

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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APPROVED LABELING

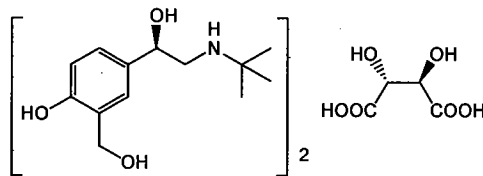
1 **XOPENEX HFA™ (levalbuterol tartrate) Inhalation Aerosol**

2 **For Oral Inhalation Only**

3 **PRESCRIBING INFORMATION**

4 **DESCRIPTION**

5 The active component of XOPENEX HFA (levalbuterol tartrate) Inhalation Aerosol is
6 levalbuterol tartrate, the (R)-enantiomer of albuterol. Levalbuterol tartrate is a relatively
7 selective beta₂-adrenergic receptor agonist (see **CLINICAL PHARMACOLOGY**).
8 Levalbuterol tartrate has the chemical name (R)-α¹-[[[(1,1-dimethylethyl)amino]methyl]-
9 4-hydroxy-1,3-benzenedimethanol L-tartrate (2:1 salt), and it has the following chemical
10 structure:



13 The molecular weight of levalbuterol tartrate is 628.71, and its empirical formula is
14 (C₁₃H₂₁NO₃)₂ · C₄H₆O₆. It is a white to light-yellow solid, freely soluble in water and
15 very slightly soluble in ethanol.

16 Levalbuterol tartrate is the generic name for (R)-albuterol tartrate in the United States.
17 XOPENEX HFA Inhalation Aerosol is a pressurized metered-dose aerosol inhaler (MDI),
18 which produces an aerosol for oral inhalation. It contains a suspension of micronized
19 levalbuterol tartrate, propellant HFA-134a (1,1,1,2-tetrafluoroethane), Dehydrated
20 Alcohol USP, and Oleic Acid NF.

21 The inhaler should be primed by releasing 4 sprays into the air, away from the face,
22 before using it for the first time and when the inhaler has not been used for more than
23 3 days. After priming with 4 actuations, each actuation delivers 59 mcg of levalbuterol
24 tartrate (equivalent to 45 mcg of levalbuterol free base) from the actuator (or
25 mouthpiece). Each 15 g canister provides 200 actuations (or inhalations).

26 This product does not contain chlorofluorocarbons (CFCs).

27 **CLINICAL PHARMACOLOGY**

28 **Mechanism of Action:** Activation of beta₂-adrenergic receptors on airway smooth
29 muscle leads to the activation of adenylate cyclase and to an increase in the intracellular
30 concentration of cyclic-3', 5'-adenosine monophosphate (cyclic AMP). The increase in
31 cyclic AMP is associated with the activation of protein kinase A, which in turn, inhibits
32 the phosphorylation of myosin and lowers intracellular ionic calcium concentrations,

33 resulting in muscle relaxation. Levalbuterol relaxes the smooth muscles of all airways,
34 from the trachea to the terminal bronchioles. Increased cyclic AMP concentrations are
35 also associated with the inhibition of the release of mediators from mast cells in the
36 airways. Levalbuterol acts as a functional antagonist to relax the airway irrespective of
37 the spasmogen involved, thus protecting against all bronchoconstrictor challenges. While
38 it is recognized that beta₂-adrenergic receptors are the predominant receptors on
39 bronchial smooth muscle, data indicate that there are beta-receptors in the human heart,
40 10% to 50% of which are beta₂-adrenergic receptors. The precise function of these
41 receptors has not been established (see **WARNINGS**). However, all beta-adrenergic
42 agonist drugs can produce a significant cardiovascular effect in some patients, as
43 measured by pulse rate, blood pressure, symptoms, and/or electrocardiographic changes.

44 **Preclinical**

45 Results from in vitro studies of binding to human beta-adrenergic receptors demonstrated
46 that levalbuterol has approximately 2-fold greater binding affinity than racemic albuterol
47 and approximately 100-fold greater binding affinity than (S)-albuterol. In guinea pig
48 airways, levalbuterol HCl and racemic albuterol decreased the response to spasmogens
49 (e.g., acetylcholine and histamine), whereas (S)-albuterol was ineffective. These results
50 suggest that the bronchodilatory effects of racemic albuterol are attributable to the
51 (R)-enantiomer.

52 Intravenous studies in rats with racemic albuterol sulfate have demonstrated that albuterol
53 crosses the blood-brain barrier and reaches brain concentrations amounting to
54 approximately 5.0% of the plasma concentrations. In structures outside the blood-brain
55 barrier (pineal and pituitary glands), racemic albuterol concentrations were found to be
56 100 times those in the whole brain.

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

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

66 In animals and humans, propellant HFA-134a was found to be rapidly absorbed and
67 rapidly eliminated, with an elimination half-life of 3 to 27 minutes in animals and 5 to
68 7 minutes in humans. Time to maximum plasma concentration (t_{max}) and mean residence
69 time are both extremely short, leading to a transient appearance of HFA-134a in the
70 blood with no evidence of accumulation.

71 **Pharmacokinetics**

72 A population pharmacokinetic (PPK) model was developed using plasma concentrations
73 of (R)-albuterol obtained from 632 asthmatic patients aged 4 to 81 years in three large
74 trials. The PPK model-derived pharmacokinetic parameters for (R)-albuterol in pediatric
75 and adolescent/adult patients receiving a 90 mcg dose of XOPENEX HFA (levalbuterol
76 tartrate) Inhalation Aerosol or a 180 mcg dose of racemic albuterol by HFA metered-dose
77 inhaler are presented in Table 1.

78 These pharmacokinetic data indicate that mean exposure to (R)-albuterol was 13% to
79 16% less in adult and 30% to 32% less in pediatric patients given XOPENEX HFA
80 Inhalation Aerosol as compared to those given a comparable dose of racemic albuterol.
81 When compared to adult patients, pediatric patients given 90 mcg of levalbuterol have a
82 17% lower mean exposure to (R)-albuterol.

Table 1: Mean Model-Predicted (R)-Albuterol Pharmacokinetic Parameters

Study Population	Parameter	Treatment	
		XOPENEX HFA Inhalation Aerosol	Racemic Albuterol HFA MDI
Adolescent/Adult Patients (≥12 years)	C _{max} (ng/mL)	0.199	0.238
	t _{max} (hr)	0.54	0.53
	AUC ₍₀₋₆₎ (ng·hr/mL)	0.695	0.798
Pediatric Patients (4-11 years)	C _{max} (ng/mL)	0.163	0.238
	t _{max} (hr)	0.76	0.78
	AUC ₍₀₋₆₎ (ng·hr/mL)	0.579	0.828

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84 **Metabolism and Elimination**

85 Information available in the published literature suggests that the primary enzyme
86 responsible for the metabolism of albuterol enantiomers in humans is SULT1A3
87 (sulfotransferase). When racemic albuterol was administered either intravenously or via
88 inhalation after oral charcoal administration, there was a 3- to 4-fold difference in the
89 area under the concentration-time curves between the (R)- and (S)-albuterol enantiomers,
90 with (S)-albuterol concentrations being consistently higher. However, without charcoal
91 pretreatment, after either oral or inhalation administration the differences were 8- to 24-
92 fold, suggesting that that (R)-albuterol is preferentially metabolized in the gastrointestinal
93 tract, presumably by SULT1A3.

94 The primary route of elimination of albuterol enantiomers is through renal excretion
95 (80% to 100%) of either the parent compound or the primary metabolite. Less than 20%
96 of the drug is detected in the feces. Following intravenous administration of racemic
97 albuterol, between 25% and 46% of the (R)-albuterol fraction of the dose was excreted as
98 unchanged (R)-albuterol in the urine.

99 **Special Populations**

100 **Hepatic Impairment:** The effect of hepatic impairment on the pharmacokinetics of
101 XOPENEX HFA Inhalation Aerosol has not been evaluated.

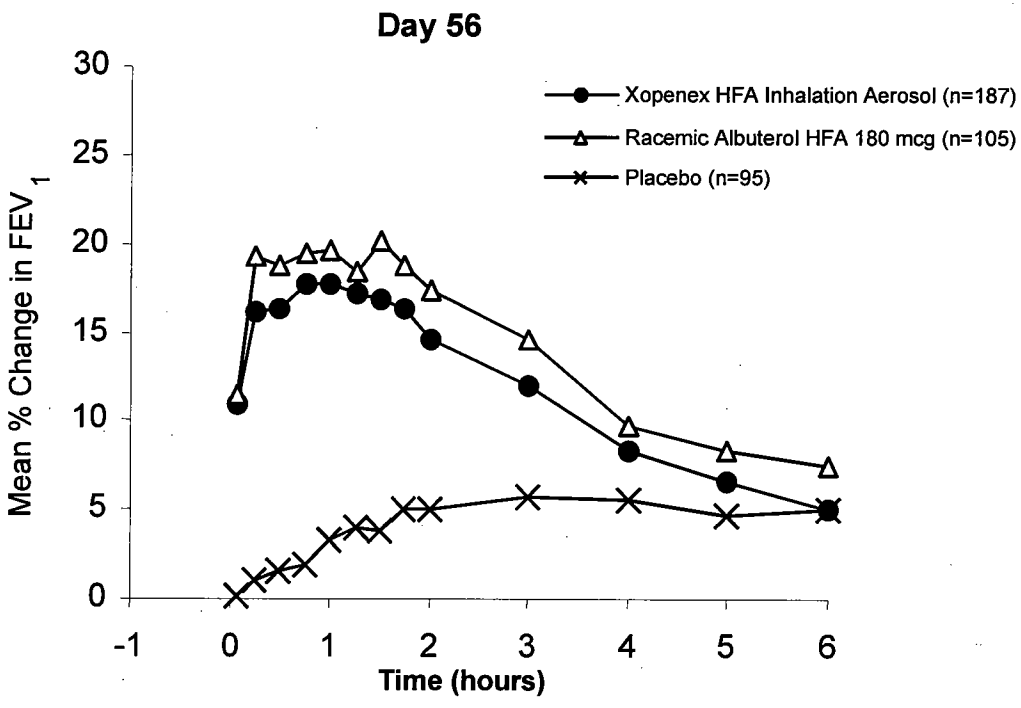
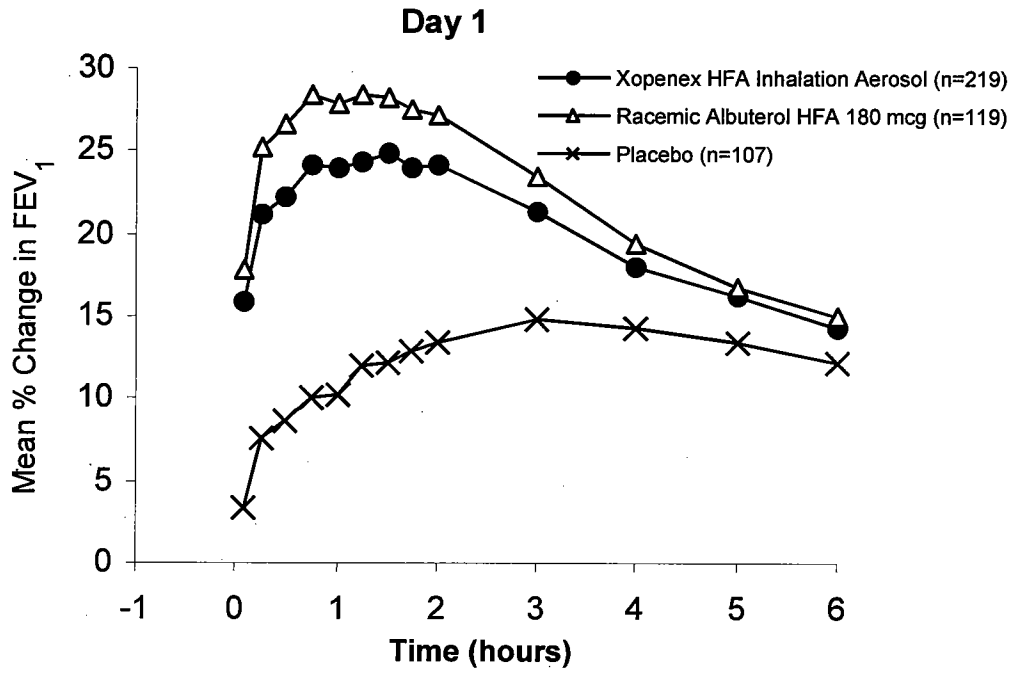
102 **Renal Impairment:** The effect of renal impairment on the pharmacokinetics of racemic
103 albuterol was evaluated in 5 subjects with creatinine clearance of 7 to 53 mL/min, and the
104 results were compared with those from healthy volunteers. Renal disease had no effect
105 on the half-life, but there was a 67% decline in racemic albuterol clearance. Caution
106 should be used when administering high doses of XOPENEX HFA Inhalation Aerosol to
107 patients with renal impairment.

108 **Clinical Trials**

109 **Adults and Adolescents:** The efficacy and safety of XOPENEX HFA Inhalation
110 Aerosol were established in two 8-week, multicenter, randomized, double-blind, active-
111 and placebo-controlled trials in 748 adults and adolescents with asthma between the ages
112 of 12 and 81 years. In these two trials, XOPENEX HFA Inhalation Aerosol (403
113 patients) was compared to an HFA-134a placebo MDI (166 patients), and the trials
114 included a marketed albuterol HFA-134a MDI (179 patients) as an active control. Serial
115 forced expiratory volume in 1 second (FEV₁) measurements demonstrated that 90 mcg
116 (2 inhalations) of XOPENEX HFA Inhalation Aerosol produced significantly greater
117 improvement in FEV₁ over the pretreatment value than placebo. The results from one of
118 the trials are shown in Figure 1 as the mean percent change in FEV₁ from test-day
119 baseline at Day 1 (n=445) and Day 56 (n=387). The results from the second trial were
120 similar.

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Figure 1: Percent Change in FEV₁ from Test-Day Baseline in Adults and Adolescents Aged 12 to 81 Years at Day 1 and Day 56



147 For XOPENEX HFA Inhalation Aerosol on Day 1, the median time to onset of a 15%
148 increase in FEV₁ ranged from 5.5 to 10.2 minutes and the median time to peak effect
149 ranged from 76 to 78 minutes. In the responder population, on Day 1 the median
150 duration of effect as measured by a 15% increase in FEV₁ was 3 to 4 hours, with duration
151 of effect in some patients of up to 6 hours.

152 **Pediatrics:** The efficacy and safety of XOPENEX HFA Inhalation Aerosol in children
153 were established in a 4-week, multicenter, randomized, double-blind, active- and
154 placebo-controlled trial in 150 pediatric patients with asthma between the ages of 4 and
155 11 years. In this trial, XOPENEX HFA Inhalation Aerosol (76 patients) was compared to
156 a placebo HFA-134a MDI (35 patients), and the trial included a marketed albuterol HFA-
157 134a MDI (39 patients) as an active control. Serial FEV₁ measurements demonstrated
158 that 90 mcg (2 inhalations) of XOPENEX HFA Inhalation Aerosol produced significantly
159 greater improvement in FEV₁ over the pretreatment value than placebo and were
160 consistent with the efficacy findings in the adult studies.

161 For XOPENEX HFA Inhalation Aerosol, on Day 1 the median time to onset of a 15%
162 increase in FEV₁ was 4.5 minutes and the median time to peak effect was 77 minutes. In
163 the responder population, the median duration of effect as measured by a 15% increase in
164 FEV₁ was 3 hours, with a duration of effect in some pediatric patients of up to 6 hours.

165 **INDICATIONS AND USAGE**

166 XOPENEX HFA (levalbuterol tartrate) Inhalation Aerosol is indicated for the treatment
167 or prevention of bronchospasm in adults, adolescents, and children 4 years of age and
168 older with reversible obstructive airway disease.

169 **CONTRAINDICATIONS**

170 XOPENEX HFA (levalbuterol tartrate) Inhalation Aerosol is contraindicated in patients
171 with a history of hypersensitivity to levalbuterol, racemic albuterol, or any other
172 component of XOPENEX HFA Inhalation Aerosol.

173 **WARNINGS**

174 **1. Paradoxical Bronchospasm:** Like other inhaled beta-adrenergic agonists,
175 XOPENEX HFA Inhalation Aerosol can produce paradoxical bronchospasm, which
176 may be life-threatening. If paradoxical bronchospasm occurs, XOPENEX HFA
177 (levalbuterol tartrate) Inhalation Aerosol should be discontinued immediately and
178 alternative therapy instituted. It should be recognized that paradoxical bronchospasm,
179 when associated with inhaled formulations, frequently occurs with the first use of a
180 new canister.

181 **2. Deterioration of Asthma:** Asthma may deteriorate acutely over a period of hours or
182 chronically over several days or longer. If the patient needs more doses of
183 XOPENEX HFA Inhalation Aerosol than usual, this may be a marker of
184 destabilization of asthma and requires reevaluation of the patient and treatment

185 regimen, giving special consideration to the possible need for anti-inflammatory
186 treatment, e.g., corticosteroids.

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

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

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

206 **6. Immediate Hypersensitivity Reactions:** Immediate hypersensitivity reactions may
207 occur after administration of racemic albuterol, as demonstrated by rare cases of
208 urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal edema.
209 The potential for hypersensitivity must be considered in the clinical evaluation of
210 patients who experience immediate hypersensitivity reactions while receiving
211 XOPENEX HFA Inhalation Aerosol.

212 **PRECAUTIONS**

213 **General**

214 XOPENEX HFA (levalbuterol tartrate) Inhalation Aerosol, like all sympathomimetic
215 amines, should be used with caution in patients with cardiovascular disorders, especially
216 coronary insufficiency, hypertension, and cardiac arrhythmias; in patients with
217 convulsive disorders, hyperthyroidism, or diabetes mellitus; and in patients who are
218 unusually responsive to sympathomimetic amines. Clinically significant changes in
219 systolic and diastolic blood pressure have been seen in individual patients and could be
220 expected to occur in some patients after the use of any beta-adrenergic bronchodilator.

221 Large doses of intravenous racemic albuterol have been reported to aggravate preexisting
222 diabetes mellitus and ketoacidosis. As with other beta-adrenergic agonist medications,
223 XOPENEX HFA Inhalation Aerosol may produce significant hypokalemia in some
224 patients, possibly through intracellular shunting, which has the potential to produce

225 adverse cardiovascular effects. The decrease is usually transient, not requiring
226 supplementation.

227 **Information for Patients**

228 See illustrated **Patient's Instructions for Use**. **SHAKE WELL BEFORE USING**.
229 Patients should be given the following information: It is recommended to prime the
230 inhaler before using for the first time and in cases where the inhaler has not been used for
231 more than 3 days by releasing 4 test sprays into the air, away from the face.

232 **KEEPING THE PLASTIC ACTUATOR CLEAN IS VERY IMPORTANT TO**
233 **PREVENT MEDICATION BUILD-UP AND BLOCKAGE. THE ACTUATOR**
234 **SHOULD BE WASHED, SHAKEN TO REMOVE EXCESS WATER, AND AIR-**
235 **DRIED THOROUGHLY AT LEAST ONCE A WEEK. THE INHALER MAY CEASE**
236 **TO DELIVER MEDICATION IF NOT PROPERLY CLEANED.**

237 The actuator should be cleaned (with the canister removed) by running warm water
238 through the top and bottom for 30 seconds at least once a week. Do not attempt to clean
239 the metal canister or allow the metal canister to become wet. Never immerse the metal
240 canister in water. The actuator must be shaken to remove excess water, then air-dried
241 thoroughly (such as overnight). Blockage from medication build-up or improper
242 medication delivery may result from failure to clean and thoroughly air-dry the actuator.

243 If the actuator becomes blocked (little or no medication coming out of the mouthpiece),
244 the blockage may be removed by washing the actuator as described above.

245 If it is necessary to use the inhaler before it is completely dry, shake excess water off the
246 plastic actuator, replace canister, shake well, test-spray twice away from face, and take
247 the prescribed dose. After such use, the actuator should be rewashed and allowed to air-
248 dry thoroughly.

249 The action of XOPENEX HFA Inhalation Aerosol should last for 4 to 6 hours.
250 XOPENEX HFA Inhalation Aerosol should not be used more frequently than
251 recommended. Do not increase the dose or frequency of doses of XOPENEX HFA
252 Inhalation Aerosol without consulting your physician. If you find that treatment with
253 XOPENEX HFA Inhalation Aerosol becomes less effective for symptomatic relief, your
254 symptoms become worse, and/or you need to use the product more frequently than usual,
255 you should seek medical attention immediately. While you are using XOPENEX HFA
256 Inhalation Aerosol, other inhaled drugs and asthma medication should be taken only as
257 directed by your physician.

258 Common adverse effects of treatment with inhaled beta-agonists include palpitations,
259 chest pain, rapid heart rate, tremor, and nervousness. If you are pregnant or nursing,
260 contact your physician about use of XOPENEX HFA Inhalation Aerosol. Effective and
261 safe use of XOPENEX HFA Inhalation Aerosol includes an understanding of the way
262 that it should be administered.

263 Use XOPENEX HFA Inhalation Aerosol only with the actuator supplied with the
264 product. Discard the canister after 200 sprays have been used. Never immerse the
265 canister in water to determine how full the canister is (“float test”).

266 In general, the technique for administering XOPENEX HFA Inhalation Aerosol to
267 children is similar to that for adults. Children should use XOPENEX HFA Inhalation
268 Aerosol under adult supervision, as instructed by the patient’s physician. (See **Patient’s**
269 **Instructions for Use.**)

270 **Drug Interactions**

271 Other short-acting sympathomimetic aerosol bronchodilators or epinephrine should be
272 used with caution with XOPENEX HFA Inhalation Aerosol. If additional adrenergic
273 drugs are to be administered by any route, they should be used with caution to avoid
274 deleterious cardiovascular effects.

275 **1. Beta-blockers:** Beta-adrenergic receptor blocking agents not only block the
276 pulmonary effect of beta-adrenergic agonists, such as XOPENEX HFA Inhalation
277 Aerosol, but may produce severe bronchospasm in asthmatic patients. Therefore,
278 patients with asthma should not normally be treated with beta-blockers. However,
279 under certain circumstances, e.g., as prophylaxis after myocardial infarction, there
280 may be no acceptable alternatives to the use of beta-adrenergic blocking agents in
281 patients with asthma. In this setting, cardioselective beta-blockers should be
282 considered, although they should be administered with caution.

283 **2. Diuretics:** The ECG changes and/or hypokalemia that may result from the
284 administration of non-potassium-sparing diuretics (such as loop and thiazide
285 diuretics) can be acutely worsened by beta-agonists, especially when the
286 recommended dose of the beta-agonist is exceeded. Although the clinical
287 significance of these effects is not known, caution is advised in the coadministration
288 of beta-agonists with non-potassium-sparing diuretics.

289 **3. Digoxin:** Mean decreases of 16% to 22% in serum digoxin levels were demonstrated
290 after single-dose intravenous and oral administration of racemic albuterol,
291 respectively, to normal volunteers who had received digoxin for 10 days. The clinical
292 significance of these findings for patients with obstructive airway disease who are
293 receiving XOPENEX HFA Inhalation Aerosol and digoxin on a chronic basis is
294 unclear. Nevertheless, it would be prudent to carefully evaluate the serum digoxin
295 levels in patients who are currently receiving digoxin and XOPENEX HFA Inhalation
296 Aerosol.

297 **4. Monoamine Oxidase Inhibitors or Tricyclic Antidepressants:** XOPENEX HFA
298 Inhalation Aerosol should be administered with extreme caution to patients being
299 treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2
300 weeks of discontinuation of such agents, because the action of albuterol on the
301 vascular system may be potentiated.

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

303 No carcinogenesis or impairment of fertility studies have been carried out with
304 levalbuterol tartrate. However, racemic albuterol sulfate has been evaluated for its
305 carcinogenic potential and ability to impair fertility.

306 In a 2-year study in Sprague-Dawley rats, racemic albuterol sulfate caused a significant
307 dose-related increase in the incidence of benign leiomyomas of the mesovarium at, and
308 above, dietary doses of 2 mg/kg/day (approximately 30 times the maximum
309 recommended daily inhalation dose of levalbuterol tartrate for adults on a mg/m² basis
310 and approximately 15 times the maximum recommended daily inhalation dose of
311 levalbuterol tartrate for children on a mg/m² basis). In another study, this effect was
312 blocked by the coadministration of propranolol, a nonselective beta-adrenergic
313 antagonist. In an 18-month study in CD-1 mice, racemic albuterol sulfate showed no
314 evidence of tumorigenicity at dietary doses up to 500 mg/kg/day (approximately 3800
315 times the maximum recommended daily inhalation dose of levalbuterol tartrate for adults
316 on a mg/m² basis and approximately 1800 times the maximum recommended daily
317 inhalation dose of levalbuterol tartrate for children on a mg/m² basis). In a 22-month
318 study in the Golden hamster, racemic albuterol sulfate showed no evidence of
319 tumorigenicity at dietary doses up to 50 mg/kg/day (approximately 500 times the
320 maximum recommended daily inhalation dose of levalbuterol tartrate for adults on a
321 mg/m² basis and approximately 240 times the maximum recommended daily inhalation
322 dose of levalbuterol tartrate for children on a mg/m² basis).

323 Levalbuterol HCl was not mutagenic in the Ames test or the CHO/HPRT Mammalian
324 Forward Gene Mutation Assay. Levalbuterol HCl was not clastogenic in the in vivo
325 micronucleus test in mouse bone marrow. Racemic albuterol sulfate was negative in an
326 in vitro chromosomal aberration assay in CHO cell cultures.

327 Reproduction studies in rats using racemic albuterol sulfate demonstrated no evidence of
328 impaired fertility at oral doses up to 50 mg/kg/day (approximately 750 times the
329 maximum recommended daily inhalation dose of levalbuterol tartrate for adults on a
330 mg/m² basis).

331 **Teratogenic Effects - Pregnancy Category C**

332 A reproduction study in New Zealand White rabbits demonstrated that levalbuterol HCl
333 was not teratogenic when administered orally at doses up to 25 mg/kg/day
334 (approximately 750 times the maximum recommended daily inhalation dose of
335 levalbuterol tartrate for adults on a mg/m² basis).

336 However, racemic albuterol sulfate has been shown to be teratogenic in mice and rabbits.
337 A study in CD-1 mice given racemic albuterol sulfate subcutaneously showed cleft palate
338 formation in 5 of 111 (4.5%) fetuses at 0.25 mg/kg/day (approximately 2 times the
339 maximum recommended daily inhalation dose of levalbuterol tartrate for adults on a
340 mg/m² basis) and in 10 of 108 (9.3%) fetuses at 2.5 mg/kg/day (approximately 20 times
341 the maximum recommended daily inhalation dose of levalbuterol tartrate for adults on a

342 mg/m² basis). The drug did not induce cleft palate formation when administered
343 subcutaneously at a dose of 0.025 mg/kg/day (less than the maximum recommended
344 daily inhalation dose of levalbuterol tartrate for adults on a mg/m² basis). Cleft palate
345 also occurred in 22 of 72 (30.5%) fetuses from females treated subcutaneously with
346 2.5 mg/kg/day of isoproterenol (positive control).

347 A reproduction study in Stride Dutch rabbits revealed cranioschisis in 7 of 19 (37%)
348 fetuses when racemic albuterol sulfate was administered orally at a dose of 50 mg/kg/day
349 (approximately 1500 times the maximum recommended daily inhalation dose of
350 levalbuterol tartrate for adults on a mg/m² basis).

351 A study in which pregnant rats were dosed with radiolabeled racemic albuterol sulfate
352 demonstrated that drug-related material is transferred from the maternal circulation to the
353 fetus.

354 There are no adequate and well-controlled studies of XOPENEX HFA Inhalation Aerosol
355 in pregnant women. Because animal reproduction studies are not always predictive of
356 human response, XOPENEX HFA Inhalation Aerosol should be used during pregnancy
357 only if the potential benefit justifies the potential risk to the fetus.

358 During marketing experience of racemic albuterol, various congenital anomalies,
359 including cleft palate and limb defects, have been rarely reported in the offspring of
360 patients being treated with racemic albuterol. Some of the mothers were taking multiple
361 medications during their pregnancies. No consistent pattern of defects can be discerned,
362 and a relationship between racemic albuterol use and congenital anomalies has not been
363 established.

364 **Use in Labor and Delivery**

365 Because of the potential for beta-adrenergic agonists to interfere with uterine
366 contractility, the use of XOPENEX HFA Inhalation Aerosol for the treatment of
367 bronchospasm during labor should be restricted to those patients in whom the benefits
368 clearly outweigh the risk.

369 **Tocolysis**

370 XOPENEX HFA Inhalation Aerosol has not been approved for the management of
371 preterm labor. The benefit:risk ratio when levalbuterol tartrate is administered for
372 tocolysis has not been established. Serious adverse reactions, including maternal
373 pulmonary edema, have been reported during or following treatment of premature labor
374 with beta₂-agonists, including racemic albuterol.

375 **Nursing Mothers**

376 Plasma concentrations of levalbuterol after inhalation of therapeutic doses are very low in
377 humans. It is not known whether levalbuterol is excreted in human milk.

378 Because of the potential for tumorigenicity shown for racemic albuterol in animal studies
379 and the lack of experience with the use of XOPENEX HFA Inhalation Aerosol by
380 nursing mothers, a decision should be made whether to discontinue nursing or to
381 discontinue the drug, taking into account the importance of the drug to the mother.
382 Caution should be exercised when XOPENEX HFA Inhalation Aerosol is administered to
383 a nursing woman.

384 **Pediatrics**

385 The safety and efficacy of XOPENEX HFA Inhalation Aerosol have been established in
386 pediatric patients 4 years of age and older in an adequate and well-controlled clinical trial
387 (see **Clinical Trials**). Use of XOPENEX HFA Inhalation Aerosol in children is also
388 supported by evidence from adequate and well-controlled studies of XOPENEX HFA
389 Inhalation Aerosol in adults, considering that the pathophysiology, systemic exposure of
390 the drug, and clinical profile in pediatric and adult patients are substantially similar.
391 Safety and effectiveness of XOPENEX HFA Inhalation Aerosol in pediatric patients
392 below the age of 4 years have not been established.

393 **Geriatrics**

394 Clinical studies of XOPENEX HFA Inhalation Aerosol did not include sufficient
395 numbers of subjects aged 65 and older to determine whether they respond differently
396 from younger subjects. Other reported clinical experience has not identified differences
397 in responses between the elderly and younger patients. In general, dose selection for an
398 elderly patient should be cautious, usually starting at the low end of the dosing range,
399 reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of
400 concomitant diseases or other drug therapy.

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

405 **ADVERSE REACTIONS**

406 Adverse event information concerning XOPENEX HFA (levalbuterol tartrate) Inhalation
407 Aerosol in adults and adolescents is derived from two 8-week, multicenter, randomized,
408 double-blind, active- and placebo-controlled trials in 748 adult and adolescent patients
409 with asthma that compared XOPENEX HFA Inhalation Aerosol, a marketed albuterol
410 HFA inhaler, and an HFA-134a placebo inhaler. Table 2 lists the incidence of all adverse
411 events (whether considered by the investigator to be related or unrelated to drug) from
412 these trials that occurred at a rate of 2% or greater in the group treated with XOPENEX
413 HFA Inhalation Aerosol and more frequently than in the HFA-134a placebo inhaler
414 group.

415 **Table 2: Adverse Event Incidence (% of Patients) in Two 8-Week Clinical**
 416 **Trials in Adults and Adolescents \geq 12 Years of Age***

Body System	XOPENEX HFA Inhalation Aerosol	Racemic Albuterol HFA	Placebo
Preferred Term	90 mcg (n=403)	180 mcg (n=179)	(n=166)
Body as a Whole			
Pain	4.0	3.4	3.6
Central Nervous System			
Dizziness	2.7	0.6	1.8
Respiratory System			
Asthma	9.4	7.3	6.0
Pharyngitis	7.9	2.2	2.4
Rhinitis	7.4	2.2	3.0

417 * This table includes all adverse events (whether considered by the investigator to be
 418 related or unrelated to drug) from these trials that occurred at a rate of 2% or greater in
 419 the group treated with XOPENEX HFA Inhalation Aerosol and more frequently than in
 420 the HFA-134a placebo inhaler group.

421
 422 Adverse events reported by less than 2% and at least 2 or more of the adolescent and
 423 adult patients receiving XOPENEX HFA Inhalation Aerosol and by a greater proportion
 424 than receiving HFA-134a placebo inhaler include cyst, flu syndrome, viral infection,
 425 constipation, gastroenteritis, myalgia, hypertension, epistaxis, lung disorder, acne, herpes
 426 simplex, conjunctivitis, ear pain, dysmenorrhea, hematuria, and vaginal moniliasis.
 427 There were no significant laboratory abnormalities observed in these studies.

428 Adverse event information concerning XOPENEX HFA Inhalation Aerosol in children is
 429 derived from a 4-week, randomized, double-blind trial of XOPENEX HFA Inhalation
 430 Aerosol, a marketed albuterol HFA inhaler, and an HFA-134a placebo inhaler in 150
 431 children aged 4 to 11 years with asthma. Table 3 lists the adverse events reported for
 432 XOPENEX HFA Inhalation Aerosol in children at a rate of 2% or greater and more
 433 frequently than for placebo.

434
435

Table 3: Adverse Event Incidence (% of Patients) in a 4-Week Trial in Children Aged 4-11 Years*

Body System Preferred Term	XOPENEX HFA Inhalation Aerosol 90 mcg (n=76)	Racemic Albuterol HFA 180 mcg (n=39)	Placebo (n=35)
Body as a Whole			
Accidental injury	9.2	10.3	5.7
Digestive System			
Vomiting	10.5	7.7	5.7
Respiratory System			
Bronchitis	2.6	0	0
Pharyngitis	6.6	12.8	5.7

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* This table includes all adverse events (whether considered by the investigator to be related or unrelated to drug) from the trial that occurred at a rate of 2% or greater in the group treated with XOPENEX HFA Inhalation Aerosol and more frequently than in the HFA-134a placebo inhaler group.

440
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442

The incidence of systemic beta-adrenergic adverse effects (e.g., tremor, nervousness) was low and comparable across all treatment groups, including placebo.

443

Postmarketing

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451

In addition to the adverse events reported in clinical trials, the following adverse events have been observed in postapproval use of levalbuterol inhalation solution. These events have been chosen for inclusion due to their seriousness, their frequency of reporting, or their likely beta-mediated mechanism: angioedema, anaphylaxis, arrhythmias (including atrial fibrillation, supraventricular tachycardia, extrasystoles), asthma, chest pain, cough increased, dyspnea, nausea, nervousness, rash, tachycardia, tremor, urticaria. Because these events have been reported spontaneously from a population of unknown size, estimates of frequency cannot be made.

452
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454

In addition, XOPENEX HFA Inhalation Aerosol, like other sympathomimetic agents, can cause adverse reactions such as hypertension, angina, vertigo, central nervous system stimulation, sleeplessness, headache, and drying or irritation of the oropharynx.

455

OVERDOSAGE

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The expected symptoms with overdosage are those of excessive beta-adrenergic receptor stimulation and/or occurrence or exaggeration of any of the symptoms listed under ADVERSE REACTIONS, e.g., seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/minute, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and sleeplessness. Hypokalemia also may occur. As with all sympathomimetic medications, cardiac arrest

462 and even death may be associated with the abuse of XOPENEX HFA (levalbuterol
463 tartrate) Inhalation Aerosol. Treatment consists of discontinuation of XOPENEX HFA
464 Inhalation Aerosol together with appropriate symptomatic therapy. The judicious use of
465 a cardioselective beta-receptor blocker may be considered, bearing in mind that such
466 medication can produce bronchospasm. There is insufficient evidence to determine if
467 dialysis is beneficial for overdosage of XOPENEX HFA Inhalation Aerosol.

468 Following intravenous administration in mice, the median lethal levalbuterol HCl dose
469 was approximately 66 mg/kg (approximately 500 times the maximum recommended
470 daily inhalation dose of levalbuterol tartrate for adults on a mg/m² basis and
471 approximately 230 times the maximum recommended daily inhalation dose of
472 levalbuterol tartrate for pediatric patients on a mg/m² basis). Following intravenous
473 administration in rats, the median lethal levalbuterol HCl dose was approximately
474 60 mg/kg (approximately 900 times the maximum recommended daily inhalation dose of
475 levalbuterol tartrate for adults on a mg/m² basis and approximately 430 times the
476 maximum recommended daily inhalation dose of levalbuterol tartrate for children on a
477 mg/m² basis). The inhalation median lethal dose has not been determined in animals. In
478 dogs, inhaled doses of levalbuterol HCl up to 2.73 mg/kg (approximately 140 times the
479 maximum recommended daily inhalation dose of levalbuterol tartrate for adults on a
480 mg/m² basis and approximately 65 times the maximum recommended daily inhalation
481 dose of levalbuterol tartrate for children on a mg/m² basis) were tolerated without animal
482 deaths.

483 **DOSAGE AND ADMINISTRATION**

484 **Adult and Pediatric Asthma:** For treatment of acute episodes of bronchospasm or
485 prevention of asthmatic symptoms, the usual dosage of XOPENEX HFA (levalbuterol
486 tartrate) Inhalation Aerosol for adults and children 4 years of age and older is
487 2 inhalations (90 mcg) repeated every 4 to 6 hours; in some patients, 1 inhalation every
488 4 hours may be sufficient. More frequent administration or a larger number of
489 inhalations is not routinely recommended. It is recommended to prime the inhaler before
490 using for the first time and in cases where the inhaler has not been used for more than
491 3 days by releasing 4 test sprays into the air, away from the face.

492 If a previously effective dosage regimen fails to provide the usual response, this may be a
493 marker of destabilization of asthma and requires reevaluation of the patient and the
494 treatment regimen, giving special consideration to the possible need for anti-
495 inflammatory treatment, e.g., corticosteroids.

496 **Cleaning:** To maintain proper use of this product, it is critical that the actuator be
497 washed and dried thoroughly at least once a week. The inhaler may cease to deliver
498 medication if not properly cleaned and dried thoroughly. See **Information for Patients**.
499 Keeping the plastic actuator clean is very important to prevent medication build-up and
500 blockage. If the actuator becomes blocked with drug, washing the actuator will remove
501 the blockage.

502 **HOW SUPPLIED**

503 XOPENEX HFA (levalbuterol tartrate) Inhalation Aerosol is supplied as a pressurized
504 aluminum canister in a box (NDC 63402-510-01). The canister is labeled with a net
505 weight of 15 g and contains 200 metered actuations (or inhalations). Each canister is
506 supplied with a blue plastic actuator (or mouthpiece), a red mouthpiece cap, and patient's
507 instructions.

508 **SHAKE WELL BEFORE USING.** Store between 20° and 25°C (68° and 77°F; see USP
509 controlled room temperature). Protect from freezing temperatures and direct sunlight.
510 Store inhaler with the actuator (or mouthpiece) down. Avoid spraying in eyes. Contents
511 under pressure. Do not puncture or incinerate. Exposure to temperatures above 120°F
512 may cause bursting. Keep out of reach of children.

513 The blue actuator supplied with XOPENEX HFA Inhalation Aerosol should not be used
514 with any other product canisters. Actuators from other products should not be used with
515 a XOPENEX HFA Inhalation Aerosol canister. The correct amount of medication in
516 each actuation cannot be assured after 200 actuations, even though the canister is not
517 completely empty. The canister should be discarded when 200 actuations have been
518 used.

519 XOPENEX HFA Inhalation Aerosol does not contain chlorofluorocarbons (CFCs) as the
520 propellant.

521 Rx only.

522

523 Manufactured for:

524

525 Sepracor Inc.

526 Marlborough, MA 01752 USA

527

528 By:

529

530 3M Drug Delivery Systems

531 Northridge, CA 91324-3213

532

533 March 2005

534

535 Code XXXXX

536

537 PHARMACIST — DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT.

538

539

PATIENT'S INSTRUCTIONS FOR USE

540 **XOPENEX HFA™ (levalbuterol tartrate) Inhalation Aerosol**

541 **Before using your XOPENEX HFA (levalbuterol tartrate) Inhalation Aerosol, read**
542 **the complete instructions carefully.**

543

ABOUT XOPENEX HFA INHALATION AEROSOL

544 **Use only as directed by a doctor. Children should use XOPENEX HFA Inhalation**
545 **Aerosol under adult supervision, as instructed by the patient's doctor.**

546 **XOPENEX HFA Inhalation Aerosol is a pressurized metered-dose inhaler that**
547 **produces an aerosol for oral inhalation. XOPENEX HFA Inhalation Aerosol does**
548 **not contain chlorofluorocarbons (CFCs).**

549 **The blue actuator (or mouthpiece) supplied with XOPENEX HFA Inhalation**
550 **Aerosol should not be used with any other product canisters. Actuators from other**
551 **products should not be used with a XOPENEX HFA Inhalation Aerosol canister.**

552

HOW TO USE YOUR XOPENEX HFA INHALATION AEROSOL

553

1. SHAKE THE INHALER WELL immediately before each use.

554

555

556

2. REMOVE THE CAP FROM THE ACTUATOR (OR MOUTHPIECE) (see
Figure 1). Inspect the actuator for the presence of foreign objects and make sure
that the canister is seated in the actuator before each use.

557

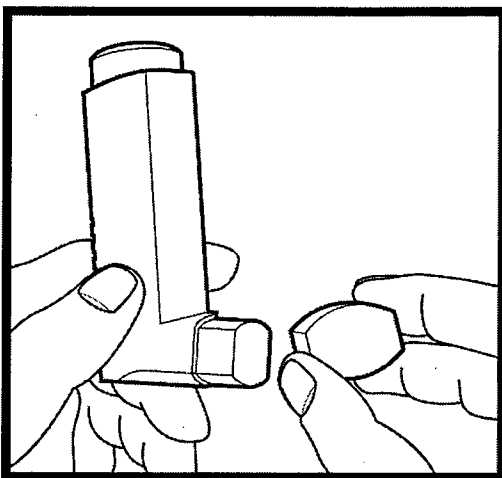


FIGURE 1

558

559

560 **PRIMING:** Priming at specified times is important for the proper delivery of your
561 medication. **SHAKE THE INHALER WELL;** then prime **XOPENEX HFA**
562 **Inhalation Aerosol** by releasing 4 test sprays into the air, away from your face, before
563 using for the first time and when the inhaler has not been used for more than 3 days.

564 **3. BREATHE OUT FULLY THROUGH YOUR MOUTH,** expelling as much air
565 from your lungs as possible. Place the mouthpiece fully into your mouth, holding
566 the inhaler in the mouthpiece-down position (see **Figure 2**) and closing your lips
567 around it.

568

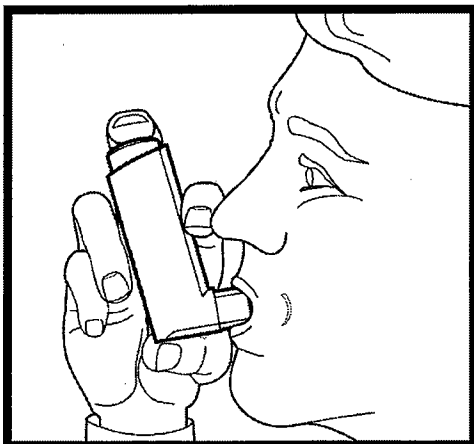


FIGURE 2

569

570

571 **4. WHILE BREATHING IN DEEPLY AND SLOWLY THROUGH YOUR**
572 **MOUTH, FULLY DEPRESS THE TOP OF THE METAL CANISTER** with
573 your middle finger as shown in **Figure 2**. Immediately after the puff is delivered,
574 release your finger from the canister and remove the inhaler from your mouth.

575

5. HOLD YOUR BREATH FOR 10 SECONDS, IF POSSIBLE.

576

577

578

6. If your doctor has prescribed more than a single inhalation/puff, wait 1 minute between inhalations. Then, **SHAKE THE INHALER WELL** and repeat steps 3 through 5.

579

7. REPLACE THE CAP ON THE MOUTHPIECE AFTER EACH USE.

580

581

582

8. CLEAN THE ACTUATOR OR MOUTHPIECE AT LEAST ONCE A WEEK. See **CLEANING YOUR XOPENEX HFA INHALATION AEROSOL** for cleaning instructions.

583

584

585

9. DISCARD THE CANISTER AFTER YOU HAVE USED 200 INHALATIONS. The correct amount of medicine in each inhalation cannot be assured after 200 sprays, even though the canister is not completely empty. Never

586 immerse the canister in water to determine how full the canister is (“float test”).
587 Before you reach 200 sprays, you should consult your doctor to determine
588 whether a refill is needed. Just as you should not take extra doses without
589 consulting your doctor, you also should not stop using XOPENEX HFA
590 Inhalation Aerosol without consulting your doctor.

591 **CLEANING YOUR XOPENEX HFA INHALATION AEROSOL**

592 **KEEPING THE BLUE PLASTIC ACTUATOR (OR MOUTHPIECE) CLEAN**
593 **IS VERY IMPORTANT TO PREVENT MEDICINE BLOCKAGE. THE**
594 **ACTUATOR SHOULD BE WASHED, SHAKEN TO REMOVE EXCESS**
595 **WATER, AND AIR-DRIED THOROUGHLY AT LEAST ONCE A WEEK.**
596 **THE INHALER MAY STOP WORKING IF NOT PROPERLY CLEANED.**

597
598 **ROUTINE CLEANING INSTRUCTIONS:**

599 **Step 1.** To clean the blue plastic actuator (or mouthpiece), remove the canister and red
600 mouthpiece cap.

601 **Step 2.** Wash the actuator through the top and bottom with warm running water for
602 30 seconds at least once a week (see Figure 3).

603 **Do not clean the metal canister or allow the metal canister to become wet. Never**
604 **immerse the metal canister in water.**

605

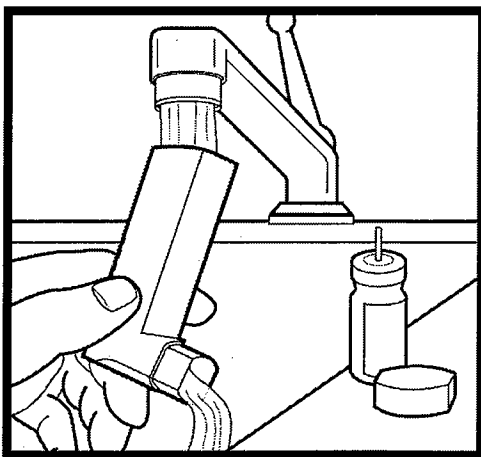


FIGURE 3

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607

608 **Step 3.** To dry, shake off excess water and let the actuator air-dry thoroughly, such as
609 overnight (see Figure 4).

610 **Step 4.** When the actuator is dry, replace the canister and the mouthpiece cap; make sure
611 the canister is fully and firmly inserted into the actuator. Blockage from medicine build-
612 up is more likely to occur if the actuator is not allowed to air-dry thoroughly.

613

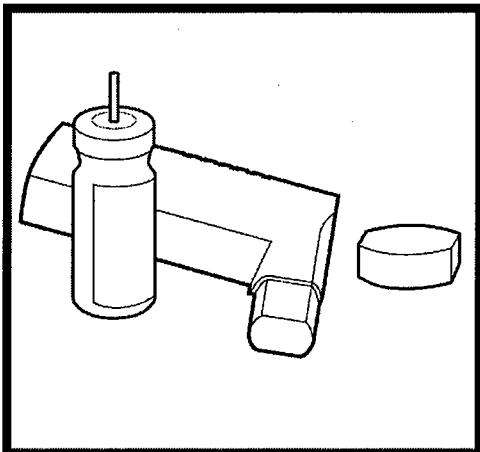


FIGURE 4

614

615

616 **IF YOUR ACTUATOR BECOMES BLOCKED** (little or no medicine coming out of
617 the mouthpiece, see Figure 5), wash your actuator as described in **Steps 1 and 2** and air-
618 dry thoroughly as described in **Step 3**.

619

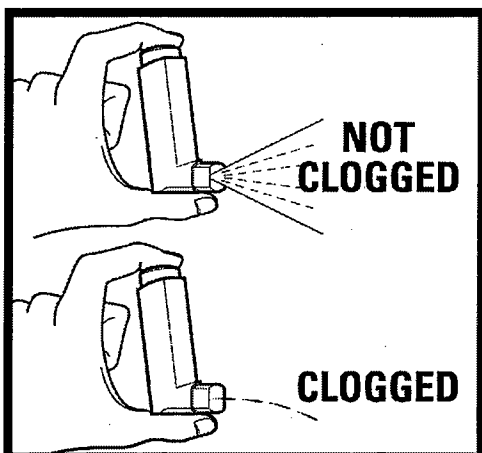


FIGURE 5

620

621

622 **IF YOU NEED TO USE YOUR INHALER BEFORE THE PLASTIC ACTUATOR**
623 **IS COMPLETELY DRY, SHAKE EXCESS WATER** off the actuator, replace the
624 canister, **shake well**, and test-spray twice into the air, away from your face, to remove
625 most of the water remaining in the actuator. Then take your dose as prescribed. **After**

626 **such use, rewash the actuator and air-dry it thoroughly as described in Steps 1**
627 **through 3.**

628 **ADDITIONAL INFORMATION ABOUT XOPENEX HFA**
629 **INHALATION AEROSOL**

630 **DOSAGE:** Use only as directed by your doctor.

631 **WARNINGS:** The action of XOPENEX HFA Inhalation Aerosol should last for 4 to 6
632 hours. XOPENEX HFA Inhalation Aerosol should not be used more frequently than
633 recommended. Do not increase the dose or frequency of doses of XOPENEX HFA
634 Inhalation Aerosol without consulting your physician. If you find that treatment with
635 XOPENEX HFA Inhalation Aerosol becomes less effective for symptomatic relief, your
636 symptoms become worse, and/or you need to use the product more frequently than usual,
637 you should seek medical attention immediately. While you are using XOPENEX HFA
638 Inhalation Aerosol, other inhaled drugs and asthma medication should be taken only as
639 directed by your physician.

640 Common adverse effects include palpitations, chest pain, rapid heart rate, tremor, and
641 nervousness. If you are pregnant or nursing, contact your physician about the use of
642 XOPENEX HFA Inhalation Aerosol. Effective and safe use of XOPENEX HFA
643 Inhalation Aerosol includes an understanding of the way that it should be administered.
644 In general, the technique for administering XOPENEX HFA Inhalation Aerosol to
645 children is similar to that for adults. Children should use XOPENEX HFA Inhalation
646 Aerosol under adult supervision, as instructed by the patient's physician.

647 **Storage:** Store canister between 20° and 25°C (68° and 77°F). Protect from freezing
648 temperatures and direct sunlight. Store inhaler with the actuator (or mouthpiece) down.
649 Contents under pressure. Do not puncture or incinerate. Exposure to temperatures above
650 120°F may cause bursting. Avoid spraying in eyes. Keep out of reach of children.

651 **CFC-Free:** XOPENEX HFA Inhalation Aerosol does not contain chlorofluorocarbons
652 (CFCs). Instead, the inhaler contains a hydrofluoroalkane (HFA-134a) as the propellant.

653
654 **Manufactured for:**

655 Sepracor Inc.
656 Marlborough, MA 01752 USA

657

658 **By:**

659

660 3M Drug Delivery Systems
661 Northridge, CA 91324-3213

662

663 March 2005

664

665 Code XXXX