life, but there was a 67% decline in albuterol clearance.
122 Caution should be used when administering high doses of ProAir HFA Inhalation
123 Aerosol to patients with renal impairment.
124

125 **Clinical Trials**

126
127 In a 6-week, randomized, double-blind, placebo-controlled trial, ProAir HFA
128 Inhalation Aerosol (58 patients) was compared to a matched placebo HFA
129 Inhalation Aerosol (58 patients) in asthmatic patients 12 to 76 years of age at a
130 dose of 180 mcg albuterol four times daily. An evaluator-blind marketed active
131 comparator HFA-134a albuterol inhaler arm (56 patients) was included.
132

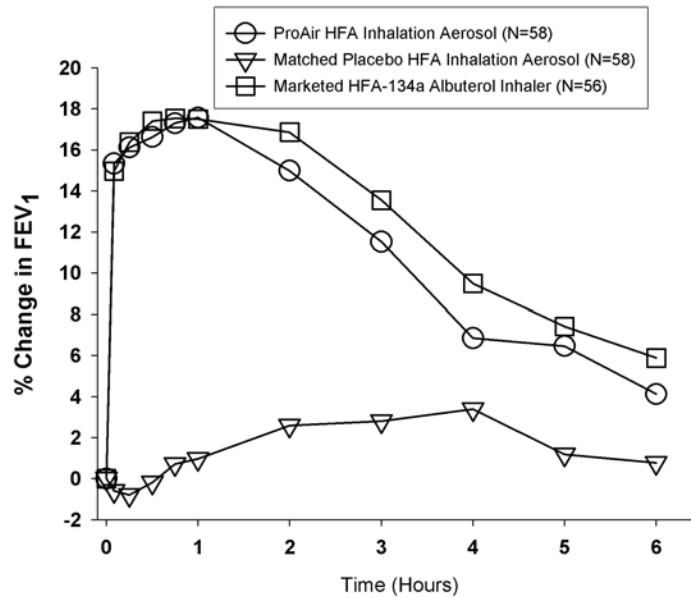
133 Serial FEV₁ measurements, shown below as percent change from test-day
134 baseline at Day 1 and at Day 43, demonstrated that two inhalations of ProAir

135 HFA Inhalation Aerosol produced significantly greater improvement in FEV₁
136 over the pre-treatment value than the matched placebo, as well as a comparable
137 bronchodilator effect to the marketed active comparator HFA-134a albuterol
138 inhaler.

139
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141
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143

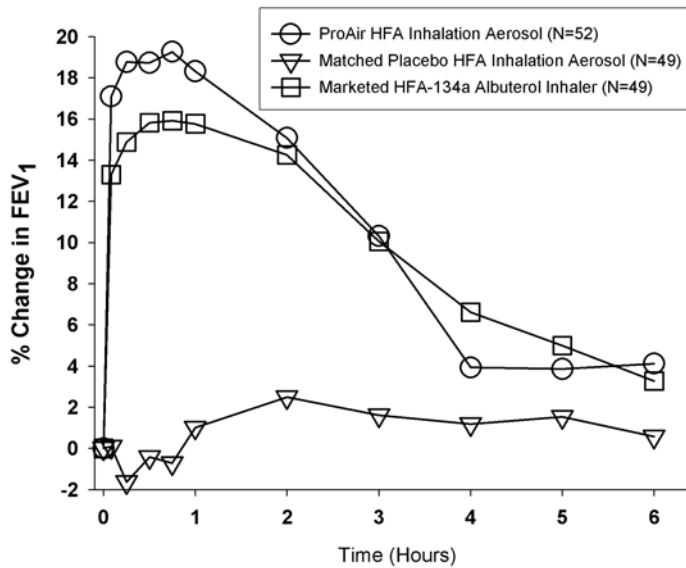
FEV₁ as Mean Percent Change from Test-Day Pre-Dose in a 6-Week Clinical Trial

Day 1



144
145

Day 43



147
148

149 In this study, 31 of 58 patients treated with ProAir HFA Inhalation Aerosol
150 achieved a 15% increase in FEV₁ within 30 minutes post-dose on Day 1. In these
151 patients, the median time to onset, median time to peak effect, and median
152 duration of effect were 8.2 minutes, 47 minutes, and approximately 3 hours,
153 respectively. In some patients, the duration of effect was as long as 6 hours.

154
155 In a placebo-controlled, single-dose, crossover study in which ProAir HFA
156 Inhalation Aerosol, administered at albuterol doses of 90, 180 and 270 mcg,
157 produced bronchodilator responses significantly greater than those observed with
158 a matched placebo HFA Inhalation Aerosol and comparable to a marketed active
159 comparator HFA-134a albuterol inhaler.

160
161 Some patients who participated in these clinical trials were using concomitant
162 steroid therapy.

163 164 **INDICATIONS AND USAGE**

165
166 ProAir HFA Inhalation Aerosol is indicated for the treatment or prevention of
167 bronchospasm in adults and children 12 years of age and older with reversible
168 obstructive airway disease.

169 170 **CONTRAINDICATIONS**

171
172 ProAir HFA Inhalation Aerosol is contraindicated in patients with a history of
173 hypersensitivity to albuterol and any other ProAir HFA Inhalation Aerosol
174 components.

175 176 **WARNINGS**

177 **Paradoxical Bronchospasm:** ProAir HFA Inhalation Aerosol can produce
178 paradoxical bronchospasm that may be life threatening. If paradoxical
179 bronchospasm occurs, ProAir HFA Inhalation Aerosol should be discontinued
180 immediately and alternative therapy instituted. It should be recognized that
181 paradoxical bronchospasm, when associated with inhaled formulations, frequently
182 occurs with the first use of a new canister.

183
184 **Deterioration of Asthma:** Asthma may deteriorate acutely over a period of
185 hours or chronically over several days or longer. If the patient needs more doses
186 of ProAir HFA Inhalation Aerosol than usual, this may be a marker of
187 destabilization of asthma and requires re-evaluation of the patient and treatment
188 regimen, giving special consideration to the possible need for anti-inflammatory
189 treatment, e.g., corticosteroids.

190
191 **Use of Anti-inflammatory Agents:** The use of beta-adrenergic-agonist
192 bronchodilators alone may not be adequate to control asthma in many patients.

193 Early consideration should be given to adding anti-inflammatory agents, e.g.,
194 corticosteroids, to the therapeutic regimen.

195
196 **Cardiovascular Effects:** ProAir HFA Inhalation Aerosol, like other beta-
197 adrenergic agonists, can produce clinically significant cardiovascular effects in
198 some patients as measured by pulse rate, blood pressure, and/or symptoms.
199 Although such effects are uncommon after administration of ProAir HFA
200 Inhalation Aerosol at recommended doses, if they occur, the drug may need to be
201 discontinued. In addition, beta-agonists have been reported to produce ECG
202 changes, such as flattening of the T wave, prolongation of the QTc interval, and
203 ST segment depression. The clinical significance of these findings is unknown.
204 Therefore, ProAir HFA Inhalation Aerosol, like all sympathomimetic amines,
205 should be used with caution in patients with cardiovascular disorders, especially
206 coronary insufficiency, cardiac arrhythmias, and hypertension.

207
208 **Do Not Exceed Recommended Dose:** Fatalities have been reported in
209 association with excessive use of inhaled sympathomimetic drugs in patients with
210 asthma. The exact cause of death is unknown, but cardiac arrest following an
211 unexpected development of a severe acute asthmatic crisis and subsequent
212 hypoxia is suspected.

213
214 **Immediate Hypersensitivity Reactions:** Immediate hypersensitivity reactions
215 may occur after administration of albuterol sulfate, as demonstrated by rare cases
216 of urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal
217 edema. The potential for hypersensitivity must be considered in the clinical
218 evaluation of patients who experience immediate hypersensitivity reactions while
219 receiving ProAir HFA Inhalation Aerosol.

220 221 **PRECAUTIONS**

222 223 **General**

224
225 ProAir HFA Inhalation Aerosol, like all sympathomimetic amines, should be used
226 with caution in patients with cardiovascular disorders, especially coronary
227 insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive
228 disorders, hyperthyroidism, or diabetes mellitus; and in patients who are
229 unusually responsive to sympathomimetic amines. Clinically significant changes
230 in systolic and diastolic blood pressure have been seen in individual patients and
231 could be expected to occur in some patients after use of any beta-adrenergic
232 bronchodilator.

233
234 Large doses of intravenous albuterol have been reported to aggravate preexisting
235 diabetes mellitus and ketoacidosis. As with other beta-agonists, ProAir HFA
236 Inhalation Aerosol may produce significant hypokalemia in some patients,

237 possibly through intracellular shunting, which has the potential to produce
238 adverse cardiovascular effects. The decrease is usually transient, not requiring
239 supplementation.

240

241 **Information for Patients**

242

243 See illustrated **Patient's Instructions for Use. Shake well before use.** Patients
244 should be given the following information:

245 Prime the inhaler before using for the first time and in cases where the inhaler has
246 not been used for more than 2 weeks by releasing three “test sprays” into the air,
247 away from the face.

248 **Keeping the plastic actuator mouthpiece clean is very important to prevent**
249 **medication build-up and blockage. Wash the mouthpiece, shake to remove**
250 **excess water, and air dry thoroughly at least once a week. The inhaler may**
251 **cease to deliver medication if not properly cleaned.**

252

253 Clean the mouthpiece (with the canister removed) by running warm water through
254 the top and bottom of the mouthpiece for 30 seconds at least once a week. Shake
255 to remove excess water, then air-dry thoroughly (such as overnight). Blockage
256 from medication build-up or improper medication delivery may result from failure
257 to thoroughly air dry the mouthpiece.

258

259 If the mouthpiece should become blocked (little or no medication coming out of
260 the mouthpiece), the blockage may be removed by washing as described above.

261

262 If it is necessary to use the inhaler before it is completely dry, shake off excess
263 water, replace canister, test spray twice away from face, and take the prescribed
264 dose. After such use, the mouthpiece should be rewashed and allowed to air dry
265 thoroughly.

266

267 The action of ProAir HFA Inhalation Aerosol should last for 4 to 6 hours. Do not
268 use ProAir HFA Inhalation Aerosol more frequently than recommended. Do not
269 increase the dose or frequency of doses of ProAir HFA Inhalation Aerosol
270 without consulting your physician. If you find that treatment with ProAir HFA
271 Inhalation Aerosol becomes less effective for symptomatic relief, your symptoms
272 become worse, and/or you need to use the product more frequently than usual,
273 seek medical attention immediately. While you are taking ProAir HFA Inhalation
274 Aerosol, other inhaled drugs and asthma medications should be taken only as
275 directed by your physician. If you are pregnant or nursing, contact your physician
276 about the use of ProAir HFA Inhalation Aerosol.

277

278 Common adverse effects of treatment with inhaled albuterol include palpitations,
279 chest pain, rapid heart rate, tremor, or nervousness. Effective and safe use of

280 ProAir HFA Inhalation Aerosol includes an understanding of the way that it
281 should be administered.

282

283 **Use ProAir HFA Inhalation Aerosol only with the actuator supplied with the**
284 **product. Discard the canister after 200 sprays have been used. Never**
285 **immerse the canister in water to determine how full the canister is (“float**
286 **test”).**

287

288

Drug Interactions

289

290 Other short-acting sympathomimetic aerosol bronchodilators should not be used
291 concomitantly with ProAir HFA Inhalation Aerosol. If additional adrenergic
292 drugs are to be administered by any route, they should be used with caution to
293 avoid deleterious cardiovascular effects.

294

295 **Beta-Blockers:** Beta-adrenergic-receptor blocking agents not only block the
296 pulmonary effect of beta-agonists, such as ProAir HFA Inhalation Aerosol, but
297 may produce severe bronchospasm in asthmatic patients. Therefore, patients with
298 asthma should not normally be treated with beta-blockers. However, under
299 certain circumstances, e.g., as prophylaxis after myocardial infarction, there may
300 be no acceptable alternatives to the use of beta-adrenergic-blocking agents in
301 patients with asthma. In this setting, cardioselective beta-blockers should be
302 considered, although they should be administered with caution.

303

304 **Diuretics:** The ECG changes and/or hypokalemia which may result from the
305 administration of non-potassium sparing diuretics (such as loop or thiazide
306 diuretics) can be acutely worsened by beta-agonists, especially when the
307 recommended dose of the beta-agonist is exceeded. Although the clinical
308 significance of these effects is not known, caution is advised in the
309 coadministration of beta-agonists with non-potassium sparing diuretics.

310

311 **Digoxin:** Mean decreases of 16% and 22% in serum digoxin levels were
312 demonstrated after single dose intravenous and oral administration of albuterol,
313 respectively, to normal volunteers who had received digoxin for 10 days. The
314 clinical significance of these findings for patients with obstructive airway disease
315 who are receiving albuterol and digoxin on a chronic basis is unclear.
316 Nevertheless, it would be prudent to carefully evaluate the serum digoxin levels
317 in patients who are currently receiving digoxin and ProAir HFA Inhalation
318 Aerosol.

319

320 **Monoamine Oxidase Inhibitors or Tricyclic Antidepressants:** ProAir HFA
321 Inhalation Aerosol should be administered with extreme caution to patients being
322 treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within

323 2 weeks of discontinuation of such agents, because the action of albuterol on the
324 cardiovascular system may be potentiated.

325

326 **Carcinogenesis, Mutagenesis and Impairment of Fertility**

327

328 In a 2-year study in Sprague-Dawley rats, albuterol sulfate caused a dose-related
329 increase in the incidence of benign leiomyomas of the mesovarium at and above
330 dietary doses of 2 mg/kg (approximately 15 times the maximum recommended
331 daily inhalation dose for adults on a mg/m² basis). In another study this effect
332 was blocked by the coadministration of propranolol, a non-selective beta-
333 adrenergic antagonist. In an 18-month study in CD-1 mice, albuterol sulfate
334 showed no evidence of tumorigenicity at dietary doses of up to 500 mg/kg
335 (approximately 1,600 times the maximum recommended daily inhalation dose for
336 adults on a mg/m² basis). In a 22-month study in Golden Hamsters, albuterol
337 sulfate showed no evidence of tumorigenicity at dietary doses of up to 50 mg/kg
338 (approximately 210 times the maximum recommended daily inhalation dose for
339 adults on a mg/m² basis).

340

341 Albuterol sulfate was not mutagenic in the Ames test or a mutation test in yeast.
342 Albuterol sulfate was not clastogenic in a human peripheral lymphocyte assay or
343 in an AH1 strain mouse micronucleus assay.

344

345 Reproduction studies in rats demonstrated no evidence of impaired fertility at oral
346 doses up to 50 mg/kg (approximately 310 times the maximum recommended
347 daily inhalation dose for adults on a mg/m² basis).

348

349 **Pregnancy: Teratogenic Effects: Pregnancy Category C**

350

351 Albuterol sulfate has been shown to be teratogenic in mice. A study in CD-1
352 mice given albuterol sulfate subcutaneously showed cleft palate formation in 5 of
353 111 (4.5%) fetuses at 0.25 mg/kg (less than the maximum recommended daily
354 inhalation dose for adults on a mg/m² basis) and in 10 of 108 (9.3%) fetuses at
355 2.5 mg/kg (approximately 8 times the maximum recommended daily inhalation
356 dose for adults on a mg/m² basis). The drug did not induce cleft palate formation
357 at the low dose 0.025 mg/kg (less than the maximum recommended daily
358 inhalation dose for adults on a mg/m² basis). Cleft palate also occurred in 22 of
359 72 (30.5%) fetuses treated subcutaneously with 2.5 mg/kg isoproterenol (positive
360 control).

361

362 A reproduction study in Stride Dutch rabbits revealed cranioschisis in 7 of
363 19 (37%) fetuses when albuterol sulfate was administered orally at 50 mg/kg
364 (approximately 630 times the maximum recommended daily inhalation dose for
365 adults on a mg/m² basis).

366

367 In an inhalation reproduction study in Sprague-Dawley rats, the albuterol
368 sulfate/HFA-134a formulation did not exhibit any teratogenic effects at
369 10.5 mg/kg (approximately 65 times the maximum recommended daily inhalation
370 dose for adults on a mg/m² basis).

371
372 A study in which pregnant rats were dosed with radiolabeled albuterol sulfate
373 demonstrated that drug-related material is transferred from the maternal
374 circulation to the fetus.

375
376 There are no adequate and well-controlled studies of albuterol sulfate in pregnant
377 women. ProAir HFA Inhalation Aerosol should be used during pregnancy only if
378 the potential benefit justifies the potential risk to the fetus.

379
380 During worldwide marketing experience, various congenital anomalies, including
381 cleft palate and limb defects, have been reported in the offspring of patients being
382 treated with albuterol. Some of the mothers were taking multiple medications
383 during their pregnancies. Because no consistent pattern of defects can be
384 discerned, a relationship between albuterol use and congenital anomalies has not
385 been established.

386 387 **Use in Labor and Delivery**

388
389 Because of the potential for beta-agonist interference with uterine contractility,
390 use of ProAir HFA Inhalation Aerosol for relief of bronchospasm during labor
391 should be restricted to those patients in whom the benefits clearly outweigh the
392 risk.

393 394 **Tocolysis:**

395
396 ProAir HFA Inhalation Aerosol has not been approved for the management of
397 pre-term labor. The benefit:risk ratio when albuterol is administered for tocolysis
398 has not been established. Serious adverse reactions, including pulmonary edema,
399 have been reported during or following treatment of premature labor with beta₂-
400 agonists, including albuterol.

401 402 **Nursing Mothers**

403
404 Plasma levels of albuterol sulfate and HFA-134a after inhaled therapeutic doses
405 are very low in humans, but it is not known whether the components of ProAir
406 HFA Inhalation Aerosol are excreted in human milk.

407
408 Caution should be exercised when ProAir HFA Inhalation Aerosol is
409 administered to a nursing woman. Because of the potential for tumorigenicity
410 shown for albuterol in animal studies and lack of experience with the use of
411 ProAir HFA Inhalation Aerosol by nursing mothers, a decision should be made

412 whether to discontinue nursing or to discontinue the drug, taking into account the
413 importance of the drug to the mother.

414

415 **Pediatrics**

416

417 The safety and effectiveness of ProAir HFA Inhalation Aerosol in pediatric
418 patients below the age of 12 years have not been established.

419

420 **Geriatrics**

421

422 Clinical studies of ProAir HFA Inhalation Aerosol did not include sufficient
423 numbers of patients aged 65 and over to determine whether they respond
424 differently from younger patients. Other reported clinical experience has not
425 identified differences in responses between elderly and younger patients. In
426 general, dose selection for an elderly patient should be cautious, usually starting
427 at the low end of the dosing range, reflecting the greater frequency of decreased
428 hepatic, renal, or cardiac function, and of concomitant disease or other drug
429 therapy.

430

431 Albuterol is known to be substantially excreted by the kidney, and the risk of
432 toxic reactions may be greater in patients with impaired renal function. Because
433 elderly patients are more likely to have decreased renal function, care should be
434 taken in dose selection, and it may be useful to monitor renal function.

435

436 **ADVERSE REACTIONS**

437

438 A total of 973 subjects were treated with ProAir HFA Inhalation Aerosol during
439 the worldwide clinical development program.

440

441 The adverse reaction information presented in the table below concerning ProAir
442 HFA Inhalation Aerosol is derived from a 6-week, blinded study which compared
443 ProAir HFA Inhalation Aerosol (180 mcg four times daily) with a double-blinded
444 matched placebo HFA-Inhalation Aerosol and an evaluator-blinded marketed
445 active comparator HFA-134a albuterol inhaler in 172 asthmatic patients 12 to
446 76 years of age. The table lists the incidence of all adverse events (whether
447 considered by the investigator drug related or unrelated to drug) from this study
448 which occurred at a rate of 3% or greater in the ProAir HFA Inhalation Aerosol
449 treatment group and more frequently in the ProAir HFA Inhalation Aerosol
450 treatment group than in the matched placebo group. Overall, the incidence and
451 nature of the adverse events reported for ProAir HFA Inhalation Aerosol and the
452 marketed active comparator HFA-134a albuterol inhaler were comparable.

Adverse Experience Incidences (% of Patients) in a Six-Week Clinical Trial*

Body System/ Adverse Event (as Preferred Term)		ProAir Inhalation Aerosol (N = 58)	Marketed active comparator HFA-134a albuterol inhaler (N = 56)	Matched Placebo HFA-134a Inhalation Aerosol (N = 58)
Body as a Whole	Headache	7	5	2
Cardiovascular	Tachycardia	3	2	0
Musculoskeletal	Pain	3	0	0
Nervous System	Dizziness	3	0	0
Respiratory System	Pharyngitis	14	7	9
	Rhinitis	5	4	2

* This table includes all adverse events (whether considered by the investigator drug related or unrelated to drug) which occurred at an incidence rate of at least 3.0% in the ProAir HFA Inhalation Aerosol group and more frequently in the ProAir HFA Inhalation Aerosol group than in the placebo HFA Inhalation Aerosol group.

454

455

456

457

458

459

460

461

Adverse events reported by less than 3% of the patients receiving ProAir HFA Inhalation Aerosol but by a greater proportion of ProAir HFA Inhalation Aerosol patients than the matched placebo patients, which have the potential to be related to ProAir HFA Inhalation Aerosol, included chest pain, infection, diarrhea, glossitis, accidental injury (nervous system), anxiety, dyspnea, ear disorder, ear pain, and urinary tract infection.

462

In small cumulative dose studies, tremor, nervousness, and headache were the most frequently occurring adverse events.

463

464

465

Postmarketing

466

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480

Post-marketing safety data with ProAir HFA Inhalation Aerosol are generally consistent with both adverse events in the clinical trials and in the use of inhaled

481 albuterol. Reports have included rare cases of aggravated bronchospasm, lack of
482 efficacy, asthma exacerbation (reported fatal in one case), muscle cramps, and
483 various oropharyngeal side-effects such as throat irritation, altered taste, glossitis,
484 tongue ulceration, and gagging.

485

486 **OVERDOSAGE**

487

488 The expected symptoms with overdosage are those of excessive beta-adrenergic
489 stimulation and/or occurrence or exaggeration of any of the symptoms listed
490 under ADVERSE REACTIONS, e.g., seizures, angina, hypertension or
491 hypotension, tachycardia with rates up to 200 beats per minute, arrhythmias,
492 nervousness, headache, tremor, dry mouth, palpitation, nausea, dizziness, fatigue,
493 malaise, and insomnia.

494

495 Hypokalemia may also occur. As with all sympathomimetic medications, cardiac
496 arrest and even death may be associated with abuse of ProAir HFA Inhalation
497 Aerosol.

498

499 Treatment consists of discontinuation of ProAir HFA Inhalation Aerosol together
500 with appropriate symptomatic therapy. The judicious use of a cardioselective
501 beta-receptor blocker may be considered, bearing in mind that such medication
502 can produce bronchospasm. There is insufficient evidence to determine if dialysis
503 is beneficial for overdosage of ProAir HFA Inhalation Aerosol.

504

505 The oral median lethal dose of albuterol sulfate in mice is greater than
506 2,000 mg/kg (approximately 6,300 times the maximum recommended daily
507 inhalation dose for adults on a mg/m² basis). In mature rats, the subcutaneous
508 median lethal dose of albuterol sulfate is approximately 450 mg/kg
509 (approximately 2,800 times the maximum recommended daily inhalation dose for
510 adults on a mg/m² basis). In young rats, the subcutaneous median lethal dose is
511 approximately 2,000 mg/kg (approximately 13,000 times the maximum
512 recommended daily inhalation dose for adults on a mg/m² basis). The inhalation
513 median lethal dose has not been determined in animals.

514

515 **DOSAGE AND ADMINISTRATION**

516

517 For treatment of acute episodes of bronchospasm or prevention of asthmatic
518 symptoms, the usual dosage of ProAir HFA Inhalation Aerosol for adults and
519 children 12 years and older is two inhalations repeated every 4 to 6 hours. More
520 frequent administration or a larger number of inhalations is not recommended. In
521 some patients, one inhalation every 4 hours may be sufficient.

522

523 It is recommended to prime the inhaler before using for the first time and in cases
524 where the inhaler has not been used for more than two weeks by releasing three
525 “test sprays” into the air, away from the face.

526 If a previously effective dosage regimen fails to provide the usual response, this
527 may be a marker of destabilization of asthma and requires re-evaluation of the
528 patient and the treatment regimen, giving special consideration to the possible
529 need for anti-inflammatory treatment, e.g., corticosteroids.

530
531 **Cleaning:** To maintain proper use of this product and to prevent medication
532 build-up and blockage, it is important to keep the plastic mouthpiece clean. Wash
533 the mouthpiece and air dry thoroughly at least once a week. If the mouthpiece
534 becomes blocked, washing the mouthpiece will remove the blockage. The inhaler
535 may cease to deliver medication if not properly cleaned and air dried. See-
536 **Information For Patients.**

537
538 **HOW SUPPLIED**

539
540 ProAir HFA (albuterol sulfate) Inhalation Aerosol is supplied as a pressurized
541 aluminum canister with a red plastic actuator and white dust cap each in boxes of
542 one. Each canister contains 8.5 g of the formulation and provides 200 actuations
543 (NDC 59310-179-20). Each actuation delivers 120 mcg of albuterol sulfate from
544 the canister valve and 108 mcg of albuterol sulfate from the actuator mouthpiece
545 (equivalent to 90 mcg of albuterol base).

546
547 **Rx only.**

548 **SHAKE WELL BEFORE USE. Store between 15° and 25°C (59° and 77°F).**
549 **Contents under pressure. Do not puncture or incinerate. Protect from**
550 **freezing temperatures and prolonged exposure to direct sunlight. Exposure**
551 **to temperatures above 120°F may cause bursting. For best results, canister**
552 **should be at room temperature before use. Avoid spraying in eyes. Keep out**
553 **of reach of children.**

554 **The red actuator supplied with ProAir HFA Inhalation Aerosol should not**
555 **be used with the canister from any other inhalation aerosol products. The**
556 **ProAir HFA Inhalation Aerosol canister should not be used with the actuator**
557 **from any other inhalation aerosol products.**

558 **The labeled amount of medication in each actuation cannot be assured after**
559 **200 actuations, even though the canister may not be completely empty.**
560 **Discard the inhaler (canister plus actuator) after 200 actuations have been**
561 **used. Never immerse the canister into water to determine how full the**
562 **canister is (“float test”).**

563 ProAir HFA Inhalation Aerosol does not contain chlorofluorocarbons (CFCs) as
564 the propellant.

565
566

567 Manufactured by
568 IVAX Pharmaceuticals Ireland
569 Waterford, Republic of Ireland
570 for
571 IVAX Laboratories, Inc.
572 Miami, FL 33137 USA

573

574

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580 ProAir TM is a trademark of IVAX Laboratories, Inc.

581

Attention Pharmacist:

Detach Patient's Instructions for use from package insert and dispense with the product.

ProAirTM HFA

(albuterol sulfate)

Inhalation Aerosol

FOR ORAL INHALATION ONLY

Patient's Instructions For Use

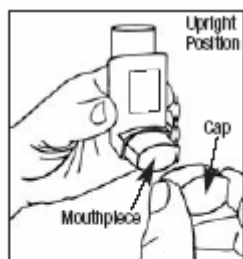


Fig. 1

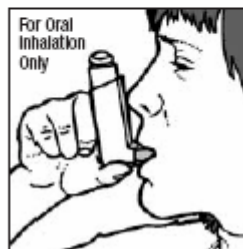


Fig. 2

Before using your ProAir HFA (albuterol sulfate) Inhalation Aerosol, read complete instructions carefully. Children should use ProAir HFA Inhalation Aerosol, under adult supervision, as instructed by the patient's doctor.

This inhalation aerosol does not contain chlorofluorocarbons (CFCs) as the propellant and is therefore CFC free.

1. **SHAKE THE INHALER WELL** immediately before each use. **Then remove the cap from the mouthpiece** (see Figure 1). **Check mouthpiece for foreign objects prior to use.** Make sure the canister is fully inserted into the actuator.
2. As with all aerosol medications, it is recommended to prime the inhaler before using for the first time and in cases where the inhaler has not been used for more than 2 weeks. Prime by releasing three "test sprays" into the air, away from your face.
3. **BREATHE OUT FULLY THROUGH THE MOUTH**, expelling as much air from your lungs as possible. Place the mouthpiece fully into your mouth holding the inhaler in its upright position and closing your lips around it (see Figure 2). Make sure your tongue is placed below the mouthpiece.

4. WHILE BREATHING IN DEEPLY AND SLOWLY THROUGH THE MOUTH, FULLY DEPRESS AND THEN IMMEDIATELY RELEASE THE TOP OF THE METAL CANISTER with your index finger (See Figure 2.)
5. HOLD YOUR BREATH AS LONG AS POSSIBLE, up to 10 seconds. Before breathing out, remove the inhaler from your mouth and release your finger from the canister.
6. If your doctor has prescribed additional puffs, wait one minute, shake the inhaler again and repeat steps 3 through 5. Replace the cap after use.
7. KEEPING THE PLASTIC MOUTHPIECE CLEAN IS EXTREMELY IMPORTANT TO PREVENT MEDICATION BUILD-UP AND BLOCKAGE (CLOGGED). THE MOUTHPIECE SHOULD BE WASHED, SHAKEN TO REMOVE EXCESS WATER, AND AIR-DRIED THOROUGHLY AT LEAST ONCE PER WEEK. INHALER MAY STOP SPRAYING IF NOT PROPERLY CLEANED.

Routine cleaning instructions: Step 1. Wash at least once a week. To clean, remove the canister and mouthpiece cap. Wash the mouthpiece through the top and bottom with warm running water for 30 seconds (see Figure A). **Never immerse the metal canister in water.**



Fig. A

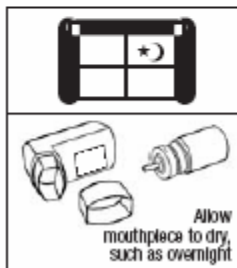
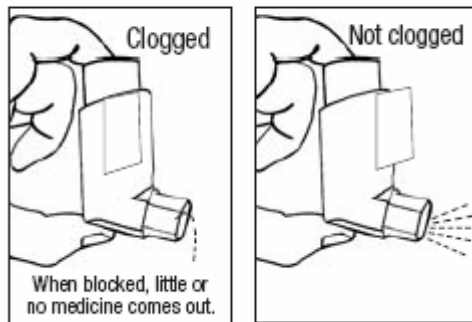


Fig. B

Fig. C



Step 2. To dry, shake off excess water and let the mouthpiece air dry thoroughly, such as overnight (see figure B). When the mouthpiece is dry, replace the canister and the mouthpiece cap. Blockage from medication build-up is more likely to occur if the mouthpiece is not allowed to air dry thoroughly.

IF YOUR INHALER BECOMES BLOCKED OR CLOGGED (little or no medication coming out of the mouthpiece, see Figure C), wash the mouthpiece as described in Step 1 and air dry properly as described in Step 2.

IF YOU NEED TO USE YOUR INHALER BEFORE IT IS COMPLETELY DRY, SHAKE, OFF EXCESS WATER, replace the canister, and test spray twice into the air, away from your face, to remove most of the remaining water inside the mouthpiece. Then take your dose as prescribed. **After such use, rewash and air dry thoroughly as described in Steps 1 and 2.**

8. The inhaler should be discarded when the labeled number of actuations (i.e. 200) has been used. The labeled amount of medication in each inhalation cannot be assured after 200 actuations, even though the canister may not be completely empty. Before you reach the specific number of actuations, you should consult your doctor to determine whether a refill is needed. You should not take extra doses without consulting your doctor, neither should you stop using ProAir HFA Inhalation Aerosol without consulting your doctor. Never immerse the canister into water to determine how full the canister is (“float test”).

You may notice a slightly different taste or force to spray with ProAir HFA Inhalation Aerosol, than you may be used to with other albuterol inhalation aerosol products.

DOSAGE:

Use only as directed by your doctor.

WARNINGS: The action of ProAir HFA Inhalation Aerosol lasts up to 4 to 6 hours. Do not use more frequently than recommended. Do not increase the number of puffs or frequency of doses of ProAir HFA Inhalation Aerosol without consulting your doctor. If you find that treatment with ProAir HFA Inhalation Aerosol becomes less effective for

symptomatic relief, your symptoms become worse, and/or you need to use the product more frequently than usual, seek medical attention immediately. While you are taking ProAir HFA Inhalation Aerosol other inhaled drugs should be taken only as directed by your doctor. If you are pregnant or nursing, contact your doctor about the use of ProAir HFA Inhalation Aerosol.

Common adverse effects of treatment with ProAir HFA Inhalation Aerosol include palpitations, chest pain, rapid heart rate, tremor, or nervousness. Effective and safe use of ProAir HFA Inhalation Aerosol includes an understanding of the way that it should be administered. Use ProAir HFA Inhalation Aerosol only with the red actuator supplied with the product.

The ProAir HFA Inhalation Aerosol actuator should not be used with the canister from other inhalation aerosol medications. The ProAir HFA Inhalation Aerosol canister should not be used with the actuator from other inhalation aerosol medications.

Store between 15° and 25° C (59° and 77° F). Avoid exposure to extreme heat and cold. For best results, canister should be at room temperature.

Shake well before use.

Contents Under Pressure. Do not puncture. Do not store near heat or open flame. Exposure to temperatures above 120°F may cause bursting. Never throw container into fire or incinerator. Avoid spraying in eyes. Keep out of reach of children.

Further Information: Your ProAir HFA (albuterol sulfate) Inhalation Aerosol, does not contain chlorofluorocarbons (CFCs) as the propellant. Instead, the inhaler contains a hydrofluoroalkane (HFA-134a) as the propellant.

Manufactured by:
IVAX Pharmaceuticals Ireland
Waterford, Ireland

For:
IVAX Laboratories, Inc.
Miami, FL 33137

ProAir is a trademark of
IVAX Laboratories Inc.

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