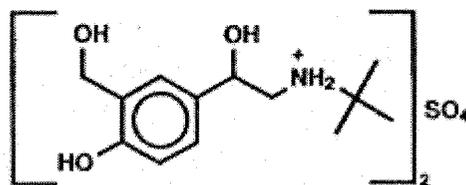


1 **[TRADE NAME] HFA (ALBUTEROL SULFATE)**
2 **INHALATION AEROSOL**
3 For Oral Inhalation Only

4 **PRESCRIBING INFORMATION**

5 **DESCRIPTION**

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



11
12 The molecular weight of albuterol sulfate is 576.7, and the empirical formula
13 is (C₁₃H₂₁NO₃)₂•H₂SO₄. Albuterol sulfate is a white to off-white crystalline
14 powder. It is soluble in water and slightly soluble in ethanol. [TRADE NAME]
15 HFA Inhalation Aerosol is a pressurized metered-dose aerosol unit for oral
16 inhalation. It contains a microcrystalline suspension of albuterol sulfate in
17 propellant HFA-134a (1, 1, 1, 2-tetrafluoroethane) and ethanol.

18 Each actuation delivers 120 mcg albuterol sulfate, from the canister valve and
19 108 mcg albuterol sulfate, from the actuator mouthpiece (equivalent to 90 mcg of
20 albuterol base from the mouthpiece). Each canister provides 200 inhalations. It is
21 recommended to prime the inhaler before using for the first time and in cases
22 where the inhaler has not been used for more than 2 weeks by releasing three “test
23 sprays” into the air, away from the face.

24
25 This product does not contain chlorofluorocarbons (CFCs) as the propellant.

26
27 **CLINICAL PHARMACOLOGY**

28 **Mechanism of Action**

29 *In vitro* studies and *in vivo* pharmacologic studies have demonstrated that
30 albuterol has a preferential effect on beta₂-adrenergic receptors compared with
31 isoproterenol. While it is recognized that beta₂-adrenergic receptors are the
32 predominant receptors on bronchial smooth muscle, data indicate that there is a
33 population of beta₂-receptors in the human heart existing in a concentration
34 between 10% and 50% of total cardiac beta-adrenergic receptors. The precise

35 function of these receptors has not been established (see **WARNINGS for**
36 **Cardiovascular Effects.**)

37 Activation of beta₂-adrenergic receptors on airway smooth muscle leads to the
38 activation of adenylyl cyclase and to an increase in the intracellular concentration of
39 cyclic-3', 5'-adenosine monophosphate (cyclic AMP). This increase of cyclic
40 AMP leads to the activation of protein kinase A, which inhibits the
41 phosphorylation of myosin and lowers intracellular ionic calcium concentrations,
42 resulting in relaxation. Albuterol relaxes the smooth muscle of all airways, from
43 the trachea to the terminal bronchioles. Albuterol acts as a functional antagonist
44 to relax the airway irrespective of the spasmogen involved, thus protecting against
45 all bronchoconstrictor challenges. Increased cyclic AMP concentrations are also
46 associated with the inhibition of release of mediators from mast cells in the
47 airway.

48 Albuterol has been shown in most clinical trials to have more effect on the
49 respiratory tract, in the form of bronchial smooth muscle relaxation, than
50 isoproterenol at comparable doses while producing fewer cardiovascular effects.
51 Controlled clinical studies and other clinical experience have shown that inhaled
52 albuterol, like other beta-adrenergic agonist drugs, can produce a significant
53 cardiovascular effect in some patients, as measured by pulse rate, blood pressure,
54 symptoms, and/or electrocardiographic changes.

55 **Preclinical**

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

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

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

76 **Pharmacokinetics**

77 The systemic levels of albuterol are low after inhalation of recommended
78 doses. In a crossover study conducted in healthy male and female volunteers, high
79 cumulative doses of [TRADE NAME] HFA Inhalation Aerosol (1,080 mcg of
80 albuterol base administered over one hour) yielded mean peak plasma
81 concentrations (C_{max}) and systemic exposure (AUC_{inf}) of approximately
82 4,100 pg/mL and 28,426 pg.hr/mL, respectively compared to approximately
83 3,900 pg/mL and 28,395 pg.hr/mL, respectively following the same dose of an
84 active HFA-134a albuterol inhaler comparator. The terminal plasma half-life of
85 albuterol delivered by [TRADE NAME] HFA Inhalation Aerosol was
86 approximately 6 hours. Comparison of the pharmacokinetic parameters
87 demonstrated no differences between the products.

88 No pharmacokinetic studies for [TRADE NAME] HFA Inhalation Aerosol
89 have been conducted in neonates, children, or elderly subjects.

90 **Clinical Trials**

91 In a 6-week, randomized, evaluator-blind, placebo-controlled trial, [TRADE
92 NAME] HFA Inhalation Aerosol (58 patients) was compared to an HFA-134a
93 placebo inhaler (58 patients) in asthmatic patients 12 to 76 years of age at a dose
94 of 180 mcg albuterol four times daily. An active comparator HFA-134a albuterol
95 inhaler arm (56 patients) was included.

96 Serial FEV_1 measurements, shown below as percent change from test-day
97 baseline at Day 1 and at Day 43, demonstrated that two inhalations of [TRADE
98 NAME] HFA Inhalation Aerosol produced significantly greater improvement in
99 FEV_1 over the pre-treatment value than placebo, as well as a comparable
100 bronchodilator effect to the active comparator HFA-134a albuterol inhaler.

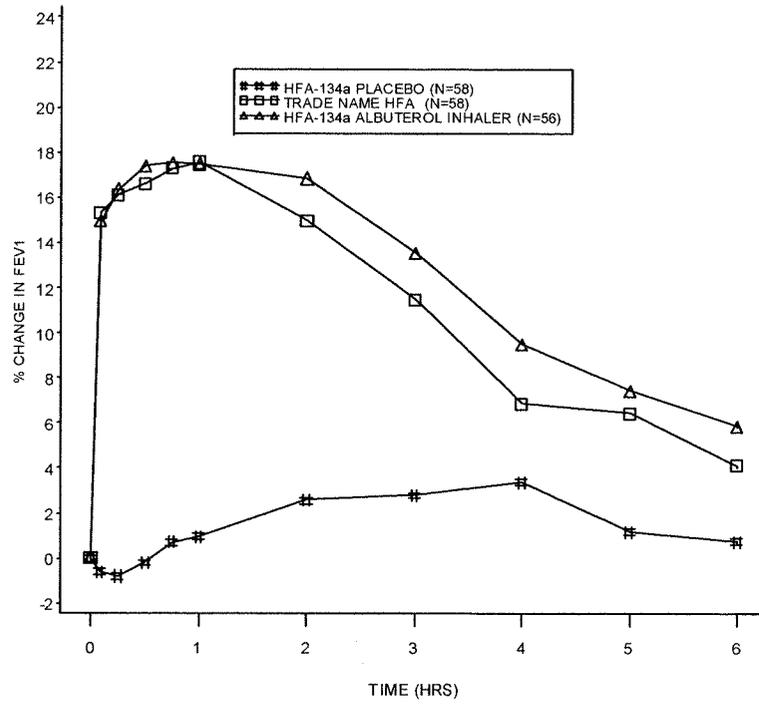
101 The mean time of onset of a 15% increase in FEV_1 at Day 1 was
102 approximately 19 minutes and the mean time to peak effect was 70 minutes. The
103 mean duration of effect as measured by a 15% increase in FEV_1 over the pre-
104 treatment value was approximately 3 hours. In some patients, the duration was as
105 long as 6 hours.

106 In a placebo-controlled single-dose, crossover study in which [TRADE
107 NAME] HFA Inhalation Aerosol, administered at albuterol doses of 90, 180 and
108 270 mcg, produced bronchodilator responses significantly greater than those
109 observed with an HFA-134a placebo inhaler and comparable to an active
110 comparator HFA-134a albuterol inhaler.

111 Some patients who participated in these clinical trials were using concomitant
112 steroid therapy.

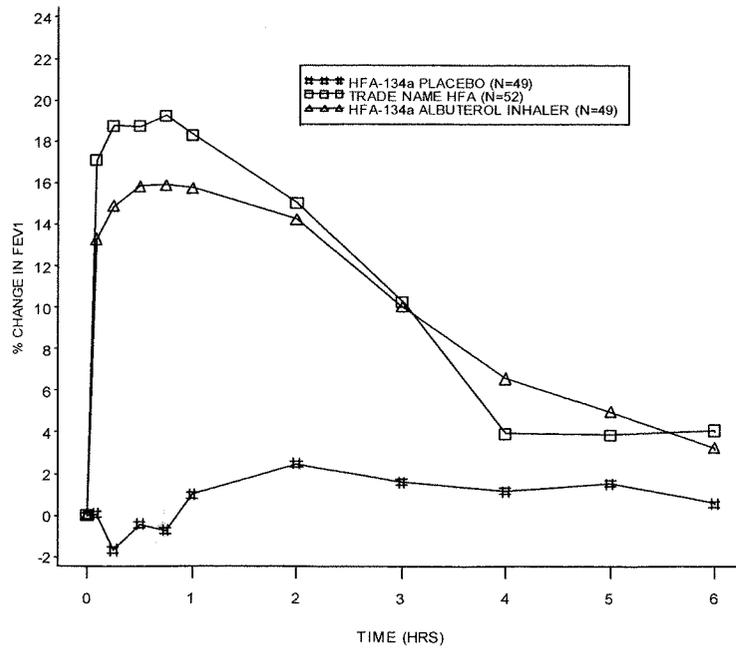
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**FEV₁ as Mean Percent Change from Test-Day Pre-Dose in a
6-Week Clinical Trial
Day 1**



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Day 43



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INDICATIONS AND USAGE

[TRADE NAME] HFA Inhalation Aerosol is indicated in adults and children 12 years of age and older for the treatment or prevention of bronchospasm with reversible obstructive airway disease.

CONTRAINDICATIONS

[TRADE NAME] HFA Inhalation Aerosol is contraindicated in patients with a history of hypersensitivity to albuterol and any other [TRADE NAME] HFA Inhalation Aerosol components.

WARNINGS

Paradoxical Bronchospasm: Inhaled albuterol sulfate can produce paradoxical bronchospasm that may be life threatening. If paradoxical bronchospasm occurs, [TRADE NAME] HFA Inhalation Aerosol should be discontinued immediately and alternative therapy instituted. It should be recognized that paradoxical bronchospasm, when associated with inhaled formulations, frequently occurs with the first use of a new canister.

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

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

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

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

160 **Immediate Hypersensitivity Reactions:** Immediate hypersensitivity reactions
161 may occur after administration of albuterol sulfate, as demonstrated by rare cases
162 of urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal
163 edema.

164 165 **PRECAUTIONS**

166 **General**

167 Albuterol sulfate, as with all sympathomimetic amines, should be used with
168 caution in patients with cardiovascular disorders, especially coronary
169 insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive
170 disorders, hyperthyroidism, or diabetes mellitus; and in patients who are unusually
171 responsive to sympathomimetic amines. Clinically significant changes in systolic
172 and diastolic blood pressure have been seen in individual patients and could be
173 expected to occur in some patients after use of any beta-adrenergic bronchodilator.

174 Large doses of intravenous albuterol have been reported to aggravate
175 preexisting diabetes mellitus and ketoacidosis. As with other beta-agonists,
176 albuterol may produce significant hypokalemia in some patients, possibly through
177 intracellular shunting, which has the potential to produce adverse cardiovascular
178 effects. The decrease is usually transient, not requiring supplementation.

179
180 **Information for Patients** See illustrated **Patient's Instructions for Use.**
181 **SHAKE WELL BEFORE USING.** Patients should be given the following
182 information:

183 It is recommended to prime the inhaler before using for the first time and in
184 cases where the inhaler has not been used for more than 2 weeks by releasing
185 three "test sprays" into the air, away from the face.

186 **KEEPING THE PLASTIC MOUTHPIECE CLEAN IS VERY IMPORTANT**
187 **TO PREVENT MEDICATION BUILD-UP AND BLOCKAGE. THE**
188 **MOUTHPIECE SHOULD BE WASHED, SHAKEN TO REMOVE EXCESS**
189 **WATER, AND AIR DRIED THOROUGHLY AT LEAST ONCE A WEEK.**
190 **THE INHALER MAY CEASE TO DELIVER MEDICATION IF NOT**
191 **PROPERLY CLEANED.**

192 The mouthpiece should be cleaned (with the canister removed) by running
193 warm water through the top and bottom of the mouthpiece for 30 seconds at least
194 once a week. The mouthpiece must be shaken to remove excess water, then air-
195 dried thoroughly (such as overnight). Blockage from medication build-up or
196 improper medication delivery may result from failure to thoroughly air dry the
197 mouthpiece.

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

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

204 The action of [TRADE NAME] HFA Inhalation Aerosol lasts up to 4 to
205 6 hours. [TRADE NAME] HFA Inhalation Aerosol should not be used more
206 frequently than recommended. Do not increase the dose or frequency of doses of
207 [TRADE NAME] HFA Inhalation Aerosol without consulting your physician. If
208 you find that treatment with [TRADE NAME] HFA Inhalation Aerosol becomes
209 less effective for symptomatic relief, your symptoms become worse, and/or you
210 need to use the product more frequently than usual, seek medical attention
211 immediately. While you are taking [TRADE NAME] HFA Inhalation Aerosol,
212 other inhaled drugs and asthma medications should be taken only as directed by
213 your physician. If you are pregnant or nursing, contact your physician about the
214 use of [TRADE NAME] HFA Inhalation Aerosol.

215 Common adverse effects of treatment with inhaled albuterol include
216 palpitations, chest pain, rapid heart rate, tremor, or nervousness. If you are
217 pregnant or nursing, contact your physician about use of [TRADE NAME] HFA
218 Inhalation Aerosol. Effective and safe use of [TRADE NAME] HFA Inhalation
219 Aerosol includes an understanding of the way that it should be administered. Use
220 [TRADE NAME] HFA Inhalation Aerosol only with the actuator supplied with
221 the product. Discard the canister after 200 sprays have been used.

222 **Drug Interactions**

223 Other short-acting sympathomimetic aerosol bronchodilators should not be
224 used concomitantly with albuterol. If additional adrenergic drugs are to be
225 administered by any route, they should be used with caution to avoid deleterious
226 cardiovascular effects.

227 **Beta-Blockers:** Beta-adrenergic-receptor blocking agents not only block the
228 pulmonary effect of beta-agonists, such as [TRADE NAME] HFA Inhalation
229 Aerosol, but may produce severe bronchospasm in asthmatic patients. Therefore,
230 patients with asthma should not normally be treated with beta-blockers. However,
231 under certain circumstances, e.g., as prophylaxis after myocardial infarction, there
232 may be no acceptable alternatives to the use of beta-adrenergic-blocking agents in
233 patients with asthma. In this setting, cardioselective beta-blockers should be
234 considered, although they should be administered with caution.

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

241 **Digoxin:** Mean decreases of 16% and 22% in serum digoxin levels were
242 demonstrated after single dose intravenous and oral administration of albuterol,
243 respectively, to normal volunteers who had received digoxin for 10 days. The
244 clinical significance of these findings for patients with obstructive airway disease
245 who are receiving albuterol and digoxin on a chronic basis is unclear.
246 Nevertheless, it would be prudent to carefully evaluate the serum digoxin levels in
247 patients who are currently receiving digoxin and albuterol.

248 **Monoamine Oxidase Inhibitors or Tricyclic Antidepressants:** [TRADE
249 NAME] HFA Inhalation Aerosol should be administered with extreme caution to
250 patients being treated with monoamine oxidase inhibitors or tricyclic
251 antidepressants, or within 2 weeks of discontinuation of such agents, because the
252 action of albuterol on the cardiovascular system may be potentiated.

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

254 In a 2-year study in Sprague-Dawley rats, albuterol sulfate caused a dose-
255 related increase in the incidence of benign leiomyomas of the mesovarium at and
256 above dietary doses of 2 mg/kg (approximately 15 times the maximum
257 recommended daily inhalation dose for adults on a mg/m² basis). In another study
258 this effect was blocked by the coadministration of propranolol, a non-selective
259 beta-adrenergic antagonist. In an 18-month study in CD-1 mice, albuterol sulfate
260 showed no evidence of tumorigenicity at dietary doses of up to 500 mg/kg
261 (approximately 1,600 times the maximum recommended daily inhalation dose for
262 adults on a mg/m² basis). In a 22-month study in Golden Hamsters, albuterol
263 sulfate showed no evidence of tumorigenicity at dietary doses of up to 50 mg/kg
264 (approximately 10 times the maximum recommended daily inhalation dose for
265 adults on a mg/m² basis).

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

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

272 **Pregnancy: Teratogenic Effects: Pregnancy Category C**

273 Albuterol sulfate has been shown to be teratogenic in mice. A study in CD-1
274 mice given albuterol sulfate subcutaneously showed cleft palate formation in 5 of
275 111 (4.5%) fetuses at 0.25 mg/kg (less than the maximum recommended daily
276 inhalation dose for adults on a mg/m² basis) and in 10 of 108 (9.3%) fetuses at
277 2.5 mg/kg (approximately 8 times the maximum recommended daily inhalation
278 dose for adults on a mg/m² basis). The drug did not induce cleft palate formation
279 at the low dose 0.025 mg/kg (less than the maximum recommended daily
280 inhalation dose for adults on a mg/m² basis). Cleft palate also occurred in 22 of
281 72 (30.5%) fetuses treated subcutaneously with 2.5 mg/kg isoproterenol (positive
282 control).

283 A reproduction study in Stride Dutch rabbits revealed cranioschisis in 7 of
284 19 (37%) fetuses when albuterol sulfate was administered orally at 50 mg/kg

285 (approximately 630 times the maximum recommended daily inhalation dose for
286 adults on a mg/m² basis).

287 In an inhalation reproduction study in Sprague-Dawley rats, the albuterol
288 sulfate/HFA-134a formulation did not exhibit any teratogenic effects at
289 10.5 mg/kg (approximately 65 times the maximum recommended daily inhalation
290 dose for adults on a mg/m² basis).

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

294 There are no adequate and well-controlled studies of albuterol sulfate in
295 pregnant women. [TRADE NAME] HFA Inhalation Aerosol should be used
296 during pregnancy only if the potential benefit justifies the potential risk to the
297 fetus.

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

304 **Use in Labor and Delivery**

305 Because of the potential for beta-agonist interference with uterine contractility,
306 use of [TRADE NAME] HFA Inhalation Aerosol for relief of bronchospasm
307 during labor should be restricted to those patients in whom the benefits clearly
308 outweigh the risk.

309 **Tocolysis:** Albuterol has not been approved for the management of pre-term
310 labor. The benefit:risk ratio when albuterol is administered for tocolysis has not
311 been established. Serious adverse reactions, including pulmonary edema, have
312 been reported during or following treatment of premature labor with beta₂-
313 agonists, including albuterol.

314 **Nursing Mothers**

315 Plasma levels of albuterol sulfate and HFA-134a after inhaled therapeutic
316 doses are very low in humans, but it is not known whether the components of
317 [TRADE NAME] HFA Inhalation Aerosol are excreted in human milk.

318 Caution should be exercised when albuterol sulfate is administered to a nursing
319 woman. Because of the potential for tumorigenicity shown for albuterol in animal
320 studies and lack of experience with the use of [TRADE NAME] HFA Inhalation
321 Aerosol by nursing mothers, a decision should be made whether to discontinue
322 nursing or to discontinue the drug, taking into account the importance of the drug
323 to the mother.

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Pediatrics

The safety and effectiveness of [TRADE NAME] HFA Inhalation Aerosol in pediatric patients below the age of 12 years have not been established.

Geriatrics

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

ADVERSE REACTIONS

A total of 973 subjects were treated with [TRADE NAME] HFA Inhalation Aerosol during the worldwide clinical development program.

The adverse reaction information presented in the table below concerning [TRADE NAME] HFA Inhalation Aerosol is derived from a 6-week, evaluator-blind study which compared [TRADE NAME] HFA Inhalation Aerosol (180 mcg four times daily) with an HFA-134a placebo inhaler and an active comparator HFA-134a albuterol inhaler in 172 asthmatic patients 12 to 76 years of age. The table lists the incidence of all adverse events (whether considered by the investigator drug related or unrelated to drug) from this study which occurred at a rate of 3% or greater in the [TRADE NAME] HFA Inhalation Aerosol treatment group and more frequently in the [TRADE NAME] HFA Inhalation Aerosol treatment group than in the placebo group. Overall, the incidence and nature of the adverse events reported for [TRADE NAME] HFA Inhalation Aerosol and the 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)		[TRADE NAME] Inhalation Aerosol (N = 58)	Active comparator HFA-134a Albuterol Inhaler (N = 56)	HFA-134a Placebo Inhaler (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 [TRADE NAME] HFA Inhalation Aerosol group and more frequently in the [TRADE NAME] HFA Inhalation Aerosol group than in the HFA-134a placebo inhaler group.

352 Adverse events reported by less than 3% of the patients receiving [TRADE
353 NAME] HFA Inhalation Aerosol but by a greater proportion of [TRADE NAME]
354 HFA Inhalation Aerosol patients than placebo patients, which have the potential
355 to be related to [TRADE NAME] HFA Inhalation Aerosol, included chest pain,
356 infection, diarrhea, glossitis, accidental injury (nervous system), anxiety, dyspnea,
357 ear disorder, ear pain, and urinary tract infection. Adverse events reported by 3%
358 or more patients receiving [TRADE NAME] and by an equal or lesser proportion
359 of [TRADE NAME] HFA Inhalation Aerosol patients than placebo patients
360 included asthma, back pain, increased cough and infection (respiratory).

361 The most frequent adverse events occurring in three studies conducted in
362 32 volunteers or 25 asthmatics in which [TRADE NAME] HFA Inhalation
363 Aerosol was administered as single cumulative albuterol doses of up to 1080 mcg
364 over an hour (volunteers) or 1350 mcg over 1½ hours (asthmatics) were consistent
365 with those associated with high-dose inhaled albuterol and included tremor,
366 nervousness, and headache.

367 Rare cases of urticaria, angioedema, rash, bronchospasm, hoarseness,
368 oropharyngeal edema, and arrhythmias (including atrial fibrillation,
369 supraventricular tachycardia, extrasystoles) have been reported after the use of
370 inhaled albuterol. In addition, albuterol, like other sympathomimetic agents, can
371 cause adverse reactions such as hypertension, angina, vertigo, central nervous
372 system stimulation, insomnia, headache, and drying or irritation of the
373 oropharynx.

374 **OVERDOSAGE**

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

381 Hypokalemia may also occur. As with all sympathomimetic medications,
382 cardiac arrest and even death may be associated with abuse of [TRADE NAME]
383 HFA Inhalation Aerosol.

384 Treatment consists of discontinuation of [TRADE NAME] HFA Inhalation
385 Aerosol together with appropriate symptomatic therapy. The judicious use of a
386 cardioselective beta-receptor blocker may be considered, bearing in mind that
387 such medication can produce bronchospasm. There is insufficient evidence to
388 determine if dialysis is beneficial for overdosage of [TRADE NAME] HFA
389 Inhalation Aerosol.

390 The oral median lethal dose of albuterol sulfate in mice is greater than
391 2,000 mg/kg (approximately 6,300 times the maximum recommended daily
392 inhalation dose for adults on a mg/m² basis). In mature rats, the subcutaneous
393 median lethal dose of albuterol sulfate is approximately 450 mg/kg
394 (approximately 2,800 times the maximum recommended daily inhalation dose for
395 adults on a mg/m² basis). In young rats, the subcutaneous median lethal dose is

396 approximately 2,000 mg/kg (approximately 13,000 times the maximum
397 recommended daily inhalation dose for adults on a mg/m² basis). The inhalation
398 median lethal dose has not been determined in animals.

399 **DOSAGE AND ADMINISTRATION**

400 For treatment of acute episodes of bronchospasm or prevention of asthmatic
401 symptoms, the usual dosage for adults and children 12 years and older is two
402 inhalations repeated every 4 to 6 hours. More frequent administration or a larger
403 number of inhalations is not recommended. In some patients, one inhalation
404 every 4 hours may be sufficient.

405 Each actuation of [TRADE NAME] HFA Inhalation Aerosol delivers 108 mcg
406 of albuterol sulfate (equivalent to 90 mcg of albuterol base) from the actuator
407 mouthpiece. It is recommended to prime the inhaler before using for the first time
408 and in cases where the inhaler has not been used for more than two weeks by
409 releasing three “test sprays” into the air, away from the face.

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

414 To maintain proper use of this product and to prevent medication build-up and
415 blockage, it is important to keep the plastic mouthpiece clean. Wash the
416 mouthpiece and air dry thoroughly at least once a week. If the mouthpiece
417 becomes blocked, washing the mouthpiece will remove the blockage. The inhaler
418 may cease to deliver medication if not properly cleaned and air dried. See-

419 **Information For Patients.**

420 **HOW SUPPLIED** [TRADE NAME] HFA (albuterol sulfate) Inhalation Aerosol
421 is supplied as a pressurized aluminum canister with a blue plastic actuator and
422 dark blue dust cap each in boxes of one. Each canister contains 8.5 g of the
423 formulation and provides 200 actuations (NDC 59310-179-20). Each actuation
424 delivers 120 mcg of albuterol sulfate from the canister valve and 108 mcg of
425 albuterol sulfate from the actuator mouthpiece (equivalent to 90 mcg of albuterol
426 base).

427 **Rx only.**

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

431 **SHAKE WELL BEFORE USE.**

432 **The blue actuator supplied with [TRADE NAME] HFA Inhalation Aerosol**
433 **should not be used with the canister from any other inhalation aerosol**
434 **products. The [TRADE NAME] HFA Inhalation Aerosol canister should not**
435 **be used with the actuator from any other inhalation aerosol products.**
436

437 **Once the labeled number of actuations (i.e. 200) has been used, the labeled**
438 **amount of medication delivered from a canister cannot be assured. As a**
439 **result, the inhaler should be discarded after 200 actuations, even though the**
440 **canister may not be completely empty. Never immerse the canister into**
441 **water to determine how full the canister is (“float test”).**

442 **WARNING:**

443 **Avoid spraying in eyes. Contents under pressure. Do not puncture or**
444 **incinerate. Exposure to temperatures above 120°F may cause bursting.**
445 **Keep out of reach of children.**
446

447 [TRADE NAME] HFA Inhalation Aerosol does not contain chlorofluorocarbons
448 (CFCs) as the propellant.

449

450

451 Manufactured by
452 IVAX Pharmaceuticals Ireland
453 Waterford, Republic of Ireland
454 for
455 IVAX Laboratories, Inc.
456 Miami, FL 33137 USA

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458

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Rev. 10/04B

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Attention Pharmacist:

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

TRADE NAME™ HFA

(albuterol sulfate)

Inhalation Aerosol

FOR ORAL INHALATION ONLY

Patient's Instructions For Use

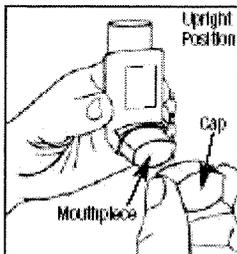


Fig. 1

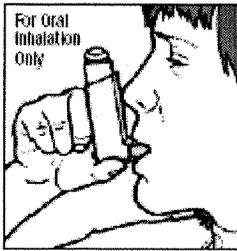


Fig. 2

Before using your [TRADE NAME] HFA (albuterol sulfate) Inhalation Aerosol, read complete instructions carefully. Children should use [TRADE NAME] 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.**

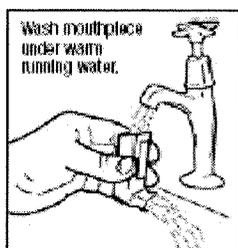


Fig. A

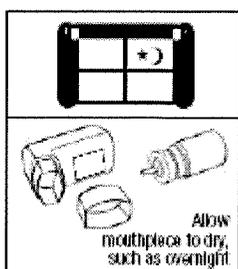
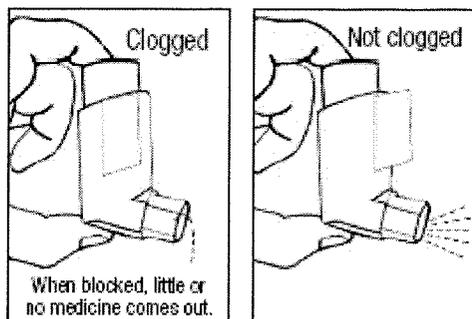


Fig. B

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 [TRADE NAME] 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 [TRADE NAME] 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 [TRADE NAME] 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 [TRADE NAME] HFA Inhalation Aerosol without

consulting your doctor. If you find that treatment with [TRADE NAME] 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 [TRADE NAME] 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 [TRADE NAME] HFA Inhalation Aerosol.

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

The [TRADE NAME] HFA Inhalation Aerosol actuator should not be used with the canister from other inhalation aerosol medications. The [TRADE NAME] 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 [TRADE NAME] 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

[TRADE NAME] is a trademark of
IVAX Laboratories Inc.

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