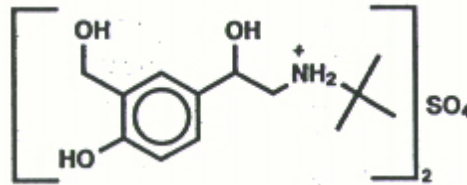


1 **ALBUTEROL SULFATE HFA**
2 **INHALATION AEROSOL**
3 For Oral Inhalation Only

4 **PRESCRIBING INFORMATION**

5 **DESCRIPTION**

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

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78 **Pharmacokinetics**

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

90 No pharmacokinetic studies for Albuterol Sulfate HFA Inhalation Aerosol
91 have been conducted in neonates, children, or elderly subjects.

92 **Clinical Trials**

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

98 Serial FEV₁ measurements, shown below as percent change from test-day
99 baseline at Day 1 and at Day 43, demonstrated that two inhalations of Albuterol
100 Sulfate HFA Inhalation Aerosol produced significantly greater improvement in
101 FEV₁ over the pre-treatment value than placebo, as well as a comparable
102 bronchodilator effect to the active comparator HFA-134a albuterol inhaler.

103 The mean time of onset of a 15% increase in FEV₁ at Day 1 was
104 approximately 19 minutes and the mean time to peak effect was 70 minutes. The
105 mean duration of effect as measured by a 15% increase in FEV₁ over the pre-
106 treatment value was approximately 3 hours. In some patients, the duration was as
107 long as 6 hours.

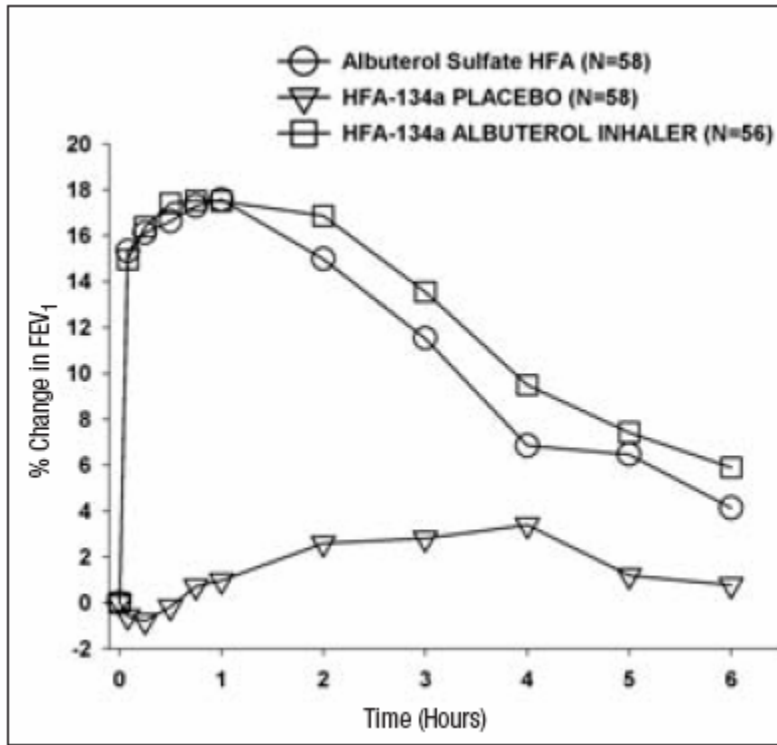
108 In a placebo-controlled single-dose, crossover study in which Albuterol
109 Sulfate HFA Inhalation Aerosol, administered at albuterol doses of 90, 180 and
110 270 mcg, produced bronchodilator responses significantly greater than those
111 observed with an HFA-134a placebo inhaler and comparable to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

113 Some patients who participated in these clinical trials were using concomitant
114 steroid therapy.

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

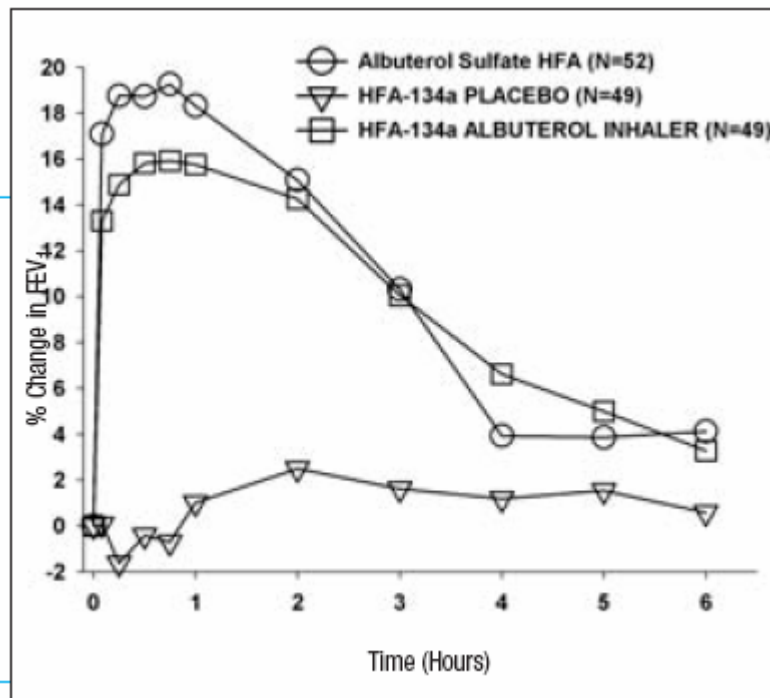
Day 1



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Day 43



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INDICATIONS AND USAGE

Albuterol Sulfate 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

Albuterol Sulfate HFA Inhalation Aerosol is contraindicated in patients with a history of hypersensitivity to albuterol and any other Albuterol Sulfate HFA Inhalation Aerosol components.

WARNINGS

Paradoxical Bronchospasm: Inhaled albuterol sulfate can produce paradoxical bronchospasm that may be life threatening. If paradoxical bronchospasm occurs, Albuterol Sulfate 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 Albuterol Sulfate 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: Albuterol Sulfate 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 Albuterol Sulfate 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, Albuterol Sulfate HFA Inhalation Aerosol, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

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

165 **Immediate Hypersensitivity Reactions:** Immediate hypersensitivity
166 reactions may occur after administration of albuterol sulfate, as demonstrated by
167 rare cases of urticaria, angioedema, rash, bronchospasm, anaphylaxis, and
168 oropharyngeal edema.

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170 **PRECAUTIONS**

171 **General**

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

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

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186 **Information for Patients** See illustrated **Patient's Instructions for Use.**
187 **SHAKE WELL BEFORE USING.** Patients should be given the following
188 information:

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

192 **KEEPING THE PLASTIC MOUTHPIECE CLEAN IS VERY IMPORTANT**
193 **TO PREVENT MEDICATION BUILD-UP AND BLOCKAGE. THE**
194 **MOUTHPIECE SHOULD BE WASHED, SHAKEN TO REMOVE EXCESS**
195 **WATER, AND AIR DRIED THOROUGHLY AT LEAST ONCE A WEEK.**
196 **THE INHALER MAY CEASE TO DELIVER MEDICATION IF NOT**
197 **PROPERLY CLEANED.**

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

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

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

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

221 Common adverse effects of treatment with inhaled albuterol include
222 palpitations, chest pain, rapid heart rate, tremor, or nervousness. If you are
223 pregnant or nursing, contact your physician about use of Albuterol Sulfate HFA
224 Inhalation Aerosol. Effective and safe use of Albuterol Sulfate HFA Inhalation
225 Aerosol includes an understanding of the way that it should be administered. Use
226 Albuterol Sulfate HFA Inhalation Aerosol only with the actuator supplied with
227 the product. Discard the canister after 200 sprays have been used.

228 **Drug Interactions**

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

233 **Beta-Blockers:** Beta-adrenergic-receptor blocking agents not only block the
234 pulmonary effect of beta-agonists, such as Albuterol Sulfate HFA Inhalation
235 Aerosol, but may produce severe bronchospasm in asthmatic patients. Therefore,
236 patients with asthma should not normally be treated with beta-blockers.
237 However, under certain circumstances, e.g., as prophylaxis after myocardial
238 infarction, there may be no acceptable alternatives to the use of beta-adrenergic-
239 blocking agents in patients with asthma. In this setting, cardioselective beta-
240 blockers should be considered, although they should be administered with
241 caution.

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

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

255 **Monoamine Oxidase Inhibitors or Tricyclic Antidepressants:** Albuterol
256 Sulfate HFA Inhalation Aerosol should be administered with extreme caution to
257 patients being treated with monoamine oxidase inhibitors or tricyclic
258 antidepressants, or within 2 weeks of discontinuation of such agents, because the
259 action of albuterol on the cardiovascular system may be potentiated.

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

261 In a 2-year study in Sprague-Dawley rats, albuterol sulfate caused a dose-
262 related increase in the incidence of benign leiomyomas of the mesovarium at and
263 above dietary doses of 2 mg/kg (approximately 15 times the maximum
264 recommended daily inhalation dose for adults on a mg/m² basis). In another
265 study this effect was blocked by the coadministration of propranolol, a non-
266 selective beta-adrenergic antagonist. In an 18-month study in CD-1 mice,
267 albuterol sulfate showed no evidence of tumorigenicity at dietary doses of up to
268 500 mg/kg (approximately 1,600 times the maximum recommended daily
269 inhalation dose for adults on a mg/m² basis). In a 22-month study in Golden
270 Hamsters, albuterol sulfate showed no evidence of tumorigenicity at dietary doses
271 of up to 50 mg/kg (approximately 210 times the maximum recommended daily
272 inhalation dose for adults on a mg/m² basis).

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

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

279 **Pregnancy: Teratogenic Effects: Pregnancy Category C**

280 Albuterol sulfate has been shown to be teratogenic in mice. A study in CD-1
281 mice given albuterol sulfate subcutaneously showed cleft palate formation in 5 of
282 111 (4.5%) fetuses at 0.25 mg/kg (less than the maximum recommended daily
283 inhalation dose for adults on a mg/m² basis) and in 10 of 108 (9.3%) fetuses at
284 2.5 mg/kg (approximately 8 times the maximum recommended daily inhalation
285 dose for adults on a mg/m² basis). The drug did not induce cleft palate formation
286 at the low dose 0.025 mg/kg (less than the maximum recommended daily
287 inhalation dose for adults on a mg/m² basis). Cleft palate also occurred in 22 of
288 72 (30.5%) fetuses treated subcutaneously with 2.5 mg/kg isoproterenol (positive
289 control).

290 A reproduction study in Stride Dutch rabbits revealed cranioschisis in 7 of
291 19 (37%) fetuses when albuterol sulfate was administered orally at 50 mg/kg

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

294 In an inhalation reproduction study in Sprague-Dawley rats, the albuterol
295 sulfate/HFA-134a formulation did not exhibit any teratogenic effects at
296 10.5 mg/kg (approximately 65 times the maximum recommended daily inhalation
297 dose for adults on a mg/m² basis).

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

301 There are no adequate and well-controlled studies of albuterol sulfate in
302 pregnant women. Albuterol Sulfate HFA Inhalation Aerosol should be used
303 during pregnancy only if the potential benefit justifies the potential risk to the
304 fetus.

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

311 **Use in Labor and Delivery**

312 Because of the potential for beta-agonist interference with uterine contractility,
313 use of Albuterol Sulfate HFA Inhalation Aerosol for relief of bronchospasm
314 during labor should be restricted to those patients in whom the benefits clearly
315 outweigh the risk.

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

321 **Nursing Mothers**

322 Plasma levels of albuterol sulfate and HFA-134a after inhaled therapeutic
323 doses are very low in humans, but it is not known whether the components of
324 Albuterol Sulfate HFA Inhalation Aerosol are excreted in human milk.

325 Caution should be exercised when albuterol sulfate is administered to a
326 nursing woman. Because of the potential for tumorigenicity shown for albuterol
327 in animal studies and lack of experience with the use of Albuterol Sulfate HFA
328 Inhalation Aerosol by nursing mothers, a decision should be made whether to
329 discontinue nursing or to discontinue the drug, taking into account the importance
330 of the drug to the mother.

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Pediatrics

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

Geriatrics

Clinical studies of Albuterol Sulfate 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 Albuterol Sulfate HFA Inhalation Aerosol during the worldwide clinical development program.

The adverse reaction information presented in the table below concerning Albuterol Sulfate HFA Inhalation Aerosol is derived from a 6-week, evaluator-blind study which compared Albuterol Sulfate 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 Albuterol Sulfate HFA Inhalation Aerosol treatment group and more frequently in the Albuterol Sulfate HFA Inhalation Aerosol treatment group than in the placebo group. Overall, the incidence and nature of the adverse events reported for Albuterol Sulfate 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)		Albuterol Sulfate 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 Albuterol Sulfate HFA Inhalation Aerosol group and more frequently in the Albuterol Sulfate HFA Inhalation Aerosol group than in the HFA-134a placebo inhaler group.

359 Adverse events reported by less than 3% of the patients receiving Albuterol
360 Sulfate HFA Inhalation Aerosol but by a greater proportion of Albuterol Sulfate
361 HFA Inhalation Aerosol patients than placebo patients, which have the potential
362 to be related to Albuterol Sulfate HFA Inhalation Aerosol, included chest pain,
363 infection, diarrhea, glossitis, accidental injury (nervous system), anxiety, dyspnea,
364 ear disorder, ear pain, and urinary tract infection. Adverse events reported by 3%
365 or more patients receiving Albuterol Sulfate and by an equal or lesser proportion
366 of Albuterol Sulfate HFA Inhalation Aerosol patients than placebo patients
367 included asthma, back pain, increased cough and infection (respiratory).

368 The most frequent adverse events occurring in three studies conducted in
369 32 volunteers or 25 asthmatics in which Albuterol Sulfate HFA Inhalation
370 Aerosol was administered as single cumulative albuterol doses of up to 1080 mcg
371 over an hour (volunteers) or 1350 mcg over 1½ hours (asthmatics) were
372 consistent with those associated with high-dose inhaled albuterol and included
373 tremor, nervousness, and headache.

374 Rare cases of urticaria, angioedema, rash, bronchospasm, hoarseness,
375 oropharyngeal edema, and arrhythmias (including atrial fibrillation,
376 supraventricular tachycardia, extrasystoles) have been reported after the use of
377 inhaled albuterol. In addition, albuterol, like other sympathomimetic agents, can
378 cause adverse reactions such as hypertension, angina, vertigo, central nervous
379 system stimulation, insomnia, headache, and drying or irritation of the
380 oropharynx.

381 **OVERDOSAGE**

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

388 Hypokalemia may also occur. As with all sympathomimetic medications,
389 cardiac arrest and even death may be associated with abuse of Albuterol Sulfate
390 HFA Inhalation Aerosol.

391 Treatment consists of discontinuation of Albuterol Sulfate HFA Inhalation
392 Aerosol together with appropriate symptomatic therapy. The judicious use of a
393 cardioselective beta-receptor blocker may be considered, bearing in mind that
394 such medication can produce bronchospasm. There is insufficient evidence to
395 determine if dialysis is beneficial for overdosage of Albuterol Sulfate HFA
396 Inhalation Aerosol.

397 The oral median lethal dose of albuterol sulfate in mice is greater than
398 2,000 mg/kg (approximately 6,300 times the maximum recommended daily
399 inhalation dose for adults on a mg/m² basis). In mature rats, the subcutaneous
400 median lethal dose of albuterol sulfate is approximately 450 mg/kg
401 (approximately 2,800 times the maximum recommended daily inhalation dose for
402 adults on a mg/m² basis). In young rats, the subcutaneous median lethal dose is
403 approximately 2,000 mg/kg (approximately 13,000 times the maximum

404 recommended daily inhalation dose for adults on a mg/m² basis). The inhalation
405 median lethal dose has not been determined in animals.

406 **DOSAGE AND ADMINISTRATION**

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

412 Each actuation of Albuterol Sulfate HFA Inhalation Aerosol delivers 108 mcg
413 of albuterol sulfate (equivalent to 90 mcg of albuterol base) from the actuator
414 mouthpiece. It is recommended to prime the inhaler before using for the first time
415 and in cases where the inhaler has not been used for more than two weeks by
416 releasing three “test sprays” into the air, away from the face.

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

421 To maintain proper use of this product and to prevent medication build-up and
422 blockage, it is important to keep the plastic mouthpiece clean. Wash the
423 mouthpiece and air dry thoroughly at least once a week. If the mouthpiece
424 becomes blocked, washing the mouthpiece will remove the blockage. The inhaler
425 may cease to deliver medication if not properly cleaned and air dried. See-
426 **Information For Patients.**

427 **HOW SUPPLIED** Albuterol Sulfate HFA Inhalation Aerosol is supplied as a
428 pressurized aluminum canister with a red plastic actuator and white dust cap each
429 in boxes of one. Each canister contains 8.5 g of the formulation and provides 200
430 actuations (NDC 59310-579-20). Each actuation delivers 120 mcg of albuterol
431 sulfate from the canister valve and 108 mcg of albuterol sulfate from the actuator
432 mouthpiece (equivalent to 90 mcg of albuterol base).

433
434 **Rx only.**

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

438 **SHAKE WELL BEFORE USE.**

439 **The red actuator supplied with Albuterol Sulfate HFA Inhalation Aerosol**
440 **should not be used with the canister from any other inhalation aerosol**
441 **products. The Albuterol Sulfate HFA Inhalation Aerosol canister should not**
442 **be used with the actuator from any other inhalation aerosol products.**

443 **Once the labeled number of actuations (i.e. 200) has been used, the labeled**
444 **amount of medication delivered from a canister cannot be assured. As a**

445 result, the inhaler should be discarded after 200 actuations, even though the
446 canister may not be completely empty. Never immerse the canister into
447 water to determine how full the canister is (“float test”).

448 **WARNING:**

449 **Avoid spraying in eyes. Contents under pressure. Do not puncture or**
450 **incinerate. Exposure to temperatures above 120°F may cause bursting.**
451 **Keep out of reach of children.**
452

453 Albuterol Sulfate HFA Inhalation Aerosol does not contain chlorofluorocarbons
454 (CFCs) as the propellant.

455

456

457 Manufactured by
458 IVAX Pharmaceuticals Ireland
459 Waterford, Republic of Ireland
460 for
461 IVAX Laboratories, Inc.
462 Miami, FL 33137 USA
463

464

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Attention Pharmacist:

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

Albuterol Sulfate HFA

Inhalation Aerosol

FOR ORAL INHALATION ONLY

Patient's Instructions For Use

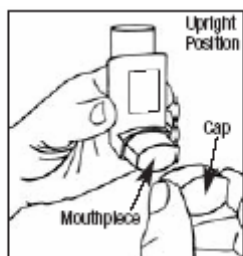


Fig. 1

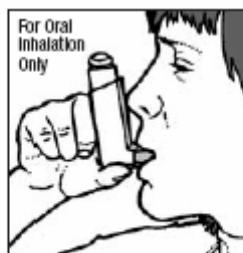


Fig. 2

Before using your Albuterol Sulfate HFA Inhalation Aerosol, read complete instructions carefully. Children should use Albuterol Sulfate 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.**

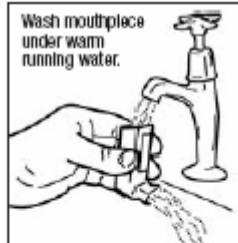


Fig. A

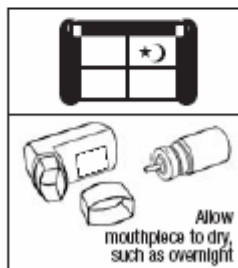
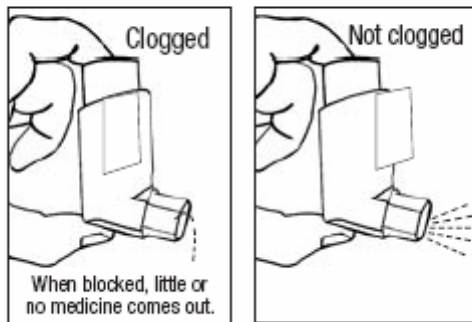


Fig. B

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 Albuterol Sulfate 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 Albuterol Sulfate 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 Albuterol Sulfate 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 Albuterol Sulfate HFA Inhalation Aerosol without

consulting your doctor. If you find that treatment with Albuterol Sulfate 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 Albuterol Sulfate 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 Albuterol Sulfate HFA Inhalation Aerosol.

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

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

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