

## HIGHLIGHTS OF PRESCRIBING INFORMATION

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

### XOPENEX HFA<sup>®</sup> (levalbuterol tartrate) Inhalation Aerosol

#### FOR ORAL INHALATION ONLY

Initial U.S. Approval: 1999

#### INDICATIONS AND USAGE

XOPENEX HFA is a beta<sub>2</sub>-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 tartrate (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 mouthpiece. 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](http://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: MM/YYYY

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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.

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21 **2.2 Administration Information**

22  
23 **FOR ORAL INHALATION ONLY**

24  
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.

28  
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 mouthpiece.

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.  
58

59 **5.2 Deterioration of Asthma**

60

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.

**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.

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

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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**

163

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 dysphonia, dyspnea, gastroesophageal reflux disease (GERD), metabolic acidosis, nausea,  
172 nervousness, rash, tachycardia, tremor, urticaria.

173

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178

179

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

## 183 **7 DRUG INTERACTIONS**

184

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

188

### 189 **7.1 Beta-blockers**

190

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

198

### 199 **7.2 Diuretics**

200

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

206

### 207 **7.3 Digoxin**

208

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

215

#### 216 **7.4 Monoamine Oxidase Inhibitors or Tricyclic Antidepressants**

217

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

222

### 223 **8 USE IN SPECIFIC POPULATIONS**

224

#### 225 **8.1 Pregnancy**

226

##### 227 **Pregnancy Category C**

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

232

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

239

240 In animal studies, oral administration of levalbuterol HCl to pregnant New Zealand White rabbits  
241 found no evidence of teratogenicity at doses up to 25 mg/kg/day (approximately 750 times the  
242 maximum recommended daily inhalation dose of levalbuterol tartrate for adults on a mg/m<sup>2</sup>  
243 basis).

244

245 However, other studies demonstrated that racemic albuterol sulfate was teratogenic in mice and  
246 rabbits at doses slightly higher than the human therapeutic range. Pregnant mice subcutaneously  
247 administered racemic albuterol sulfate had dose-related fetal incidences of cleft palate at doses 2-  
248 fold greater or more than the maximum recommended daily inhalation (MRDI) dose of  
249 levalbuterol tartrate for adults on a mg/m<sup>2</sup> basis. No teratogenic findings occurred at a dose  
250 typically less than the human therapeutic range (0.2 times the MRDI dose). Oral administration  
251 of racemic albuterol sulfate to pregnant rabbits resulted in an increased incidence of cranioschisis  
252 in fetuses (approximately 1500 times the MRDI dose of levalbuterol tartrate for adults on a  
253 mg/m<sup>2</sup> basis). [see *Animal Toxicology and/or Pharmacology* (13.2)].

254

255

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

258

259 **8.2 Labor and Delivery**

260

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

264

265 XOPENEX HFA has not been approved for the management of preterm labor. The benefit:risk  
266 ratio when levalbuterol tartrate is administered for tocolysis has not been established. Serious  
267 adverse reactions, including maternal pulmonary edema, have been reported during or following  
268 treatment of premature labor with beta<sub>2</sub>-agonists, including racemic albuterol.

269

270 **8.3 Nursing Mothers**

271

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

274

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

280

281 **8.4 Pediatric Use**

282

283 The safety and efficacy of XOPENEX HFA have been established in pediatric patients 4 years of  
284 age and older in an adequate and well-controlled clinical trial [see *Clinical Studies (14)*]. Use of  
285 XOPENEX HFA in children is also supported by evidence from adequate and well-controlled  
286 studies of XOPENEX HFA in adults, considering that the pathophysiology, systemic exposure of  
287 the drug, and clinical profile in pediatric and adult patients are substantially similar. Safety and  
288 effectiveness of XOPENEX HFA in pediatric patients below the age of 4 years have not been  
289 established.

290

291 **8.5 Geriatric Use**

292

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

299

300 **8.6 Renal Impairment**

301

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

306 **10 OVERDOSAGE**

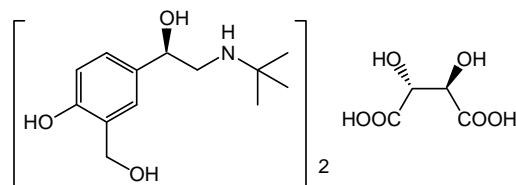
307

308 The expected symptoms with overdosage are those of excessive beta-adrenergic receptor  
309 stimulation and/or occurrence or exaggeration of any of the symptoms listed under **ADVERSE**  
310 **REACTIONS**, e.g., seizures, angina, hypertension or hypotension, tachycardia with rates up to  
311 200 beats/minute, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, nausea,  
312 dizziness, fatigue, malaise, and sleeplessness. Hypokalemia also may occur. As with all  
313 sympathomimetic medications, cardiac arrest and even death may be associated with the abuse of  
314 XOPENEX HFA. Treatment consists of discontinuation of XOPENEX HFA together with  
315 appropriate symptomatic therapy. The judicious use of a cardioselective beta-receptor blocker  
316 may be considered, bearing in mind that such medication can produce bronchospasm. There is  
317 insufficient evidence to determine if dialysis is beneficial for overdosage of XOPENEX HFA.  
318

319 **11 DESCRIPTION**

320

321 The active component of XOPENEX HFA is levalbuterol tartrate, the (R)-enantiomer of  
322 albuterol. Levalbuterol tartrate is a relatively selective beta<sub>2</sub>-adrenergic receptor agonist [see  
323 *Clinical Pharmacology* (12)]. Levalbuterol tartrate has the chemical name (R)-α<sup>1</sup>-[[[1,1-  
324 dimethylethyl)amino]methyl]-4-hydroxy-1,3-benzenedimethanol L-tartrate (2:1 salt), and it has  
325 the following chemical structure:  
326



327

328

329 The molecular weight of levalbuterol tartrate is 628.71, and its empirical formula is  
330 (C<sub>13</sub>H<sub>21</sub>NO<sub>3</sub>)<sub>2</sub> · C<sub>4</sub>H<sub>6</sub>O<sub>6</sub>. It is a white to light-yellow solid, freely soluble in water and very  
331 slightly soluble in ethanol.

332

333 Levalbuterol tartrate is the generic name for (R)-albuterol tartrate in the United States.  
334 XOPENEX HFA is a pressurized metered-dose aerosol inhaler (MDI), which produces an  
335 aerosol for oral inhalation. It contains a suspension of micronized levalbuterol tartrate,  
336 propellant HFA-134a (1,1,1,2-tetrafluoroethane), Dehydrated Alcohol USP, and Oleic Acid NF.  
337

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

343 **12 CLINICAL PHARMACOLOGY**

344 **12.1 Mechanism of Action**

345

346 Activation of beta<sub>2</sub>-adrenergic receptors on airway smooth muscle leads to the activation of  
347 adenylate cyclase and to an increase in the intracellular concentration of cyclic-3', 5'-adenosine

348 monophosphate (cyclic AMP). The increase in cyclic AMP is associated with the activation of  
349 protein kinase A, which in turn, inhibits the phosphorylation of myosin and lowers intracellular  
350 ionic calcium concentrations, resulting in muscle relaxation. Levalbuterol relaxes the smooth  
351 muscles of all airways, from the trachea to the terminal bronchioles. Increased cyclic AMP  
352 concentrations are also associated with the inhibition of the release of mediators from mast cells  
353 in the airways. Levalbuterol acts as a functional antagonist to relax the airway irrespective of the  
354 spasmogen involved, thus protecting against all bronchoconstrictor challenges. While it is  
355 recognized that beta<sub>2</sub>-adrenergic receptors are the predominant receptors on bronchial smooth  
356 muscle, data indicate that there are beta-receptors in the human heart, 10% to 50% of which are  
357 beta<sub>2</sub>-adrenergic receptors. The precise function of these receptors has not been established [see  
358 *Warnings and Precautions* (5)]. However, all beta-adrenergic agonist drugs can produce a  
359 significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure,  
360 symptoms, and/or electrocardiographic changes.

## 361 **12.2 Pharmacokinetics**

362 A population pharmacokinetic model was developed using plasma concentrations of (R)-  
363 albuterol obtained from 632 asthmatic patients aged 4 to 81 years in three large trials. For  
364 adolescent and adult patients 12 years and older, following 90 mcg dose of XOPENEX HFA,  
365 yielded mean peak plasma concentrations (C<sub>max</sub>) and systemic exposure (AUC<sub>0-6</sub>) of  
366 approximately 199 pg/mL and 695 pg•h/mL, respectively, compared to approximately 238  
367 pg/mL and 798 pg•h/mL, respectively, following 180 mcg dose of Racemic Albuterol HFA  
368 metered-dose inhaler. For pediatric patients from 4 to 11 years of age, following 90 mcg dose of  
369 XOPENEX HFA, yielded C<sub>max</sub> and AUC<sub>0-6</sub> of approximately 163 pg/mL and 579 pg•h/mL,  
370 respectively, compared to approximately 238 pg/mL and 828 pg•h/mL, respectively, following  
371 180 mcg dose of Racemic Albuterol HFA metered-dose inhaler.

372  
373 These pharmacokinetic data indicate that mean exposure to (R)-albuterol was 13% to 16% less in  
374 adult and 30% to 32% less in pediatric patients given XOPENEX HFA as compared to those  
375 given a comparable dose of racemic albuterol. When compared to adult patients, pediatric  
376 patients given 90 mcg of levalbuterol have a 17% lower mean exposure to (R)-albuterol.  
377

## 378 ***Metabolism and Elimination***

379  
380 Information available in the published literature suggests that the primary enzyme responsible for  
381 the metabolism of albuterol enantiomers in humans is SULT1A3 (sulfotransferase). When  
382 racemic albuterol was administered either intravenously or via inhalation after oral charcoal  
383 administration, there was a 3- to 4-fold difference in the area under the concentration-time curves  
384 between the (R)- and (S)-albuterol enantiomers, with (S)-albuterol concentrations being  
385 consistently higher. However, without charcoal pretreatment, after either oral or inhalation  
386 administration the differences were 8- to 24-fold, suggesting that (R)-albuterol is preferentially  
387 metabolized in the gastrointestinal tract, presumably by SULT1A3.  
388

389 The primary route of elimination of albuterol enantiomers is through renal excretion (80% to  
390 100%) of either the parent compound or the primary metabolite. Less than 20% of the drug is  
391 detected in the feces. Following intravenous administration of racemic albuterol, between 25%  
392 and 46% of the (R)-albuterol fraction of the dose was excreted as unchanged (R)-albuterol in the  
393 urine.  
394  
395

396 ***Special Populations***

397 ***Hepatic Impairment***

398

399 The effect of hepatic impairment on the pharmacokinetics of XOPENEX HFA has not been  
400 evaluated.

401 ***Renal Impairment***

402

403 The effect of renal impairment on the pharmacokinetics of racemic albuterol was evaluated in 5  
404 subjects with creatinine clearance of 7 to 53 mL/min, and the results were compared with those  
405 from healthy volunteers. Renal disease had no effect on the half-life, but there was a 67%  
406 decline in racemic albuterol clearance. Caution should be used when administering high doses  
407 of XOPENEX HFA to patients with renal impairment [see *Use in Specific Populations (8.5)*].  
408

409 **13 NONCLINICAL TOXICOLOGY**

410 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

411

412 ***Carcinogenesis***

413 Although there have been no carcinogenesis studies with levalbuterol tartrate, racemic albuterol  
414 sulfate has been evaluated for its carcinogenic potential.  
415

416 In a 2-year study in Sprague-Dawley rats, dietary administration of racemic albuterol sulfate  
417 resulted in a significant dose-related increase in the incidence of benign leiomyomas of the  
418 mesovarium at doses of 2 mg/kg/day and greater (approximately 30 times the MRDI) dose of  
419 levalbuterol tartrate for adults and approximately 15 times the MRDI dose of levalbuterol tartrate  
420 for children on a mg/m<sup>2</sup> basis). In an 18-month study in CD-1 mice and a 22-month study in the  
421 golden hamster, dietary administration of racemic albuterol sulfate showed no evidence of  
422 tumorigenicity. Dietary doses in CD-1 mice were up to 500 mg/kg/day (approximately 3800  
423 times the MRDI dose of levalbuterol tartrate for adults and approximately 1800 times the MRDI  
424 dose of levalbuterol tartrate for children on a mg/m<sup>2</sup> basis) and doses in the golden hamster study  
425 were up to 50 mg/kg/day (approximately 500 times the MRDI dose of levalbuterol tartrate for  
426 adults on a mg/m<sup>2</sup> basis and approximately 240 times the MRDI dose of levalbuterol tartrate for  
427 children on a mg/m<sup>2</sup> basis).  
428

429 ***Mutagenesis***

430 Levalbuterol HCl was not mutagenic in the Ames test or the CHO/HPRT Mammalian Forward  
431 Gene Mutation Assay. Levalbuterol HCl was not clastogenic in the *in vivo* micronucleus test in  
432 mouse bone marrow. Racemic albuterol sulfate was not clastogenic in an *in vitro* chromosomal  
433 aberration assay in CHO cell cultures.  
434

435 ***Impairment of Fertility***

436 No fertility studies have been conducted with levalbuterol tartrate. Reproduction studies in rats  
437 using racemic albuterol sulfate demonstrated no evidence of impaired fertility at oral doses up to  
438 50 mg/kg/day (approximately 750 times the maximum recommended daily inhalation dose of  
439 levalbuterol tartrate for adults on a mg/m<sup>2</sup> basis).  
440

440

441

## 442 13.2 Animal Toxicology and/or Pharmacology

443

### 444 *Propellant HFA-134a*

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

455

### 456 *Embryo-fetal Development*

457 Pregnant mice administered racemic albuterol sulfate subcutaneously resulted in a dose-related  
458 increased incidence of cleft palate in their fetuses (4.5% of fetuses at 0.25 mg/kg/day or greater,  
459 corresponding to approximately 2 times MRDI dose, 9.3% of fetuses at 2.5 mg/kg/day,  
460 approximately 20 times MRDI dose of levalbuterol tartrate for adults on a mg/m<sup>2</sup> basis). The  
461 drug did not induce cleft palate formation when administered subcutaneously at a dose of  
462 0.025 mg/kg/day (approximately 0.2 times MRDI dose of levalbuterol tartrate for adults on a  
463 mg/m<sup>2</sup> basis).

## 464 14 CLINICAL STUDIES

### 465 14.1 Bronchospasm Associated with Asthma

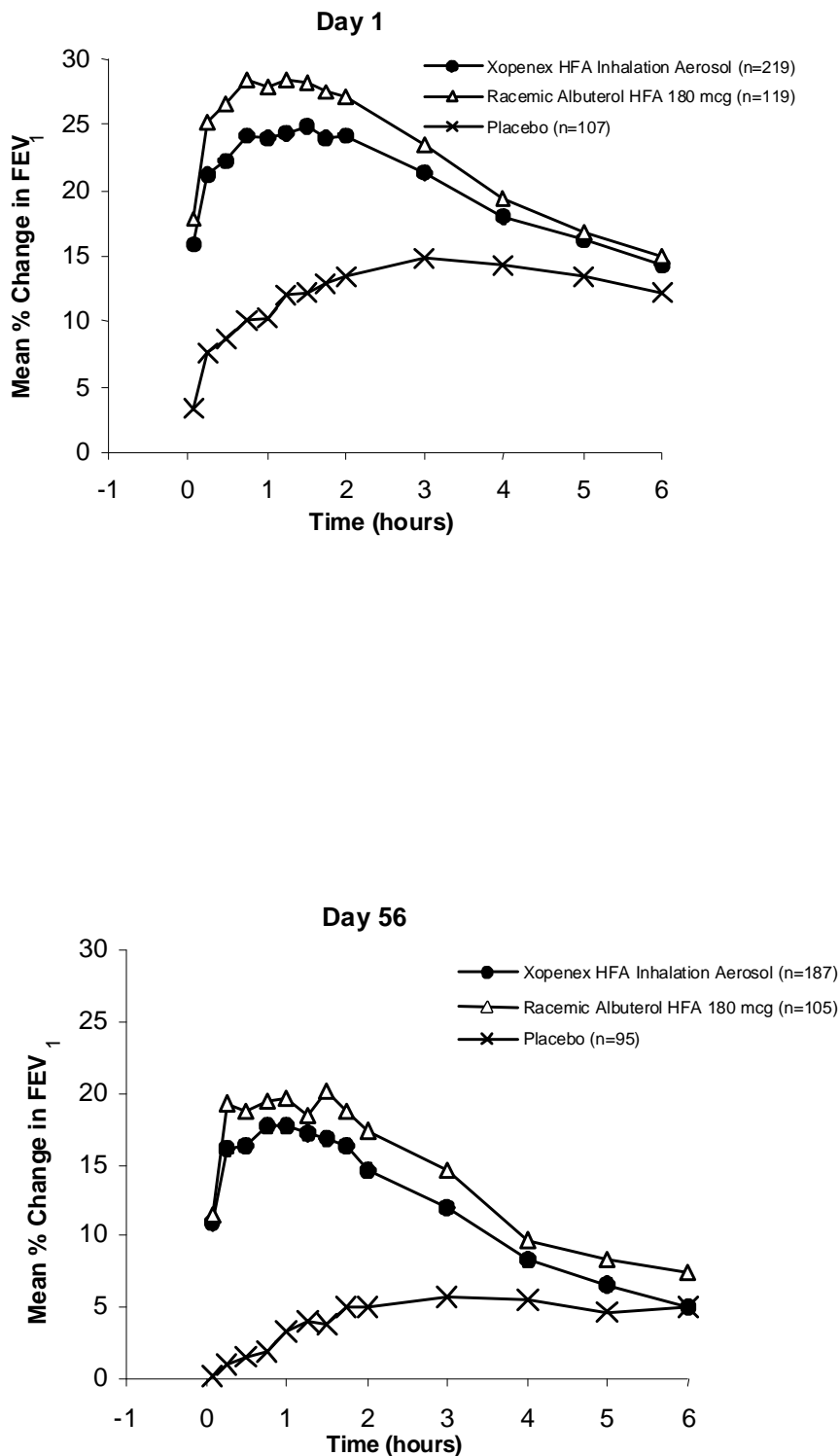
466

467 **Adults and Adolescent Patients 12 Years of Age and Older:** The efficacy and safety of  
468 XOPENEX HFA were established in two 8-week, multicenter, randomized, double-blind, active-  
469 and placebo-controlled trials in 748 adults and adolescents with asthma between the ages of 12  
470 and 81 years. In these two trials, XOPENEX HFA (403 patients) was compared to an HFA-134a  
471 placebo MDI (166 patients), and the trials included a marketed albuterol HFA-134a MDI (179  
472 patients) as an active control. Serial forced expiratory volume in 1 second (FEV<sub>1</sub>) measurements  
473 demonstrated that 90 mcg (2 inhalations) of XOPENEX HFA produced significantly greater  
474 improvement in FEV<sub>1</sub> over the pretreatment value than placebo. The results from one of the  
475 trials are shown in [Figure 1](#) as the mean percent change in FEV<sub>1</sub> from test-day baseline at Day 1  
476 (n=445) and Day 56 (n=387). The results from the second trial were similar.

477

478

Figure 1: Percent Change in FEV<sub>1</sub> from Test-Day Baseline in Adults and Adolescents Aged 12 to 81 Years at Day 1 and Day 56



535 For XOPENEX HFA on Day 1, the median time to onset of a 15% increase in FEV<sub>1</sub> ranged from  
536 5.5 to 10.2 minutes and the median time to peak effect ranged from 76 to 78 minutes. In the  
537 responder population, on Day 1 the median duration of effect as measured by a 15% increase in  
538 FEV<sub>1</sub> was 3 to 4 hours, with duration of effect in some patients of up to 6 hours.

539

540 **Pediatric Patients 4 to 11 Years of Age:** The efficacy and safety of XOPENEX HFA in  
541 children were established in a 4-week, multicenter, randomized, double-blind, active- and  
542 placebo-controlled trial in 150 pediatric patients with asthma between the ages of 4 and 11 years.  
543 In this trial, XOPENEX HFA (76 patients) was compared to a placebo HFA-134a MDI (35  
544 patients), and the trial included a marketed albuterol HFA-134a MDI (39 patients) as an active  
545 control. Serial FEV<sub>1</sub> measurements demonstrated that 90 mcg (2 inhalations) of XOPENEX  
546 HFA produced significantly greater improvement in FEV<sub>1</sub> over the pretreatment value than  
547 placebo and were consistent with the efficacy findings in the adult studies.

548

549 For XOPENEX HFA, on Day 1 the median time to onset of a 15% increase in FEV<sub>1</sub> was 4.5  
550 minutes and the median time to peak effect was 77 minutes. In the responder population, the  
551 median duration of effect as measured by a 15% increase in FEV<sub>1</sub> was 3 hours, with a duration  
552 of effect in some pediatric patients of up to 6 hours.

## 553 **16 HOW SUPPLIED/STORAGE AND HANDLING**

554

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

560

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

564

### 565 **CONTENTS UNDER PRESSURE**

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

568

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

575

576 Rx only.

## 577 **17 PATIENT COUNSELING INFORMATION**

578

579 See FDA-Approved Patient Labeling ([Patient Information](#) and [Instructions for Using XOPENEX](#)  
580 [HFA](#)).

581

582 Patients should be given the following information:

583

### 584 **17.1 Frequency of Use**

585

586 The action of XOPENEX HFA should last for 4 to 6 hours. Do not use XOPENEX HFA more  
587 frequently than recommended. Instruct patients to not increase the dose or frequency of doses of  
588 XOPENEX HFA without consulting their physician. If patients find that treatment with  
589 XOPENEX HFA becomes less effective for symptomatic relief, symptoms become worse, or  
590 they need to use the product more frequently than usual, they should seek medical attention  
591 immediately.

592

### 593 **17.2 Priming, Cleaning and Storage**

594

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

600

601 Cleaning: To ensure proper dosing and prevent actuator orifice blockage, instruct patients to  
602 wash the actuator in warm water and air-dry thoroughly at least once a week. Patients should be  
603 informed that detailed cleaning instructions are included in the FDA-Approved Patient Labeling.  
604

605

#### Storage:

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

608

### 609 **17.3 Paradoxical Bronchospasm**

610 Inform patients that XOPENEX HFA can produce paradoxical bronchospasm. Instruct patients  
611 to discontinue XOPENEX HFA if paradoxical bronchospasm occurs.

612

### 613 **17.4 Concomitant Drug Use**

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

616

### 617 **17.5 Common Adverse Reactions**

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

620

### 621 **17.6 Pregnancy**

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

624

### 625 **17.7 General Information on Use**

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

628

629 Shake the inhaler well immediately before each use.

630

631 Use XOPENEX HFA only with the actuator supplied with the product. Discard the canister after  
632 200 sprays have been used from the 15 g canister or after 80 sprays have been used from the 8.4  
633 g canister. Never immerse the canister in water to determine how full the canister is (“float  
634 test”).

635

636 In general, the technique for administering XOPENEX HFA to children is similar to that for  
637 adults. Children should use XOPENEX HFA under adult supervision, as instructed by the  
638 patient’s physician. [see **FDA-Approved Patient Labeling** – ([Patient Information](#) and  
639 [Instructions for Using XOPENEX HFA](#))].

640



SUNOVION

641

642 Manufactured for

643 **Sunovion Pharmaceuticals Inc.**

644 Marlborough, MA 01752 USA

645

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647

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

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

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

651

652

653 Month Year

654 901715R01

655

656  
657  
658 PHARMACIST — DETACH HERE AND GIVE LEAFLET TO PATIENT.  
659

660  
661  
662  
663  
664  
665

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**PATIENT INFORMATION**

**XOPENEX HFA<sup>®</sup>** (pronounced zō-pen-eks hfa)  
**(levalbuterol tartrate)**  
**Inhalation Aerosol**

**For Oral Inhalation Only**

666  
667  
668 Read this Patient Information before you start to use XOPENEX HFA and each time  
669 you get a refill. There may be new information. This information does not take the  
670 place of talking with your doctor about your medical condition or your treatment.  
671

672 **What is XOPENEX HFA?**

673  
674 XOPENEX HFA is an inhaled prescription medicine used for the treatment or  
675 prevention of asthma in people 4 years of age and older.  
676

677 It is not known if XOPENEX HFA is safe and effective in children younger than 4  
678 years of age.  
679

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

681  
682 **Do not use XOPENEX HFA if you** are allergic to levalbuterol, racemic albuterol or  
683 any of the ingredients in XOPENEX HFA. See the end of this leaflet for a complete  
684 list of ingredients in XOPENEX HFA.  
685

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

687  
688 **Before you use XOPENEX HFA, tell your doctor if you have:**

- 689
- 690 • heart problems
  - 691 • high blood pressure
  - 692 • seizures
  - 693 • diabetes
  - 694 • thyroid problems
  - 695 • any other medical conditions
  - 696 • are pregnant or planning to become pregnant. It is not known if XOPENEX HFA  
697 will harm your unborn baby. Talk to your doctor if you are pregnant or plan to  
698 become pregnant.

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

702 **Tell your doctor about all the medicines you take**, including prescription and  
703 non-prescription medicines, vitamins, and herbal supplements. XOPENEX HFA may  
704 affect the way other medicines work, and other medicines may affect how XOPENEX  
705 HFA works.

706  
707 Especially tell your doctor if you take:

- 708 • other asthma medicines
- 709 • heart medicines
- 710 • medicines that increase urination (diuretics)
- 711 • antidepressants
- 712 • medicine to treat chronic obstructive pulmonary disease (COPD)
- 713 (methylxanthines)

714  
715 Ask your doctor if you are not sure if any of your medicines are the kinds listed  
716 above.

717  
718 Know the medicines you take. Keep a list of them and show it to your doctor and  
719 pharmacist when you get a new medicine.

#### 720 721 **How should I use XOPENEX HFA?**

- 722  
723 • Read the step-by-step Instructions for Using XOPENEX HFA at the end of this  
724 leaflet.
- 725  
726 • Use XOPENEX HFA exactly as your doctor tells you to. **Do not** change your dose  
727 without talking to your doctor first.
- 728  
729 • Your doctor will tell you how many times and when to use your XOPENEX HFA.
- 730 • An adult should help a child use XOPENEX HFA.
- 731 • **Do not use your XOPENEX HFA more often than your doctor tells you to.**
- 732 • **Get medical help right away if XOPENEX HFA:**
  - 733 ○ does not work as well for your asthma symptoms or
  - 734 ○ your asthma symptoms get worse or
  - 735 ○ you need to use your XOPENEX HFA more often than usual
- 736 • If you also use another medicine by inhalation, you should ask your doctor for  
737 instructions on when to use it while you are also using XOPENEX HFA.

#### 738 739 **What are the possible side effects of XOPENEX HFA?**

740  
741 **XOPENEX HFA can cause serious side effects including:**

- 742  
743 • **sudden shortness of breath (bronchospasm).** Sudden shortness of breath  
744 can happen right away after using XOPENEX HFA.
- 745 • **worsening asthma.**

746 • **heart problems.**

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

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

- 751 ○ swelling of the face, throat or tongue
- 752 ○ hives
- 753 ○ rash
- 754 ○ breathing problems

755 • **low potassium levels in your blood.**

756  
757 Call your doctor or go to the nearest hospital emergency room right away if you  
758 have any of the serious side effects listed above or if you have worsening lung  
759 symptoms.

760

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

- 762 • accidental injury
- 763 • bronchitis
- 764 • dizziness
- 765 • pain
- 766 • sore throat
- 767 • runny nose
- 768 • vomiting
- 769 • palpitations
- 770 • chest pain
- 771 • fast heart rate
- 772 • tremors
- 773 • nervousness

774

775 Tell your doctor if you have any side effects that bother you or that do not go away.

776

777

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

780

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

783

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

785

786 • Store XOPENEX HFA between 68°F to 77°F (20°C to 25°C).

787 • Keep XOPENEX HFA inhaler away from heat or open flame.

788 • Keep XOPENEX HFA inhaler away from freezing temperatures and direct  
789 sunlight.

790 • Do not puncture the XOPENEX HFA inhaler.

791 • Store XOPENEX HFA inhaler with the mouthpiece down.

- 792       • The XOPENEX HFA inhaler should be safely thrown away after using:  
793             o 200 actuations for the 15 gram canister.  
794             o 80 actuations for the 8.4 gram canister.  
795       • Do not throw XOPENEX HFA inhaler into a fire or an incinerator.

796

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

798

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

800

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

805

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

810

811

812 For more information, go to [www.XOPENEX.com](http://www.XOPENEX.com).

813

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

815

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

816

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

817

818

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

820

821 Active ingredient: levalbuterol tartrate

822 Inactive ingredients: propellant HFA-134a, Dehydrated Alcohol USP, Oleic Acid NF

823

824

825

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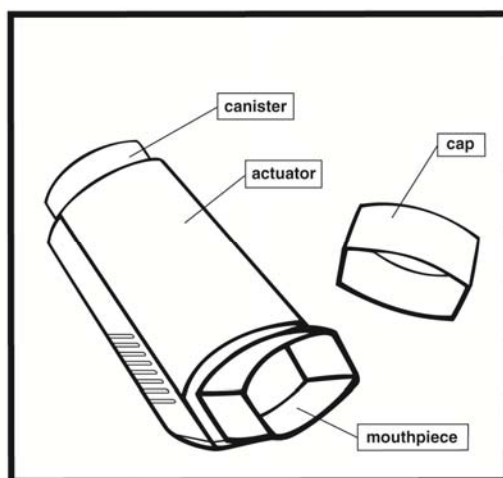
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**Instructions for Using XOPENEX HFA**

843

844

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



845

**Figure 1**

846

847

848

849 **Using your XOPENEX HFA inhaler**

850

• **XOPENEX HFA should be at room temperature before you use it.**

851

• **Priming the inhaler:**

852

Before you use XOPENEX HFA for the first time, you must prime the inhaler so that

853

you will get the right amount of medicine when you use it.

854

- 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.

855

**Avoid spraying in your eyes.** Shake and spray the inhaler like this 3 more times to finish priming it.

856

857

858

- You must prime the inhaler again if you have not used it in more than 3 days.

859

860

- An adult should help a child use XOPENEX HFA.

861

862

**Read the following 6 steps** before using XOPENEX HFA and follow them **before**

863

each use. If you have any questions, ask your doctor or pharmacist.

864

865

**1. Take the cap off the mouthpiece of the actuator** (see [Figure 2](#)).

866

Look inside the mouthpiece for foreign objects, and remove any that you see.

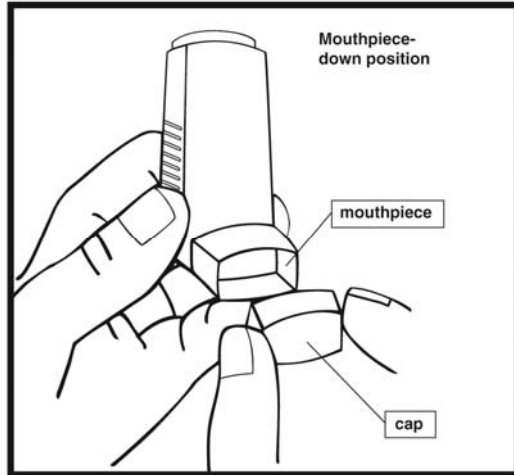
867

Make sure the canister fits firmly in the actuator.

868

**Shake the inhaler well** for 5 seconds.

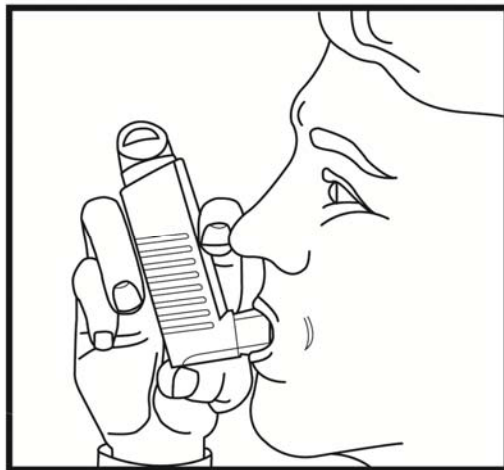
869



**Figure 2**

870  
871  
872  
873  
874  
875  
876

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**

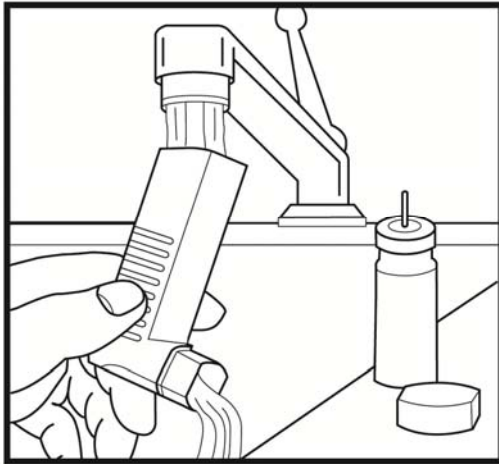
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883  
884

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.

- 885 5. Wait about 1 minute, then shake the inhaler well. Repeat steps 2 through 4.  
886  
887 6. Put the cap back on the mouthpiece after each time you use the XOPENEX HFA.  
888 Make sure the cap snaps firmly into place.  
889

890 **Cleaning your XOPENEX HFA inhaler:**



891  
892 **Figure 4**

893 • **The inhaler may stop working if you do not properly clean the blue**  
894 **plastic actuator (mouthpiece) at least one time a week** (see Figure 4).

895 **To clean the actuator:**

- 896 ○ Remove the canister and red mouthpiece cap. Do not clean the metal  
897 canister or allow the metal canister to become wet.  
898 ○ Wash the actuator through the top and bottom with warm running  
899 water for at least 30 seconds.  
900 ○ Shake the actuator to remove excess water.  
901 ○ Air-dry the actuator completely. Blockage from medicine build-up is  
902 more likely to happen if the actuator is not allowed to air-dry  
903 thoroughly.
- 904 • When the actuator is dry, replace the canister and the mouthpiece cap.  
905 • Make sure the canister is fully and firmly inserted into the actuator.  
906 • If your actuator becomes blocked, it means that little or no medicine is coming  
907 out of the mouthpiece (see [Figure 5](#)). Wash your actuator and air-dry completely as  
908 described above.

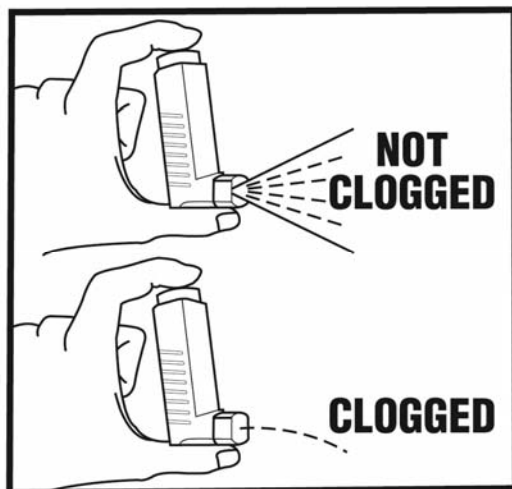


Figure 5

909  
910  
911  
912 • **If you need to use your inhaler before the plastic actuator is completely**  
913 **dry:**

- 914     ○ Shake the excess water off the actuator.  
915     ○ Replace the canister and shake well.  
916     ○ Test-spray twice into the air, away from your face, to remove most of  
917     the water remaining in the actuator.  
918     ○ Take your dose as prescribed.  
919     ○ Rewash the actuator and air-dry it thoroughly as described above.  
920

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

- 922     • Store XOPENEX HFA between 68°F to 77°F (20°C to 25°C).  
923     • Keep XOPENEX HFA inhaler away from heat or open flame.  
924     • Keep XOPENEX HFA inhaler away from freezing temperatures and direct  
925 sunlight.  
926     • Do not puncture the XOPENEX HFA inhaler.  
927     • Store XOPENEX HFA with the mouthpiece down.  
928     • The XOPENEX HFA inhaler should be safely thrown away after using:  
929         ○ 200 actuations for the 15 gram canister.  
930         ○ 80 actuations for the 8.4 gram canister.  
931     • Do not throw your XOPENEX HFA inhaler into a fire or incinerator.

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



933 **SUNOVION**  
934 Manufactured for  
935 **Sunovion Pharmaceuticals Inc.**  
936 Marlborough, MA 01752 USA

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

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

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

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945 Revised Month Year

946 901715R01

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