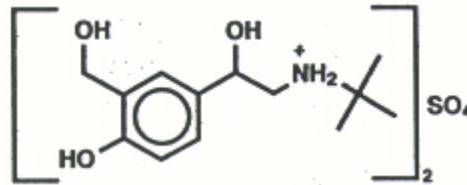


1 **PROAIR™ HFA (ALBUTEROL SULFATE)**
2 **INHALATION AEROSOL**
3 For Oral Inhalation Only

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 sulfate is the World
17 Health Organization recommended generic name. PROAIR HFA Inhalation
18 Aerosol is a pressurized metered-dose aerosol unit for oral inhalation. It contains
19 a 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
83 base administered over one hour) yielded mean peak plasma concentrations (C_{max})
84 and systemic exposure (AUC_{inf}) of approximately 4,100 pg/mL and 28,426
85 pg•hr/mL, respectively compared to approximately 3,900 pg/mL and 28,395
86 pg•hr/mL, respectively following the same dose of an active HFA-134a albuterol

87 inhaler comparator. The terminal plasma half-life of albuterol delivered by
88 PROAIR HFA 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 no 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
123 Inhalation 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

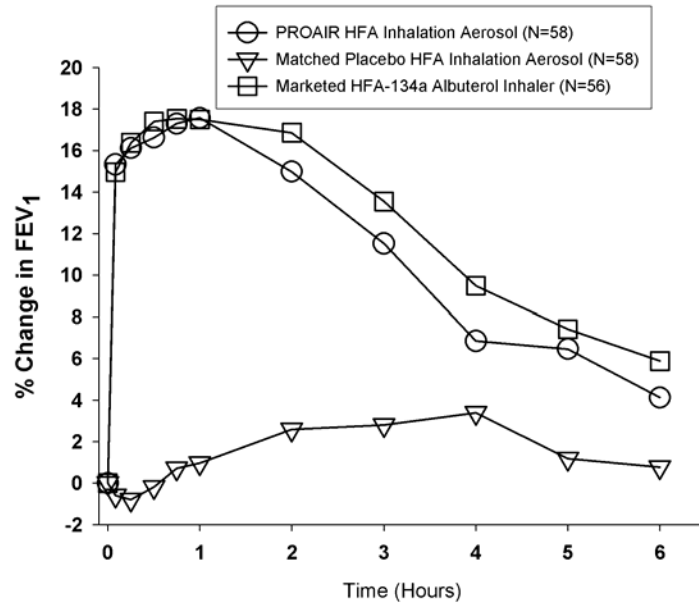
133 Serial FEV₁ measurements, shown below as percent change from test-day
134 baseline at Day 1 and at Day 43, demonstrated that two inhalations of PROAIR

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
140
141

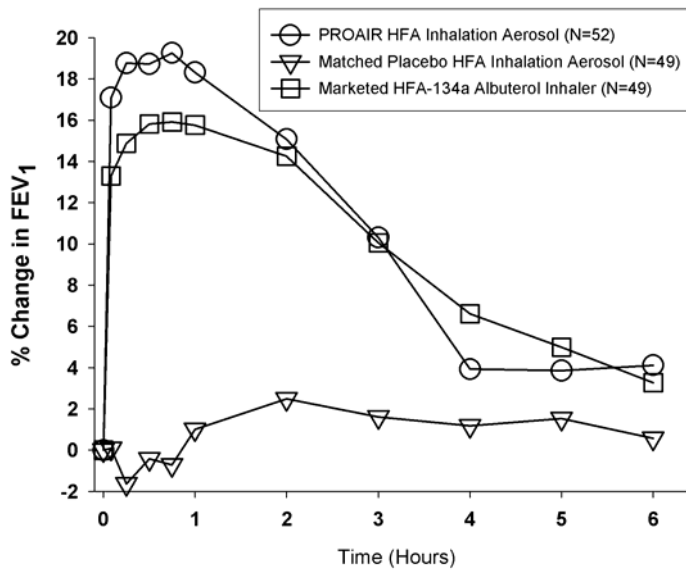
FEV₁ as Mean Percent Change from Test-Day Pre-Dose in a 6-Week Clinical Trial

Day 1



142
143
144

Day 43



145

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

151
152 In a placebo-controlled, single-dose, crossover study in which PROAIR HFA
153 Inhalation Aerosol, administered at albuterol doses of 90, 180 and 270 mcg,
154 produced bronchodilator responses significantly greater than those observed with
155 a matched placebo HFA Inhalation Aerosol and comparable to a marketed active
156 comparator HFA-134a albuterol inhaler.

157
158 In a randomized, single-dose, crossover study in 24 adults and adolescents with
159 exercise-induced bronchospasm (EIB), two inhalations of PROAIR HFA taken 30
160 minutes before exercise prevented EIB for the hour following exercise (defined as
161 maintenance of FEV₁ within 80% of post-dose, pre-exercise baseline values) in
162 83% (20 of 24) of patients as compared to 25% (6 of 24) of patients when they
163 received placebo.

164
165 Some patients who participated in these clinical trials were using concomitant
166 steroid therapy.

167

168 **INDICATIONS AND USAGE**

169

170 PROAIR HFA Inhalation Aerosol is indicated in adults and children 12 years of
171 age and older for the treatment or prevention of bronchospasm with reversible
172 obstructive airway disease and for the prevention of exercise-induced
173 bronchospasm.

174

175 **CONTRAINDICATIONS**

176

177 PROAIR HFA Inhalation Aerosol is contraindicated in patients with a history of
178 hypersensitivity to albuterol and any other PROAIR HFA Inhalation Aerosol
179 components.

180

180 **WARNINGS**

181

182 **Paradoxical Bronchospasm:** PROAIR HFA Inhalation Aerosol can produce
183 paradoxical bronchospasm that may be life threatening. If paradoxical
184 bronchospasm occurs, PROAIR HFA Inhalation Aerosol should be discontinued
185 immediately and alternative therapy instituted. It should be recognized that
186 paradoxical bronchospasm, when associated with inhaled formulations, frequently
187 occurs with the first use of a new canister.

188

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

195
196 **Use of Anti-inflammatory Agents:** The use of beta-adrenergic-agonist
197 bronchodilators alone may not be adequate to control asthma in many patients.
198 Early consideration should be given to adding anti-inflammatory agents, e.g.,
199 corticosteroids, to the therapeutic regimen.

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

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

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

225

226 **PRECAUTIONS**

227

228 **General**

229

230 PROAIR HFA Inhalation Aerosol, like all sympathomimetic amines, should be
231 used with caution in patients with cardiovascular disorders, especially coronary
232 insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive

233 disorders, hyperthyroidism, or diabetes mellitus; and in patients who are
234 unusually responsive to sympathomimetic amines. Clinically significant changes
235 in systolic and diastolic blood pressure have been seen in individual patients and
236 could be expected to occur in some patients after use of any beta-adrenergic
237 bronchodilator.

238
239 Large doses of intravenous albuterol have been reported to aggravate preexisting
240 diabetes mellitus and ketoacidosis. As with other beta-agonists, PROAIR HFA
241 Inhalation Aerosol may produce significant hypokalemia in some patients,
242 possibly through intracellular shunting, which has the potential to produce
243 adverse cardiovascular effects. The decrease is usually transient, not requiring
244 supplementation.

245 246 **Information for Patients**

247
248 See illustrated **Patient's Instructions for Use. Shake well before use.** Patients
249 should be given the following information:

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

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

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

263
264 If the mouthpiece should become blocked (little or no medication coming out of
265 the mouthpiece), the blockage may be removed by washing as described above.

266
267 If it is necessary to use the inhaler before it is completely dry, shake off excess
268 water, replace canister, test spray twice away from face, and take the prescribed
269 dose. After such use, the mouthpiece should be rewashed and allowed to air dry
270 thoroughly.

271
272 The action of PROAIR HFA Inhalation Aerosol should last for 4 to 6 hours. Do
273 not use PROAIR HFA Inhalation Aerosol more frequently than recommended.
274 Do not increase the dose or frequency of doses of PROAIR HFA Inhalation
275 Aerosol without consulting your physician. If you find that treatment with
276 PROAIR HFA Inhalation Aerosol becomes less effective for symptomatic relief,

277 your symptoms become worse, and/or you need to use the product more
278 frequently than usual, seek medical attention immediately. While you are taking
279 PROAIR HFA Inhalation Aerosol, other inhaled drugs and asthma medications
280 should be taken only as directed by your physician. If you are pregnant or
281 nursing, contact your physician about the use of PROAIR HFA Inhalation
282 Aerosol.

283

284 Common adverse effects of treatment with inhaled albuterol include palpitations,
285 chest pain, rapid heart rate, tremor, or nervousness. Effective and safe use of
286 PROAIR HFA Inhalation Aerosol includes an understanding of the way that it
287 should be administered.

288

289 **Use PROAIR HFA Inhalation Aerosol only with the actuator supplied with**
290 **the product. Discard the canister after 200 sprays have been used. Never**
291 **immerse the canister in water to determine how full the canister is (“float**
292 **test”).**

293

294 **Drug Interactions**

295

296 Other short-acting sympathomimetic aerosol bronchodilators should not be used
297 concomitantly with PROAIR HFA Inhalation Aerosol. If additional adrenergic
298 drugs are to be administered by any route, they should be used with caution to
299 avoid deleterious cardiovascular effects.

300

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

309

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

316

317 **Digoxin:** Mean decreases of 16% and 22% in serum digoxin levels were
318 demonstrated after single dose intravenous and oral administration of albuterol,
319 respectively, to normal volunteers who had received digoxin for 10 days. The
320 clinical significance of these findings for patients with obstructive airway disease

321 who are receiving albuterol and digoxin on a chronic basis is unclear.
322 Nevertheless, it would be prudent to carefully evaluate the serum digoxin levels
323 in patients who are currently receiving digoxin and PROAIR HFA Inhalation
324 Aerosol.

325
326 **Monoamine Oxidase Inhibitors or Tricyclic Antidepressants:** PROAIR HFA
327 Inhalation Aerosol should be administered with extreme caution to patients being
328 treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within
329 2 weeks of discontinuation of such agents, because the action of albuterol on the
330 cardiovascular system may be potentiated.

331
332 **Carcinogenesis, Mutagenesis and Impairment of Fertility**

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

346
347 Albuterol sulfate was not mutagenic in the Ames test or a mutation test in yeast.
348 Albuterol sulfate was not clastogenic in a human peripheral lymphocyte assay or
349 in an AH1 strain mouse micronucleus assay.

350
351 Reproduction studies in rats demonstrated no evidence of impaired fertility at oral
352 doses up to 50 mg/kg (approximately 310 times the maximum recommended
353 daily inhalation dose for adults on a mg/m² basis).

354
355 **Pregnancy: Teratogenic Effects: Pregnancy Category C**

356
357 Albuterol sulfate has been shown to be teratogenic in mice. A study in CD-1
358 mice given albuterol sulfate subcutaneously showed cleft palate formation in 5 of
359 111 (4.5%) fetuses at 0.25 mg/kg (less than the maximum recommended daily
360 inhalation dose for adults on a mg/m² basis) and in 10 of 108 (9.3%) fetuses at
361 2.5 mg/kg (approximately 8 times the maximum recommended daily inhalation
362 dose for adults on a mg/m² basis). The drug did not induce cleft palate formation
363 at the low dose 0.025 mg/kg (less than the maximum recommended daily
364 inhalation dose for adults on a mg/m² basis). Cleft palate also occurred in 22 of

365 72 (30.5%) fetuses treated subcutaneously with 2.5 mg/kg isoproterenol (positive
366 control).

367

368 A reproduction study in Stride Dutch rabbits revealed cranioschisis in 7 of
369 19 (37%) fetuses when albuterol sulfate was administered orally at 50 mg/kg
370 (approximately 630 times the maximum recommended daily inhalation dose for
371 adults on a mg/m² basis).

372

373 In an inhalation reproduction study in Sprague-Dawley rats, the albuterol
374 sulfate/HFA-134a formulation did not exhibit any teratogenic effects at
375 10.5 mg/kg (approximately 65 times the maximum recommended daily inhalation
376 dose for adults on a mg/m² basis).

377

378 A study in which pregnant rats were dosed with radiolabeled albuterol sulfate
379 demonstrated that drug-related material is transferred from the maternal
380 circulation to the fetus.

381

382 There are no adequate and well-controlled studies of albuterol sulfate in pregnant
383 women. PROAIR HFA Inhalation Aerosol should be used during pregnancy only
384 if the potential benefit justifies the potential risk to the fetus.

385

386 During worldwide marketing experience, various congenital anomalies, including
387 cleft palate and limb defects, have been reported in the offspring of patients being
388 treated with albuterol. Some of the mothers were taking multiple medications
389 during their pregnancies. Because no consistent pattern of defects can be
390 discerned, a relationship between albuterol use and congenital anomalies has not
391 been established.

392

393 **Use in Labor and Delivery**

394

395 Because of the potential for beta-agonist interference with uterine contractility,
396 use of PROAIR HFA Inhalation Aerosol for relief of bronchospasm during labor
397 should be restricted to those patients in whom the benefits clearly outweigh the
398 risk.

399

400 **Tocolysis:**

401

402 PROAIR HFA Inhalation Aerosol has not been approved for the management of
403 pre-term labor. The benefit:risk ratio when albuterol is administered for tocolysis
404 has not been established. Serious adverse reactions, including pulmonary edema,
405 have been reported during or following treatment of premature labor with beta₂-
406 agonists, including albuterol.

407

408 **Nursing Mothers**

409

410 Plasma levels of albuterol sulfate and HFA-134a after inhaled therapeutic doses
411 are very low in humans, but it is not known whether the components of PROAIR
412 HFA Inhalation Aerosol are excreted in human milk.

413

414 Caution should be exercised when PROAIR HFA Inhalation Aerosol is
415 administered to a nursing woman. Because of the potential for tumorigenicity
416 shown for albuterol in animal studies and lack of experience with the use of
417 PROAIR HFA Inhalation Aerosol by nursing mothers, a decision should be made
418 whether to discontinue nursing or to discontinue the drug, taking into account the
419 importance of the drug to the mother.

420

421 **Pediatrics**

422

423 The safety and effectiveness of PROAIR HFA Inhalation Aerosol in pediatric
424 patients below the age of 12 years have not been established.

425

426 **Geriatrics**

427

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

436

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

441

442 **ADVERSE REACTIONS**

443

444 A total of 973 subjects were treated with PROAIR HFA Inhalation Aerosol
445 during the worldwide clinical development program.

446

447 The adverse reaction information presented in the table below concerning
448 PROAIR HFA Inhalation Aerosol is derived from a 6-week, blinded study which
449 compared PROAIR HFA Inhalation Aerosol (180 mcg four times daily) with a
450 double-blinded matched placebo HFA-Inhalation Aerosol and an evaluator-
451 blinded marketed active comparator HFA-134a albuterol inhaler in 172 asthmatic
452 patients 12 to 76 years of age. The table lists the incidence of all adverse events
453 (whether considered by the investigator drug related or unrelated to drug) from
454 this study which occurred at a rate of 3% or greater in the PROAIR HFA

455 Inhalation Aerosol treatment group and more frequently in the PROAIR HFA
456 Inhalation Aerosol treatment group than in the matched placebo group. Overall,
457 the incidence and nature of the adverse events reported for PROAIR HFA
458 Inhalation Aerosol and the marketed active comparator HFA-134a albuterol
459 inhaler were comparable.

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

Body System/ Adverse Event (as Preferred Term)		PROAIR HFA 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.

461

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468

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.

469

470

471

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

472

Postmarketing

473

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485

486

487

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

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

492

493 **OVERDOSAGE**

494

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

501

502 Hypokalemia may also occur. As with all sympathomimetic medications, cardiac
503 arrest and even death may be associated with abuse of PROAIR HFA Inhalation
504 Aerosol.

505

506 Treatment consists of discontinuation of PROAIR HFA Inhalation Aerosol
507 together with appropriate symptomatic therapy. The judicious use of a
508 cardioselective beta-receptor blocker may be considered, bearing in mind that
509 such medication can produce bronchospasm. There is insufficient evidence to
510 determine if dialysis is beneficial for overdosage of PROAIR HFA Inhalation
511 Aerosol.

512

513 The oral median lethal dose of albuterol sulfate in mice is greater than
514 2,000 mg/kg (approximately 6,300 times the maximum recommended daily
515 inhalation dose for adults on a mg/m² basis). In mature rats, the subcutaneous
516 median lethal dose of albuterol sulfate is approximately 450 mg/kg
517 (approximately 2,800 times the maximum recommended daily inhalation dose for
518 adults on a mg/m² basis). In young rats, the subcutaneous median lethal dose is
519 approximately 2,000 mg/kg (approximately 13,000 times the maximum
520 recommended daily inhalation dose for adults on a mg/m² basis). The inhalation
521 median lethal dose has not been determined in animals.

522

523 **DOSAGE AND ADMINISTRATION**

524

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

530

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

534

535 Exercise-Induced Bronchospasm Prevention: The usual dosage for adults and
536 children 12 years of age or older is two inhalations 15 to 30 minutes before
537 exercise.

538

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

543

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

550

551 **HOW SUPPLIED**

552

553 PROAIR HFA (albuterol sulfate) Inhalation Aerosol is supplied as a pressurized
554 aluminum canister with a red plastic actuator and white dust cap each in boxes of
555 one. Each canister contains 8.5 g of the formulation and provides 200 actuations
556 (NDC 59310-179-20). Each actuation delivers 120 mcg of albuterol sulfate from
557 the canister valve and 108 mcg of albuterol sulfate from the actuator mouthpiece
558 (equivalent to 90 mcg of albuterol base).

559

560 **Rx only.**

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

567 **The red actuator supplied with PROAIR HFA Inhalation Aerosol should not**
568 **be used with the canister from any other inhalation aerosol products. The**
569 **PROAIR HFA Inhalation Aerosol canister should not be used with the**
570 **actuator from any other inhalation aerosol products.**

571 **The labeled amount of medication in each actuation cannot be assured after**
572 **200 actuations, even though the canister may not be completely empty.**

573 **Discard the inhaler (canister plus actuator) after 200 actuations have been**
574 **used. Never immerse the canister into water to determine how full the**
575 **canister is (“float test”).**

576 PROAIR HFA Inhalation Aerosol does not contain chlorofluorocarbons (CFCs)
577 as the propellant.

578

579

580 Manufactured by:
581 IVAX Pharmaceuticals Ireland
582 Waterford, Ireland
583 For
584 IVAX Laboratories, Inc.
585 Miami, FL 33137 USA

586

587

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