

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use XOPENEX HFA® Inhalation Aerosol safely and effectively. See full prescribing information for XOPENEX HFA®.

XOPENEX HFA® (levalbuterol tartrate) Inhalation Aerosol

FOR ORAL INHALATION ONLY

Initial U.S. Approval: 1999

INDICATIONS AND USAGE

XOPENEX HFA is a beta₂-adrenergic agonist indicated for:

- Treatment or prevention of bronchospasm in patients 4 years of age and older with reversible obstructive airway disease (1.1)

DOSAGE AND ADMINISTRATION

FOR ORAL INHALATION ONLY (2.2)

- Treatment of bronchospasm or prevention of asthmatic symptoms in adults and children 4 years of age and older: 2 inhalations repeated every 4 to 6 hours; in some patients, 1 inhalation every 4 hours may be sufficient. (2.1).
- Priming information: Prime XOPENEX HFA before using for the first time and when the inhaler has not been used for more than 3 days. To prime XOPENEX HFA, release 4 sprays into the air away from the face. (2.2)
- Cleaning information: At least once a week, wash the actuator with warm water and let it air-dry completely. (2.2)

DOSAGE FORMS AND STRENGTHS

Inhalation Aerosol: Each actuation of Xopenex HFA Inhalation Aerosol delivers 67.8 mcg levalbuterol (equivalent to 51.6 mcg of levalbuterol free base) from the valve and 59 mcg levalbuterol tartrate (equivalent to 45 mcg of levalbuterol free base) from the actuator mouth piece. Supplied in 15 g pressurized canister containing 200 actuations and 8.4 g canister containing 80 actuations. (3)

CONTRAINDICATIONS

- Hypersensitivity to levalbuterol, racemic albuterol or any other component of XOPENEX HFA Inhalation Aerosol. (4)

WARNINGS AND PRECAUTIONS

- Life-threatening paradoxical bronchospasm may occur. Discontinue XOPENEX HFA immediately and treat with alternative therapy. (5.1)
- Need for more doses of XOPENEX HFA than usual may be a sign of deterioration of asthma and requires reevaluation of treatment (5.2)
- XOPENEX HFA is not a substitute for corticosteroids. (5.3)
- Cardiovascular effects may occur. Consider discontinuation of XOPENEX HFA if these effects occur. Use with caution in patients with underlying cardiovascular disorders. (5.4)
- Excessive use may be fatal. Do not exceed recommended dose (5.5)
- Immediate hypersensitivity reactions may occur. Discontinue XOPENEX HFA immediately. (5.6)
- Hypokalemia and changes in blood glucose may occur. (5.7, 5.8)

ADVERSE REACTIONS

Most common adverse reactions (≥2% and >placebo) are accidental injury, bronchitis, dizziness, pain, pharyngitis, rhinitis, and vomiting. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Sunovion Pharmaceuticals Inc. at 1-877-737-7226 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

For customer service, call 1-888-394-7377

For medical information, call 1-800-739-0565

DRUG INTERACTIONS

- Other short-acting sympathomimetic aerosol bronchodilators and adrenergic drugs: May potentiate effect. (7)
- Beta-blockers: May block bronchodilatory effects of beta-agonists and produce severe bronchospasm. Patients with asthma should not normally be treated with beta-blockers. (7.1)
- Diuretics: May worsen electrocardiographic changes or hypokalemia associated with diuretics may worsen. Consider monitoring potassium levels. (7.2)
- Digoxin: May decrease serum digoxin levels. Consider monitoring digoxin levels. (7.3)
- Monoamine oxidase inhibitors (MAOs) or tricyclic antidepressants: May potentiate effect of albuterol on the cardiovascular system. (7.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: July 2012

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*Sections or subsections omitted from the full prescribing information are not listed.

1 **FULL PRESCRIBING INFORMATION**

2 **1 INDICATIONS AND USAGE**

3 **1.1 Bronchospasm**

4

5 XOPENEX HFA is indicated for the treatment or prevention of bronchospasm in adults,
6 adolescents, and children 4 years of age and older with reversible obstructive airway disease.

7 **2 DOSAGE AND ADMINISTRATION**

8 **2.1 Recommended Dosages**

9

10 For treatment of acute episodes of bronchospasm or prevention of asthmatic symptoms, the usual
11 dosage of XOPENEX HFA for adults and children 4 years of age and older is 2 inhalations (90
12 mcg) repeated every 4 to 6 hours; in some patients, 1 inhalation every 4 hours may be sufficient.
13 More frequent administration or a larger number of inhalations is not routinely recommended.

14

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

19

20

21 **2.2 Administration Information:**

22

23 **FOR ORAL INHALATION ONLY**

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25 **Priming:** It is recommended to prime the inhaler before using for the first time and in cases
26 where the inhaler has not been used for more than 3 days by releasing 4 test sprays into the air,
27 away from the face.

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29

30 **Cleaning:** To maintain proper use of this product, it is critical that the actuator be washed with
31 warm water and air-dried thoroughly at least once a week. The inhaler may cease to deliver
32 medication if not properly cleaned and dried thoroughly. Keeping the plastic actuator clean is
33 very important to prevent medication build-up and blockage. If the actuator becomes blocked
34 with drug, washing the actuator will remove the blockage.

35 **3 DOSAGE FORMS AND STRENGTHS**

36

37 XOPENEX HFA is supplied as a pressurized aluminum canister in a box (NDC 63402-510-01 or
38 NDC 63402-510-04). The canister is labeled with a net weight of 15 g or 8.4 g and contains 200
39 metered actuations or 80 metered actuations (or inhalations), respectively. Each canister is
40 supplied with a blue plastic actuator (or mouthpiece), a red mouthpiece cap, and patient's
41 instructions. After priming, each actuation of the inhaler delivers 67.8 mcg levalbuterol tartrate
42 (equivalent to 51.6 mcg of levalbuterol free base) from the valve and 59 mcg levalbuterol tartrate
43 (equivalent to 45 mcg of levalbuterol free base) from the actuator mouth piece.

44

45 **4 CONTRAINDICATIONS**

46

47 XOPENEX HFA is contraindicated in patients with a history of hypersensitivity to levalbuterol,
48 racemic albuterol, or any other component of XOPENEX HFA. Reactions have included
49 urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal edema.

50

51 **5 WARNINGS AND PRECAUTIONS**

52 **5.1 Paradoxical Bronchospasm**

53

54 XOPENEX HFA can produce paradoxical bronchospasm, which may be life-threatening. If
55 paradoxical bronchospasm occurs, XOPENEX HFA should be discontinued immediately and
56 alternative therapy instituted. It should be recognized that paradoxical bronchospasm, when
57 associated with inhaled formulations, frequently occurs with the first use of a new canister.

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59 **5.2 Deterioration of Asthma**

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61 Asthma may deteriorate acutely over a period of hours or chronically over several days or longer.
62 If the patient needs more doses of XOPENEX HFA than usual, this may be a marker of
63 destabilization of asthma and requires reevaluation of the patient and treatment regimen, giving
64 special consideration to the possible need for anti-inflammatory treatment, e.g., corticosteroids.

65

66 **5.3 Use of Anti-Inflammatory Agents**

67

68 The use of a beta-adrenergic agonist alone may not be adequate to control asthma in many
69 patients. Early consideration should be given to adding anti-inflammatory agents, e.g.,
70 corticosteroids, to the therapeutic regimen.

71

72 **5.4 Cardiovascular Effects**

73

74 XOPENEX HFA, like other beta-adrenergic agonists, can produce clinically significant
75 cardiovascular effects in some patients, as measured by heart rate, blood pressure, and
76 symptoms. Although such effects are uncommon after administration of XOPENEX HFA at
77 recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-
78 agonists have been reported to produce electrocardiogram (ECG) changes, such as flattening of
79 the T wave, prolongation of the QTc interval, and ST segment depression. The clinical
80 significance of these findings is unknown. Therefore, XOPENEX HFA, like all
81 sympathomimetic amines, should be used with caution in patients with cardiovascular disorders,
82 especially coronary insufficiency, cardiac arrhythmias, and hypertension.

83

84 **5.5 Do Not Exceed Recommended Dose**

85 Fatalities have been reported in association with excessive use of inhaled sympathomimetic
86 drugs in patients with asthma. The exact cause of death is unknown, but cardiac arrest following
87 an unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is
88 suspected.

89

90 **5.6 Immediate Hypersensitivity Reactions**

91 Immediate hypersensitivity reactions may occur after administration of racemic albuterol, as
92 demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, anaphylaxis, and
93 oropharyngeal edema. The potential for hypersensitivity must be considered in the clinical
94 evaluation of patients who experience immediate hypersensitivity reactions while receiving
95 XOPENEX HFA

96 97 **5.7 Coexisting Conditions**

98
99 XOPENEX HFA, like all sympathomimetic amines, should be used with caution in patients with
100 cardiovascular disorders, especially coronary insufficiency, hypertension, and cardiac
101 arrhythmias; in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus; and in
102 patients who are unusually responsive to sympathomimetic amines. Clinically significant
103 changes in systolic and diastolic blood pressure have been seen in individual patients and could
104 be expected to occur in some patients after the use of any beta-adrenergic bronchodilator.

105
106 Large doses of intravenous racemic albuterol have been reported to aggravate preexisting
107 diabetes mellitus and ketoacidosis.

108 109 **5.8 Hypokalemia**

110
111 As with other beta-adrenergic agonist medications, XOPENEX HFA may produce significant
112 hypokalemia in some patients, possibly through intracellular shunting, which has the potential to
113 produce adverse cardiovascular effects. The decrease is usually transient, not requiring
114 supplementation.

115 **6 ADVERSE REACTIONS**

116
117 Use of XOPENEX HFA may be associated with the following:

- 118 • Paradoxical bronchospasm [see *Warnings and Precautions (5.1)*]
- 119 • Cardiovascular effects [see *Warnings and Precautions (5.4)*]
- 120 • Immediate hypersensitivity reactions [see *Warnings and Precautions (5.6)*]
- 121 • Hypokalemia [see *Warnings and Precautions (5.8)*]

122 123 124 **6.1 Clinical Trials Experience**

125 Because clinical trials are conducted under widely varying conditions, adverse reaction rates
126 observed in the clinical trials of the drug cannot be directly compared with rates in the clinical
127 trials of another drug and may not reflect the rates observed in practice.

128
129 **Adult and Adolescents 12 Years of Age and Older:** Adverse reaction information concerning
130 XOPENEX HFA in adults and adolescents is derived from two 8-week, multicenter, randomized,
131 double-blind, active- and placebo-controlled trials in 748 adult and adolescent patients with
132 asthma that compared XOPENEX HFA, a marketed albuterol HFA inhaler, and an HFA-134a
133 placebo inhaler. Table 1 lists the incidence of all adverse reactions (whether considered by the
134 investigator to be related or unrelated to drug) from these trials that occurred at a rate of 2% or
135 greater in the group treated with XOPENEX HFA and more frequently than in the HFA-134a
136 placebo inhaler group.

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Table 1: Adverse Reaction Incidence (% of Patients) in Two 8-Week Clinical Trials in Adults and Adolescents ≥ 12 Years of Age*

Body System	Preferred Term	XOPENEX HFA 90 mcg (n=403)	Racemic Albuterol HFA 180 mcg (n=179)	Placebo (n=166)
Body as a Whole	Pain	4	3	4
Central Nervous System	Dizziness	3	1	2
Respiratory System	Asthma	9	7	6
	Pharyngitis	8	2	2
	Rhinitis	7	2	3
*This table includes all adverse reactions (whether considered by the investigator to be related or unrelated to drug) from these trials that occurred at a rate of 2% or greater in the group treated with XOPENEX HFA and more frequently than in the HFA-134a placebo inhaler group.				

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

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Pediatric Patients 4 to 11 Years of Age: Adverse reaction information concerning XOPENEX HFA in children is derived from a 4-week, randomized, double-blind trial of XOPENEX HFA, a marketed albuterol HFA inhaler, and an HFA-134a placebo inhaler in 150 children aged 4 to 11 years with asthma. Table 2 lists the adverse reactions reported for XOPENEX HFA in children at a rate of 2% or greater and more frequently than for placebo.

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156
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Table 2: Adverse Reaction Incidence (% of Patients) in a 4-Week Clinical Trials in Children 4-11 Years*

Body System	Preferred Term	XOPENEX HFA 90 mcg (n=76)	Racemic Albuterol HFA 180 mcg (n=39)	Placebo (n=35)
Body as a Whole	Accidental injury	9	10	6
Digestive System	Vomiting	11	8	6
Respiratory System	Bronchitis	3	0	0
	Pharyngitis	7	13	6
* This table includes all adverse reactions (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 and more frequently than in the HFA-134a placebo inhaler group.				

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

161

162 **6.2 Post-marketing Experience**

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164 In addition to the adverse reactions reported in clinical trials, the following adverse reactions
165 have been observed in postapproval use of levalbuterol inhalation solution. Because these
166 reactions are reported voluntarily from a population of uncertain size, it is not always possible to
167 reliably estimate their frequency or establish a causal relationship to drug exposure. These events
168 have been chosen for inclusion due to their seriousness, their frequency of reporting, or their
169 likely beta-mediated mechanism: angioedema, anaphylaxis, arrhythmias (including atrial
170 fibrillation, supraventricular tachycardia, extrasystoles), asthma, chest pain, cough increased,
171 dyspnea, metabolic acidosis, nausea, nervousness, rash, tachycardia, tremor, urticaria.

172

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

176 **7 DRUG INTERACTIONS**

177

178 Other short-acting sympathomimetic aerosol bronchodilators or epinephrine should not be used
179 concomitantly with XOPENEX HFA. If additional adrenergic drugs are to be administered by
180 any route, they should be used with caution to avoid deleterious cardiovascular effects.

181

182 **7.1 Beta-blockers**

183

184 Beta-blockers: Beta-adrenergic receptor blocking agents not only block the pulmonary effect of
185 beta-adrenergic agonists, such as XOPENEX HFA, but may produce severe bronchospasm in
186 asthmatic patients. Therefore, patients with asthma should not normally be treated with beta-
187 blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction,
188 there may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients
189 with asthma. In this setting, cardioselective beta-blockers should be considered, although they
190 should be administered with caution.

191

192 **7.2 Diuretics**

193

194 The ECG changes or hypokalemia that may result from the administration of non-potassium-
195 sparing diuretics (such as loop and thiazide diuretics) can be acutely worsened by beta-agonists,
196 especially when the recommended dose of the beta-agonist is exceeded. Although the clinical
197 significance of these effects is not known, caution is advised in the coadministration of beta-
198 agonists with non-potassium-sparing diuretics. Consider monitoring potassium levels.

199

200 **7.3 Digoxin**

201

202 Mean decreases of 16% to 22% in serum digoxin levels were demonstrated after single-dose
203 intravenous and oral administration of racemic albuterol, respectively, to normal volunteers who
204 had received digoxin for 10 days. The clinical significance of these findings for patients with
205 obstructive airway disease who are receiving XOPENEX HFA and digoxin on a chronic basis is
206 unclear. Nevertheless, it would be prudent to carefully evaluate the serum digoxin levels in
207 patients who are currently receiving digoxin and XOPENEX HFA.

208

209 **7.4 Monamine Oxidase Inhibitors or Tricyclic Antidepressants**

210

211 XOPENEX HFA should be administered with extreme caution to patients being treated with
212 monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation
213 of such agents, because the action of albuterol on the vascular system may be potentiated.
214 Consider alternative therapy in patients taking MAO inhibitors or tricyclic antidepressants.

215

216 **8 USE IN SPECIFIC POPULATIONS**

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218 **8.1 Pregnancy**

219

220 **Pregnancy Category C**

221 There are no adequate and well-controlled studies of XOPENEX HFA in pregnant women.
222 Because animal reproduction studies are not always predictive of human response, XOPENEX
223 HFA should be used during pregnancy only if the potential benefit justifies the potential risk to
224 the fetus.

225

226 Rare instances of congenital anomalies, including cleft palate and limb defects, were reported in
227 newborns of women treated with racemic albuterol in which the levalbuterol isomer (active drug
228 substance of XOPENEX HFA) is present. However, since multiple medications were taken
229 during their pregnancies and there was no consistent pattern of anomalies, it was not possible to
230 establish a relationship between racemic albuterol use and the occurrence of these congenital
231 anomalies.

232

233 In animal studies, oral administration of levalbuterol HCl to pregnant New Zealand White rabbits
234 found no evidence of teratogenicity at doses up to 25 mg/kg/day (approximately 750 times the
235 maximum recommended daily inhalation dose of levalbuterol tartrate for adults on a mg/m²
236 basis).

237

238 However, other studies demonstrated that racemic albuterol sulfate was teratogenic in mice and
239 rabbits at doses slightly higher than the human therapeutic range. Pregnant mice subcutaneously
240 administered racemic albuterol sulfate had dose-related fetal incidences of cleft palate at doses 2-
241 fold greater or more than the maximum recommended daily inhalation (MRDI) dose of
242 levalbuterol tartrate for adults on a mg/m² basis. No teratogenic findings occurred at a dose
243 typically less than the human therapeutic range (0.2 times the MRDI dose). Oral administration
244 of racemic albuterol sulfate to pregnant rabbits resulted in an increased incidence of cranioschisis
245 in fetuses (approximately 1500 times the MRDI dose of levalbuterol tartrate for adults on a
246 mg/m² basis). Refer to section 13.2 for additional details.

247

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

250

251 **8.2 Labor and Delivery**

252

253 Because of the potential for beta-adrenergic agonists to interfere with uterine contractility, the
254 use of XOPENEX HFA for the treatment of bronchospasm during labor should be restricted to
255 those patients in whom the benefits clearly outweigh the risk.

256

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

261

262 **8.3 Nursing Mothers**

263

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

266

267 Because of the potential for tumorigenicity shown for racemic albuterol in animal studies and the
268 lack of experience with the use of XOPENEX HFA by nursing mothers, a decision should be
269 made whether to discontinue nursing or to discontinue the drug, taking into account the
270 importance of the drug to the mother. Caution should be exercised when XOPENEX HFA is
271 administered to a nursing woman.

272

273 **8.4 Pediatric Use**

274

275 The safety and efficacy of XOPENEX HFA have been established in pediatric patients 4 years of
276 age and older in an adequate and well-controlled clinical trial (see **Clinical Trials**). Use of
277 XOPENEX HFA in children is also supported by evidence from adequate and well-controlled
278 studies of XOPENEX HFA in adults, considering that the pathophysiology, systemic exposure of
279 the drug, and clinical profile in pediatric and adult patients are substantially similar. Safety and
280 effectiveness of XOPENEX HFA in pediatric patients below the age of 4 years have not been
281 established.

282

283

8.5 Geriatric Use

284

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

291

8.6 Renal Impairment

292

293 Albuterol is known to be substantially excreted by the kidney, and the risk of toxic reactions may
294 be greater in patients with impaired renal function. Because elderly patients are more likely to
295 have decreased renal function, care should be taken in dose selection, and it may be useful to
296 monitor renal function.
297

10 OVERDOSAGE

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299

300 The expected symptoms with overdosage are those of excessive beta-adrenergic receptor
301 stimulation and/or occurrence or exaggeration of any of the symptoms listed under ADVERSE
302 REACTIONS, e.g., seizures, angina, hypertension or hypotension, tachycardia with rates up to
303 200 beats/minute, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, nausea,
304 dizziness, fatigue, malaise, and sleeplessness. Hypokalemia also may occur. As with all
305 sympathomimetic medications, cardiac arrest and even death may be associated with the abuse of
306 XOPENEX HFA. Treatment consists of discontinuation of XOPENEX HFA together with
307 appropriate symptomatic therapy. The judicious use of a cardioselective beta-receptor blocker
308 may be considered, bearing in mind that such medication can produce bronchospasm. There is
309 insufficient evidence to determine if dialysis is beneficial for overdosage of XOPENEX HFA.
310

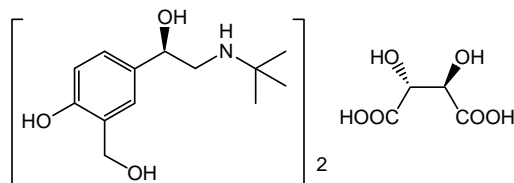
11 DESCRIPTION

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312

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

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319

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321 The molecular weight of levalbuterol tartrate is 628.71, and its empirical formula is
322 (C₁₃H₂₁NO₃)₂ · C₄H₆O₆. It is a white to light-yellow solid, freely soluble in water and very
323 slightly soluble in ethanol.
324

324

325 Levalbuterol tartrate is the generic name for (R)-albuterol tartrate in the United States.
326 XOPENEX HFA is a pressurized metered-dose aerosol inhaler (MDI), which produces an
327 aerosol for oral inhalation. It contains a suspension of micronized levalbuterol tartrate,
328 propellant HFA-134a (1,1,1,2-tetrafluoroethane), Dehydrated Alcohol USP, and Oleic Acid NF.
329

330 The inhaler should be primed by releasing 4 sprays into the air, away from the face, before using
331 it for the first time and when the inhaler has not been used for more than 3 days. After priming
332 with 4 actuations, each actuation delivers 59 mcg of levalbuterol tartrate (equivalent to 45 mcg of
333 levalbuterol free base) from the actuator (or mouthpiece). Each 15 g canister provides 200
334 actuations (or inhalations) and each 8.4 g canister provides 80 actuations (or inhalations).

335 12 CLINICAL PHARMACOLOGY

336 12.1 Mechanism of Action

337
338 Activation of beta₂-adrenergic receptors on airway smooth muscle leads to the activation of
339 adenylate cyclase and to an increase in the intracellular concentration of cyclic-3', 5'-adenosine
340 monophosphate (cyclic AMP). The increase in cyclic AMP is associated with the activation of
341 protein kinase A, which in turn, inhibits the phosphorylation of myosin and lowers intracellular
342 ionic calcium concentrations, resulting in muscle relaxation. Levalbuterol relaxes the smooth
343 muscles of all airways, from the trachea to the terminal bronchioles. Increased cyclic AMP
344 concentrations are also associated with the inhibition of the release of mediators from mast cells
345 in the airways. Levalbuterol acts as a functional antagonist to relax the airway irrespective of the
346 spasmogen involved, thus protecting against all bronchoconstrictor challenges. While it is
347 recognized that beta₂-adrenergic receptors are the predominant receptors on bronchial smooth
348 muscle, data indicate that there are beta-receptors in the human heart, 10% to 50% of which are
349 beta₂-adrenergic receptors. The precise function of these receptors has not been established (see
350 **WARNINGS**). However, all beta-adrenergic agonist drugs can produce a significant
351 cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms,
352 and/or electrocardiographic changes.

353 12.2 Pharmacokinetics

354 A population pharmacokinetic model was developed using plasma concentrations of (R)-
355 albuterol obtained from 632 asthmatic patients aged 4 to 81 years in three large trials. For
356 adolescent and adult patients 12 years and older, following 90 mcg dose of XOPENEX HFA,
357 yielded mean peak plasma concentrations (C_{max}) and systemic exposure (AUC₀₋₆) of
358 approximately 199 pg/mL and 695 pg•h/mL, respectively compared to approximately 238 pg/mL
359 and 798 pg•h/mL, respectively following 180 mcg dose of Racemic Albuterol HFA metered-
360 dose inhaler. For pediatric patients from 4 to 11 years of age, following 90 mcg dose of
361 XOPENEX HFA, yielded C_{max} and AUC₀₋₆ of approximately 163 pg/mL and 579 pg•h/mL,
362 respectively compared to approximately 238 pg/mL and 828 pg•h/mL, respectively following
363 180 mcg dose of Racemic Albuterol HFA metered-dose inhaler.

364
365 These pharmacokinetic data indicate that mean exposure to (R)-albuterol was 13% to 16% less in
366 adult and 30% to 32% less in pediatric patients given XOPENEX HFA as compared to those
367 given a comparable dose of racemic albuterol. When compared to adult patients, pediatric
368 patients given 90 mcg of levalbuterol have a 17% lower mean exposure to (R)-albuterol.

370 *Metabolism and Elimination*

371

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

380
381 The primary route of elimination of albuterol enantiomers is through renal excretion (80% to
382 100%) of either the parent compound or the primary metabolite. Less than 20% of the drug is
383 detected in the feces. Following intravenous administration of racemic albuterol, between 25%
384 and 46% of the (R)-albuterol fraction of the dose was excreted as unchanged (R)-albuterol in the
385 urine.

386 387 *Special Populations*

388 *Hepatic Impairment*

389
390 The effect of hepatic impairment on the pharmacokinetics of XOPENEX HFA has not been
391 evaluated.

392 *Renal Impairment*

393
394 The effect of renal impairment on the pharmacokinetics of racemic albuterol was evaluated in 5
395 subjects with creatinine clearance of 7 to 53 mL/min, and the results were compared with those
396 from healthy volunteers. Renal disease had no effect on the half-life, but there was a 67%
397 decline in racemic albuterol clearance. Caution should be used when administering high doses
398 of XOPENEX HFA to patients with renal impairment. [see *Use in Specific Populations* (8.5)]
399

400 **13 NONCLINICAL TOXICOLOGY**

401 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

402 403 *Carcinogenesis*

404 Although there have been no carcinogenesis studies with levalbuterol tartrate, racemic albuterol
405 sulfate has been evaluated for its carcinogenic potential.

406
407 In a 2-year study in Sprague-Dawley rats, dietary administration of racemic albuterol sulfate
408 resulted in a significant dose-related increase in the incidence of benign leiomyomas of the
409 mesovarium at doses of 2 mg/kg/day and greater (approximately 30 times the MRDI) dose of
410 levalbuterol tartrate for adults and approximately 15 times the MRDI dose of levalbuterol tartrate
411 for children on a mg/m² basis). In an 18-month study in CD-1 mice and a 22-month study in the
412 golden hamster, dietary administration of racemic albuterol sulfate showed no evidence of
413 tumorigenicity. Dietary doses in CD-1 mice were up to 500 mg/kg/day (approximately 3800
414 times the MRDI dose of levalbuterol tartrate for adults and approximately 1800 times the MRDI
415 dose of levalbuterol tartrate for children on a mg/m² basis) and doses in the golden hamster study
416 were up to 50 mg/kg/day (approximately 500 times the MRDI dose of levalbuterol tartrate for

417 adults on a mg/m² basis and approximately 240 times the MRDI dose of levalbuterol tartrate for
418 children on a mg/m² basis).

419

420 *Mutagenesis*

421 Levalbuterol HCl was not mutagenic in the Ames test or the CHO/HPRT Mammalian Forward
422 Gene Mutation Assay. Levalbuterol HCl was not clastogenic in the in vivo micronucleus test in
423 mouse bone marrow. Racemic albuterol sulfate was not clastogenic in an in vitro chromosomal
424 aberration assay in CHO cell cultures.

425

426 *Impairment of fertility*

427 No fertility studies have been conducted with levalbuterol tartrate. Reproduction studies in rats
428 using racemic albuterol sulfate demonstrated no evidence of impaired fertility at oral doses up to
429 50 mg/kg/day (approximately 750 times the maximum recommended daily inhalation dose of
430 levalbuterol tartrate for adults on a mg/m² basis).

431

432 **13.2 Animal Toxicology and/or Pharmacology**

433

434 *Propellant HFA-134a*

435 In animals and humans, propellant HFA-134a was found to be rapidly absorbed and rapidly
436 eliminated, with an elimination half-life of 3 to 27 minutes in animals and 5 to 7 minutes in
437 humans. Time to maximum plasma concentration (t_{max}) and mean residence time are both
438 extremely short, leading to a transient appearance of HFA-134a in the blood with no evidence of
439 accumulation. Based on studies in animals, the propellant HFA-134a had no detectable
440 toxicological activity at amounts less than 380 times the maximum human exposure based on
441 comparisons of AUC values). The toxicological effects observed at these very high doses
442 included ataxia, tremors, dyspnea, or salivation, similar to effects produced by the structurally
443 related chlorofluorocarbons (CFCs) used in metered-dose inhalers, that were extensively used in
444 the past.

445

446 *Embryo-fetal Development*

447 Pregnant mice administered racemic albuterol sulfate subcutaneously resulted in a dose-related
448 increased incidence of cleft palate in their fetuses (4.5% of fetuses at 0.25 mg/kg/day or greater,
449 corresponding to approximately 2 times MRDI dose, 9.3% of fetuses at 2.5 mg/kg/day
450 approximately 20 times MRDI dose of levalbuterol tartrate for adults on a mg/m² basis). The
451 drug did not induce cleft palate formation when administered subcutaneously at a dose of 0.025
452 mg/kg/day (approximately 0.2 times MRDI dose of levalbuterol tartrate for adults on a mg/m²
453 basis).

454 **14 CLINICAL STUDIES**

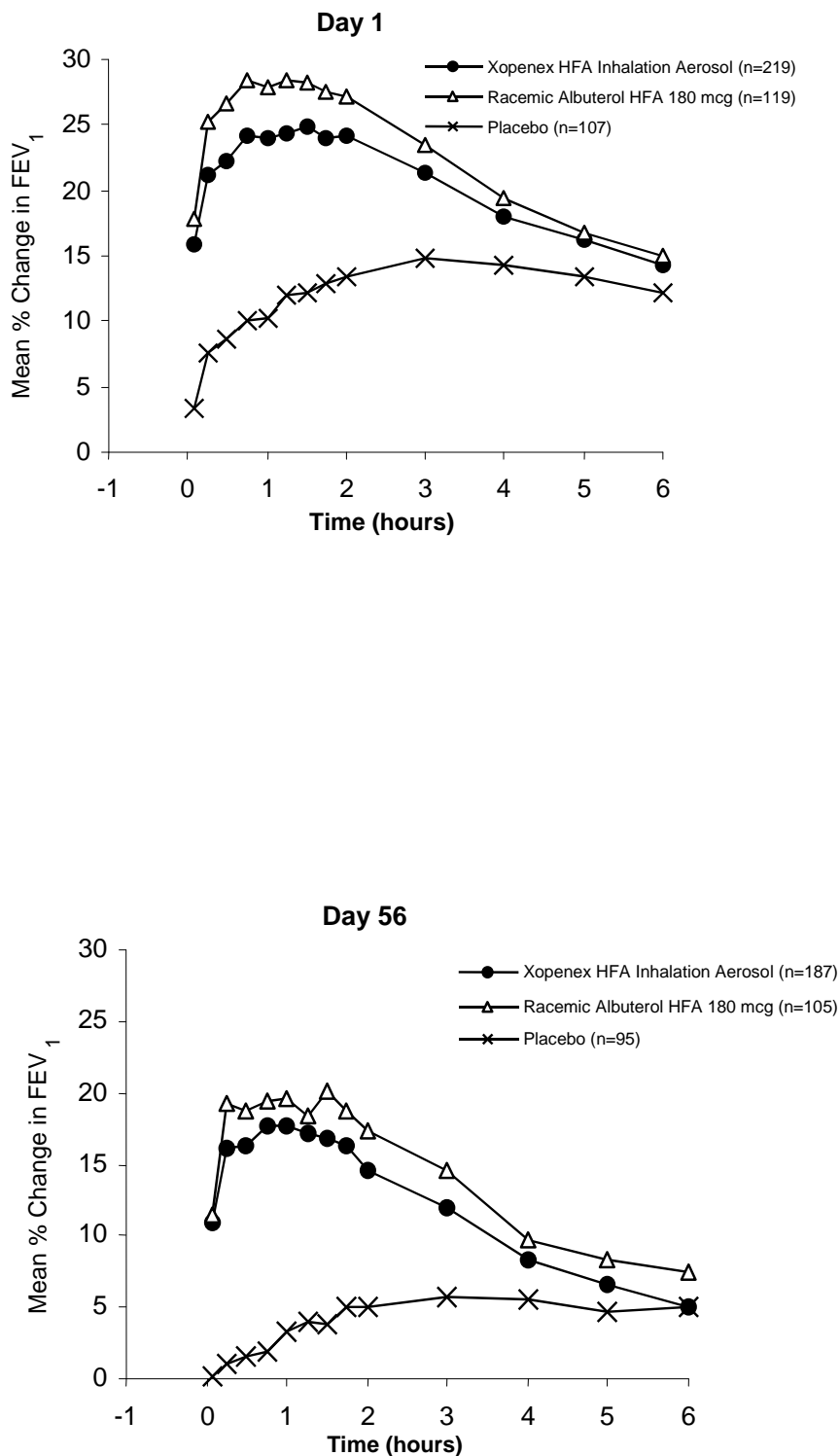
455 **14.1 Bronchospasm Associated with Asthma**

456

457 **Adults and Adolescent Patients 12 Years of Age and Older:** The efficacy and safety of
458 XOPENEX HFA were established in two 8-week, multicenter, randomized, double-blind, active-
459 and placebo-controlled trials in 748 adults and adolescents with asthma between the ages of 12
460 and 81 years. In these two trials, XOPENEX HFA (403 patients) was compared to an HFA-134a
461 placebo MDI (166 patients), and the trials included a marketed albuterol HFA-134a MDI (179
462 patients) as an active control. Serial forced expiratory volume in 1 second (FEV₁) measurements
463 demonstrated that 90 mcg (2 inhalations) of XOPENEX HFA produced significantly greater
464 improvement in FEV₁ over the pretreatment value than placebo. The results from one of the

465 trials are shown in Figure 1 as the mean percent change in FEV₁ from test-day baseline at Day 1
466 (n=445) and Day 56 (n=387). The results from the second trial were similar.
467

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



524 For XOPENEX HFA on Day 1, the median time to onset of a 15% increase in FEV₁ ranged from
525 5.5 to 10.2 minutes and the median time to peak effect ranged from 76 to 78 minutes. In the
526 responder population, on Day 1 the median duration of effect as measured by a 15% increase in
527 FEV₁ was 3 to 4 hours, with duration of effect in some patients of up to 6 hours.

528

529 **Pediatric Patients 4 to 11 Years of Age:** The efficacy and safety of XOPENEX HFA in
530 children were established in a 4-week, multicenter, randomized, double-blind, active- and
531 placebo-controlled trial in 150 pediatric patients with asthma between the ages of 4 and 11 years.
532 In this trial, XOPENEX HFA (76 patients) was compared to a placebo HFA-134a MDI (35
533 patients), and the trial included a marketed albuterol HFA-134a MDI (39 patients) as an active
534 control. Serial FEV₁ measurements demonstrated that 90 mcg (2 inhalations) of XOPENEX
535 HFA produced significantly greater improvement in FEV₁ over the pretreatment value than
536 placebo and were consistent with the efficacy findings in the adult studies.

537

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

542 **16 HOW SUPPLIED/STORAGE AND HANDLING**

543

544 XOPENEX HFA is supplied as a pressurized aluminum canister in a box (NDC 63402-510-01 or
545 NDC 63402-510-04). The canister is labeled with a net weight of 15 g or 8.4 g and contains 200
546 metered actuations or 80 metered actuations (or inhalations), respectively. Each canister is
547 supplied with a blue plastic actuator (or mouthpiece), a red mouthpiece cap, and patient's
548 instructions.

549

550 SHAKE WELL BEFORE USING. Store between 20° and 25°C (68° and 77°F; see USP
551 controlled room temperature). Protect from freezing temperatures and direct sunlight. Store
552 inhaler with the actuator (or mouthpiece) down. Avoid spraying in eyes.

553

554 **CONTENTS UNDER PRESSURE**

555 Do not puncture or incinerate. Exposure to temperatures above 120°F may cause bursting. Keep
556 out of reach of children.

557

558 The blue actuator supplied with XOPENEX HFA should not be used with any other product
559 canisters. Actuators from other products should not be used with a XOPENEX HFA canister.
560 The correct amount of medication in each actuation cannot be assured after 200 actuations from
561 the 15 g canister or 80 actuations from the 8.4 g canister, even though the canister is not
562 completely empty. The canister should be discarded when 200 actuations have been used from
563 the 15 g canister or 80 actuations have been used from the 8.4 g canister.

564

565 Rx only.

566 **17 PATIENT COUNSELING INFORMATION**

567

568 See FDA-approved patient labeling (Patient Information and Instructions for Using XOPENEX
569 HFA)

570

571 Patients should be given the following information:

572

573 **17.1 Frequency of Use**

574

575 The action of XOPENEX HFA should last for 4 to 6 hours. Do not use XOPENEX HFA more
576 frequently than recommended. Instruct patients to not increase the dose or frequency of doses of
577 XOPENEX HFA without consulting your physician. If patients find that treatment with
578 XOPENEX HFA becomes less effective for symptomatic relief, symptoms become worse, or
579 they need to use the product more frequently than usual, they should seek medical attention
580 immediately.

581

582 **17.2 Priming, Cleaning and Storage**

583

584 Priming: SHAKE WELL BEFORE USING. Patients should be instructed that priming
585 XOPENEX HFA is essential to ensure appropriate levalbuterol content in each actuation.
586 Patients should prime XOPENEX HFA before using for the first time and in cases where the
587 inhaler has not been used for more than 3 days by releasing 4 test sprays into the air, away from
588 the face.

589

590 Cleaning: To ensure proper dosing and prevent actuator orifice blockage, instruct patients to
591 wash the actuator in warm water and air-dry thoroughly at least once a week. Patients should be
592 informed that detailed cleaning instructions are included in the FDA-Approved Patient Labeling.
593

594

Storage:

595 Store canister between 20° and 25°C (68° and 77°F). Protect from freezing temperatures and
596 direct sunlight.

597

598 **17.3 Paradoxical Bronchospasm**

599 Inform patients that XOPENEX HFA can produce paradoxical bronchospasm. Instruct patients
600 to discontinue XOPENEX HFA if paradoxical bronchospasm occurs.

601

602 **17.4 Concomitant Drug Use**

603 While patients are using XOPENEX HFA, other inhaled drugs and asthma medications should
604 be taken only as directed by the physician.

605

606 **17.5 Common Adverse Reactions**

607 Common adverse effects of treatment with inhaled beta-agonists include palpitations, chest pain,
608 rapid heart rate, tremor, and nervousness.

609

610 **17.6 Pregnancy**

611 Patients who are pregnant or nursing should contact their physicians about the use of XOPENEX
612 HFA.

613

614 **17.7 General Information on Use**

615 Effective and safe use of XOPENEX HFA includes an understanding of the way that it should be
616 administered.

617

618 Shake the inhaler well immediately before each use.

619

620 Use XOPENEX HFA only with the actuator supplied with the product. Discard the canister after
621 200 sprays have been used from the 15 g canister or after 80 sprays have been used from the 8.4
622 g canister. Never immerse the canister in water to determine how full the canister is (“float
623 test”).

624

625 In general, the technique for administering XOPENEX HFA to children is similar to that for
626 adults. Children should use XOPENEX HFA under adult supervision, as instructed by the
627 patient’s physician. (See **FDA-Approved Patient Labeling – (Patient Information and**
628 **Instructions for Using XOPENEX HFA)**)

629

630

631 Manufactured for:

632 **Sunovion Pharmaceuticals Inc.**

633 Marlborough, MA 01752 USA

634

635

636 Month Year

637 900874R05

638
639
640 PHARMACIST — DETACH HERE AND GIVE LEAFLET TO PATIENT.
641 -----

642 **PATIENT INFORMATION**

643
644 **XOPENEX HFA**[®] (pronounced zō-pen- eks hfa)
645 **(levalbuterol tartrate)**
646 **Inhalation Aerosol**
647

For Oral Inhalation Only

648
649
650 Read this Patient Information before you start to use XOPENEX HFA and each time
651 you get a refill. There may be new information. This information does not take the
652 place of talking with your doctor about your medical condition or your treatment.
653

654 **What is XOPENEX HFA?**

655
656 XOPENEX HFA is an inhaled prescription medicine used for the treatment or
657 prevention of asthma in people 4 years of age and older.
658

659 It is not known if XOPENEX HFA is safe and effective in children younger than 4
660 years of age.
661

662 **Who should not use XOPENEX HFA?**

663
664 **Do not use XOPENEX HFA if you** are allergic to levalbuterol, racemic albuterol
665 or any of the ingredients in XOPENEX HFA. See the end of this leaflet for a complete
666 list of ingredients in XOPENEX HFA.
667

668 **What should I tell my doctor before using XOPENEX HFA?**

669
670 **Before you use XOPENEX HFA, tell your doctor if you have:**

- 671
- 672 • heart problems
 - 673 • high blood pressure
 - 674 • seizures
 - 675 • diabetes
 - 676 • thyroid problems
 - 677 • any other medical conditions
 - 678 • are pregnant or planning to become pregnant. It is not known if XOPENEX HFA
679 will harm your unborn baby. Talk to your doctor if you are pregnant or plan to
680 become pregnant.

681 • are breastfeeding or plan to breastfeed. It is not known if XOPENEX HFA passes
682 into your breast milk. You and your doctor should decide if you will use XOPENEX
683 HFA or breastfeed. You should not do both.

684 **Tell your doctor about all the medicines you take** including prescription and
685 non-prescription medicines, vitamins, and herbal supplements. XOPENEX HFA may
686 affect the way other medicines work, and other medicines may affect how XOPENEX
687 HFA works.

688
689 Especially tell your doctor if you take:

- 690 • other asthma medicines
- 691 • heart medicines
- 692 • medicines that increase urination (diuretics)
- 693 • antidepressants
- 694 • medicine to treat chronic obstructive pulmonary disease (COPD)
- 695 (methylxanthines)

696
697 Ask your doctor if you are not sure if any of your medicines are the kinds listed
698 above.

699
700 Know the medicines you take. Keep a list of them and show it to your doctor and
701 pharmacist when you get a new medicine.

702 703 **How should I use XOPENEX HFA?**

- 704
705 • Read the step-by-step Instructions for Using XOPENEX HFA at the end of this
706 leaflet.
- 707
708 • Use XOPENEX HFA exactly as your doctor tells you to. **Do not** change your dose
709 without talking to your doctor first.
- 710
711 • Your doctor will tell you how many times and when to use your XOPENEX HFA.
- 712 • An adult should help a child use XOPENEX HFA.
- 713 • **Do not use your XOPENEX HFA more often than your doctor tells you to.**
- 714 • **Get medical help right away if XOPENEX HFA:**
 - 715 ○ does not work as well for your asthma symptoms or
 - 716 ○ your asthma symptoms get worse or
 - 717 ○ you need to use your XOPENEX HFA more often than usual
- 718 • If you also use another medicine by inhalation, you should ask your doctor for
719 instructions on when to use it while you are also using XOPENEX HFA.

720 721 **What are the possible side effects of XOPENEX HFA?**

722
723 **XOPENEX HFA can cause serious side effects including:**

- 724
725 • **sudden shortness of breath (bronchospasm).** Sudden shortness of breath
726 can happen right away after using XOPENEX HFA.
- 727 • **worsening asthma.**

728 • **heart problems.**

729 • **death.** If you use too much XOPENEX HFA you can have heart or lung problems
730 that can lead to death.

731 • **serious allergic reactions.** Call your doctor and stop using XOPENEX HFA right
732 away if you have any symptoms of an allergic reaction such as:

- 733 ○ swelling of the face, throat or tongue
- 734 ○ hives
- 735 ○ rash
- 736 ○ breathing problems

737 • **low potassium levels in your blood**

738
739 Call your doctor or go to the nearest hospital emergency room right away if you
740 have any of the serious side effects listed above or if you have worsening lung
741 symptoms.

742

743 **The most common side effects of XOPENEX HFA include:**

- 744 • accidental injury
- 745 • bronchitis
- 746 • dizziness
- 747 • pain
- 748 • sore throat
- 749 • runny nose
- 750 • vomiting
- 751 • palpitations
- 752 • chest pain
- 753 • fast heart rate
- 754 • tremors
- 755 • nervousness

756

757 Tell your doctor if you have any side effects that bother you or that does not go
758 away.

759

760 These are not all the possible side effects of XOPENEX HFA. For more information
761 ask your doctor or pharmacist.

762

763 Call your doctor for medical advice about side effects. You may report side effects
764 to FDA at 1-800-FDA-1088.

765

766 **How should I store XOPENEX HFA?**

767

- 768 • Store XOPENEX HFA between 68°F to 77°F (20°C to 25°C).
- 769 • Keep XOPENEX HFA Inhaler away from heat or open flame.
- 770 • Keep XOPENEX HFA Inhaler away from freezing temperatures and direct
771 sunlight.
- 772 • Do not puncture the XOPENEX HFA Inhaler.
- 773 • Store XOPENEX HFA Inhaler with the mouthpiece down.

774 The XOPENEX HFA Inhaler should be safely thrown away after using:

775 o 200 actuations for the 15 gram canister.

776 o 80 actuations for the 8.4 gram canister.

777 • Do not throw XOPENEX HFA Inhaler into a fire or an incinerator.

778

779 **Keep XOPENEX HFA and all medicines out of the reach of children.**

780

781 **General information about the safe and effective use of XOPENEX HFA**

782

783 Medicines are sometimes prescribed for purposes other than those listed in a
784 Patient Information leaflet. Do not use XOPENEX HFA for a condition for which it
785 was not prescribed. Do not give XOPENEX HFA to other people, even if they have
786 the same symptoms that you have. It may harm them.

787

788 This Patient Information leaflet summarizes the most important information about
789 XOPENEX HFA. If you would like more information, talk with your doctor. You can
790 ask your pharmacist or doctor for information about XOPENEX HFA that is written
791 for health professionals.

792

793

794 For more information go to www.XOPENEX.com.

795

796 For customer service, call 1-888-394-7377.

797 To report adverse events, call 1-877-737-7226.

798 For medical information, call 1-800-739-0565

799

800

801 **What are the ingredients in XOPENEX HFA?**

802

803 Active ingredient: levalbuterol tartrate

804 Inactive ingredient: propellant HFA-134a, Dehydrated Alcohol USP, Oleic Acid NF

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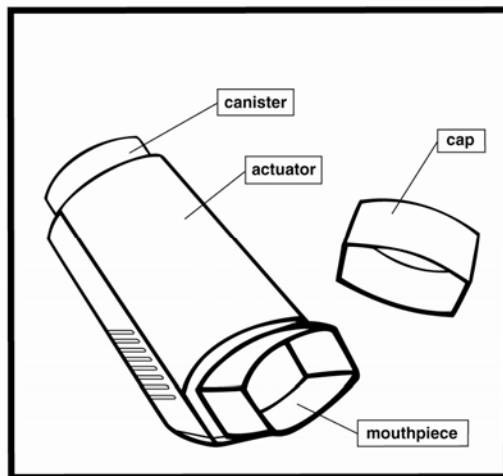
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823
824

Instructions for Using XOPENEX HFA

825
826

The parts of your XOPENEX HFA inhaler (See Figure 1):



827
828
829
830

Figure 1

831
832
833

Using your XOPENEX HFA inhaler

- **XOPENEX HFA should be at room temperature before you use it.**
- **Priming the inhaler:**

834
835

Before you use XOPENEX HFA for the first time, you must prime the inhaler so that you will get the right amount of medicine when you use it.

836
837
838
839
840
841
842
843

- To prime the inhaler, take the cap off the mouthpiece and shake the inhaler well. Then spray the inhaler into the air away from your face. **Avoid spraying in your eyes.** Shake and spray the inhaler like this 3 more times to finish priming it.
- You must prime the inhaler again if you have not used it in more than 3 days.
- An adult should help a child use XOPENEX HFA.

844
845
846

Read the following 6 steps before using XOPENEX HFA and follow them **before** each use. If you have any questions, ask your doctor or pharmacist.

847
848
849
850
851

1. **Take the cap off the mouthpiece of the actuator** (See Figure 2).
Look inside the mouthpiece for foreign objects, and remove any that you see.
Make sure the canister fits firmly in the actuator.
Shake the inhaler well for 5 seconds.

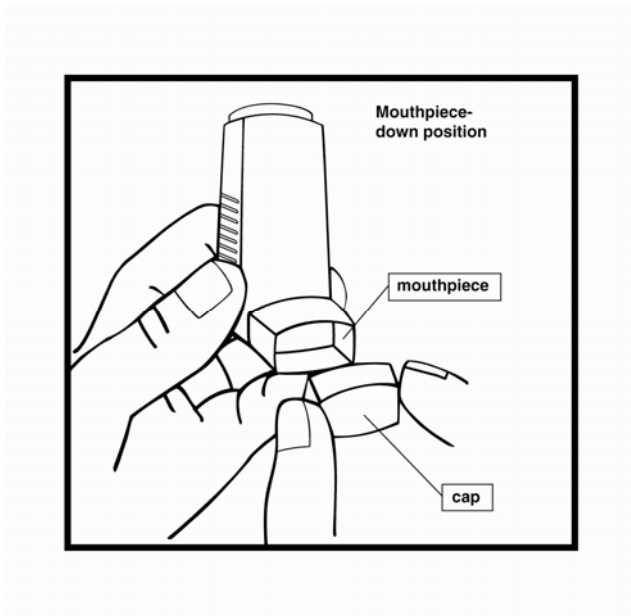


Figure 2

852
853
854
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856
857
858

2. Hold the inhaler with the mouthpiece down (See Figure 2). **Before you put the mouthpiece in your mouth, breathe out through your mouth** and push out as much air from your lungs as you can. Put the mouthpiece in your mouth and close your lips around it.

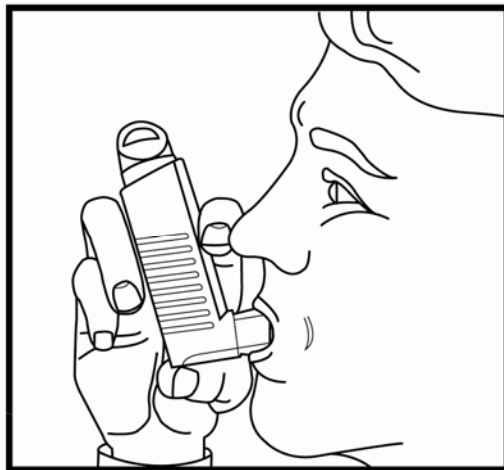


Figure 3

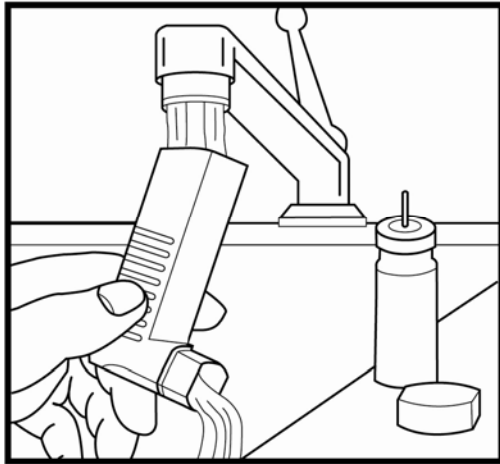
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865
866

3. Push the top of the canister all the way down while you breathe in deeply and slowly through your mouth (See Figure 3). Right after the spray comes out, take your finger off the canister. After you have breathed in all the way, take the inhaler out of your mouth and close your mouth.

4. Hold your breath for 10 seconds if possible. Then breathe normally.

- 867 5. Wait about 1 minute, then shake the inhaler well. Repeat steps 2 through 4.
868
869 6. Put the cap back on the mouthpiece after each time you use the XOPENEX HFA.
870 Make sure the cap snaps firmly into place.

871
872 **Cleaning your XOPENEX HFA inhaler:**



873
874 **Figure 4**

875 • **The inhaler may stop working if you do not properly clean the blue**
876 **plastic actuator (mouthpiece) at least one time a week. See Figure 4.**
877 **To clean the actuator:**

- 878 ○ Remove the canister and red mouthpiece cap. Do not clean the metal
879 canister or allow the metal canister to become wet.
880 ○ Wash the actuator through the top and bottom with warm running
881 water for at least 30 seconds.
882 ○ Shake the actuator to remove excess water
883 ○ Air-dry the actuator completely. Blockage from medicine build-up is
884 more likely to happen if the actuator is not allowed to air-dry
885 thoroughly.
- 886 • When the actuator is dry, replace the canister and the mouthpiece cap.
887 • Make sure the canister is fully and firmly inserted into the actuator.
888 • If your actuator becomes blocked, it means that little or no medicine is coming
889 out of the mouthpiece. See Figure 5. Wash your actuator and air-dry completely as
890 described above.

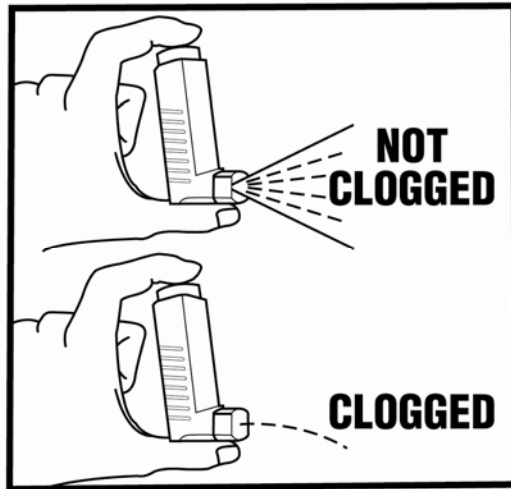


Figure 5

891
892
893
894 • **If you need to use your inhaler before the plastic actuator is completely**
895 **dry:**

- 896 ○ Shake the excess water off the actuator.
- 897 ○ Replace the canister and shake well.
- 898 ○ Test-spray twice into the air, away from your face, to remove most of
- 899 the water remaining in the actuator.
- 900 ○ Take your dose as prescribed.
- 901 ○ Rewash the actuator and air-dry it thoroughly as described above.
- 902

903 **How should I store XOPENEX HFA?**

- 904 • Store XOPENEX HFA between 68°F to 77°F (20°C to 25°C).
- 905 • Keep XOPENEX HFA Inhaler away from heat or open flame.
- 906 • Keep XOPENEX HFA Inhaler away from freezing temperatures and direct
- 907 sunlight.
- 908 • Do not puncture the XOPENEX HFA Inhaler.
- 909 • Store XOPENEX HFA with the mouthpiece down.
- 910 • The XOPENEX HFA inhaler should be safely thrown away after using:
 - 911 ○ 200 actuations for the 15 gram canister.
 - 912 ○ 80 actuations or the 8.4 gram canister.
- 913 • Do not throw your XOPENEX HFA inhaler into a fire or incinerator.

914 Keep XOPENEX HFA and all medicines out of the reach of children.

915
916 Manufactured for:
917 **Sunovion Pharmaceuticals Inc**
918 Marlborough, MA 01752 USA

919

920 Revised Month Year
921