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 beta$_2$-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*.

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

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Bronchospasm

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

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosages

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

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

2.2 Administration Information

FOR ORAL INHALATION ONLY

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

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

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Paradoxical Bronchospasm

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

5.2 Deterioration of Asthma

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

5.3 Use of Anti-Inflammatory Agents

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

5.4 Cardiovascular Effects

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

5.5 Do Not Exceed Recommended Dose

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

5.6 Immediate Hypersensitivity Reactions

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

5.7 Coexisting Conditions

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

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

5.8 Hypokalemia

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

6 ADVERSE REACTIONS

Use of XOPENEX HFA may be associated with the following:

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

6.1 Clinical Trials Experience

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

Adult and Adolescents 12 Years of Age and Older: Adverse reaction information concerning XOPENEX HFA in adults and adolescents is derived from two 8-week, multicenter, randomized, double-blind, active- and placebo-controlled trials in 748 adult and adolescent patients with asthma that compared XOPENEX HFA, a marketed albuterol HFA inhaler, and an HFA-134a placebo inhaler. Table 1 lists the incidence of 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.

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.

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*

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.

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

6.2 Post-marketing Experience

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

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

7 DRUG INTERACTIONS

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

7.1 Beta-blockers

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

7.2 Diuretics

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

7.3 Digoxin

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

7.4 Monoamine Oxidase Inhibitors or Tricyclic Antidepressants

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

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

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

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

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

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

8.2 Labor and Delivery

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

XOPENEX HFA has not been approved for the management of preterm labor. The benefit:risk ratio when levalbuterol tartrate is administered for tocolysis has not been established. Serious adverse reactions, including maternal pulmonary edema, have been reported during or following treatment of premature labor with $beta_2$-agonists, including racemic albuterol.

8.3 Nursing Mothers

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

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

8.6 Renal Impairment

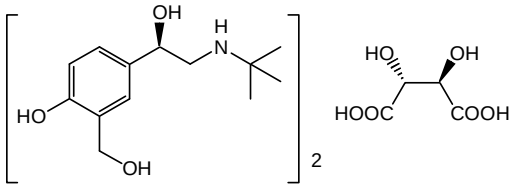
Albuterol is known to be substantially excreted by the kidney, and the risk of toxic reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal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

10 OVERDOSAGE

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

11 DESCRIPTION

The active component of XOPENEX HFA is levalbuterol tartrate, the (R)-enantiomer of albuterol. Levalbuterol tartrate is a relatively selective beta$_2$-adrenergic receptor agonist [see *Clinical Pharmacology (12)*]. Levalbuterol tartrate has the chemical name (R)-α^1-[[(1,1-dimethylethyl)amino]methyl]-4-hydroxy-1,3-benzenedimethanol L-tartrate (2:1 salt), and it has the following chemical structure:



The molecular weight of levalbuterol tartrate is 628.71, and its empirical formula is $(C_{13}H_{21}NO_3)_2 \cdot C_4H_6O_6$. It is a white to light-yellow solid, freely soluble in water and very slightly soluble in ethanol.

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

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Activation of beta$_2$-adrenergic receptors on airway smooth muscle leads to the activation of adenylate cyclase and to an increase in the intracellular concentration of cyclic-3', 5'-adenosine

monophosphate (cyclic AMP). The increase in cyclic AMP is associated with the activation of protein kinase A, which in turn, inhibits the phosphorylation of myosin and lowers intracellular ionic calcium concentrations, resulting in muscle relaxation. Levalbuterol relaxes the smooth muscles of all airways, from the trachea to the terminal bronchioles. Increased cyclic AMP concentrations are also associated with the inhibition of the release of mediators from mast cells in the airways. Levalbuterol acts as a functional antagonist to relax the airway irrespective of the spasmogen involved, thus protecting against all bronchoconstrictor challenges. While it is recognized that beta$_2$-adrenergic receptors are the predominant receptors on bronchial smooth muscle, data indicate that there are beta-receptors in the human heart, 10% to 50% of which are beta$_2$-adrenergic receptors. The precise function of these receptors has not been established [see *Warnings and Precautions (5)*]. However, all beta-adrenergic agonist drugs can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms, and/or electrocardiographic changes.

12.2 Pharmacokinetics

A population pharmacokinetic model was developed using plasma concentrations of (R)-albuterol obtained from 632 asthmatic patients aged 4 to 81 years in three large trials. For adolescent and adult patients 12 years and older, following 90 mcg dose of XOPENEX HFA, yielded mean peak plasma concentrations (C_{max}) and systemic exposure (AUC_{0-6}) of approximately 199 pg/mL and 695 pg•h/mL, respectively, compared to approximately 238 pg/mL and 798 pg•h/mL, respectively, following 180 mcg dose of Racemic Albuterol HFA metered-dose inhaler. For pediatric patients from 4 to 11 years of age, following 90 mcg dose of XOPENEX HFA, yielded C_{max} and AUC_{0-6} of approximately 163 pg/mL and 579 pg•h/mL, respectively, compared to approximately 238 pg/mL and 828 pg•h/mL, respectively, following 180 mcg dose of Racemic Albuterol HFA metered-dose inhaler.

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

Metabolism and Elimination

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

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

Special Populations

Hepatic Impairment

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

Renal Impairment

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

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

13.2 Animal Toxicology and/or Pharmacology

Propellant HFA-134a

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

Embryo-fetal Development

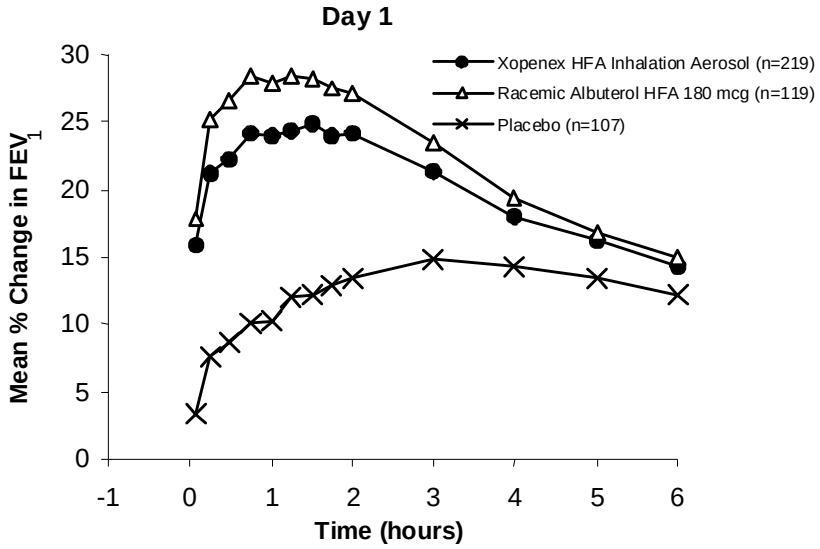
Pregnant mice administered racemic albuterol sulfate subcutaneously resulted in a dose-related increased incidence of cleft palate in their fetuses (4.5% of fetuses at 0.25 mg/kg/day or greater, corresponding to approximately 2 times MRDI dose, 9.3% of fetuses at 2.5 mg/kg/day, approximately 20 times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

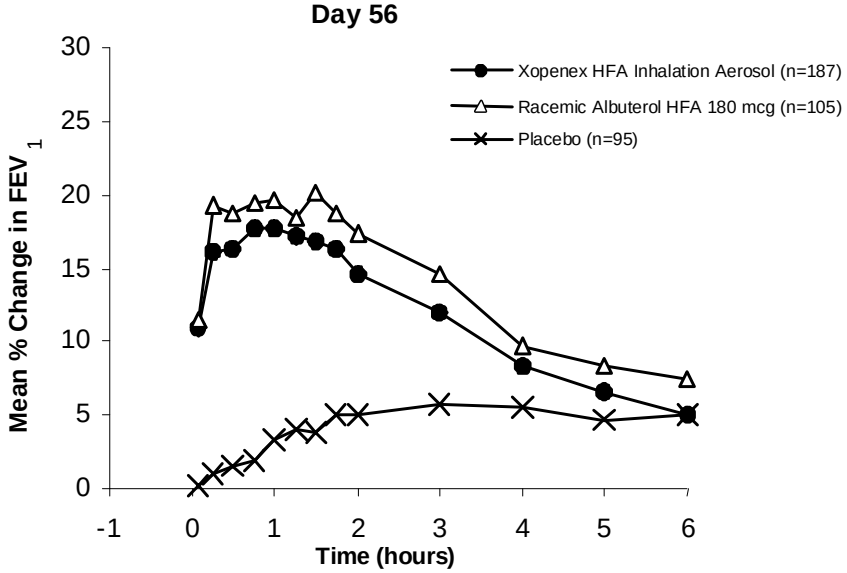
14 CLINICAL STUDIES

14.1 Bronchospasm Associated with Asthma

Adults and Adolescent Patients 12 Years of Age and Older: The efficacy and safety of XOPENEX HFA were established in two 8-week, multicenter, randomized, double-blind, active- and placebo-controlled trials in 748 adults and adolescents with asthma between the ages of 12 and 81 years. In these two trials, XOPENEX HFA (403 patients) was compared to an HFA-134a placebo MDI (166 patients), and the trials included a marketed albuterol HFA-134a MDI (179 patients) as an active control. Serial forced expiratory volume in 1 second (FEV_1) measurements demonstrated that 90 mcg (2 inhalations) of XOPENEX HFA produced significantly greater improvement in FEV_1 over the pretreatment value than placebo. The results from one of the trials are shown in Figure 1 as the mean percent change in FEV_1 from test-day baseline at Day 1 (n=445) and Day 56 (n=387). The results from the second trial were similar.

Figure 1: Percent Change in FEV_1 from Test-Day Baseline in Adults and Adolescents Aged 12 to 81 Years at Day 1 and Day 56





For XOPENEX HFA on Day 1, the median time to onset of a 15% increase in FEV_1 ranged from 5.5 to 10.2 minutes and the median time to peak effect ranged from 76 to 78 minutes. In the responder population, on Day 1 the median duration of effect as measured by a 15% increase in FEV_1 was 3 to 4 hours, with duration of effect in some patients of up to 6 hours.

Pediatric Patients 4 to 11 Years of Age: The efficacy and safety of XOPENEX HFA in children were established in a 4-week, multicenter, randomized, double-blind, active- and placebo-controlled trial in 150 pediatric patients with asthma between the ages of 4 and 11 years. In this trial, XOPENEX HFA (76 patients) was compared to a placebo HFA-134a MDI (35 patients), and the trial included a marketed albuterol HFA-134a MDI (39 patients) as an active control. Serial FEV_1 measurements demonstrated that 90 mcg (2 inhalations) of XOPENEX HFA produced significantly greater improvement in FEV_1 over the pretreatment value than placebo and were consistent with the efficacy findings in the adult studies.

For XOPENEX HFA, on Day 1 the median time to onset of a 15% increase in FEV_1 was 4.5 minutes and the median time to peak effect was 77 minutes. In the responder population, the median duration of effect as measured by a 15% increase in FEV_1 was 3 hours, with a duration of effect in some pediatric patients of up to 6 hours.

16 HOW SUPPLIED/STORAGE AND HANDLING

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

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

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

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

Rx only.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Patient Information and Instructions for Using XOPENEX HFA).

Patients should be given the following information:

17.1 Frequency of Use

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

17.2 Priming, Cleaning and Storage

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

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

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

17.3 Paradoxical Bronchospasm

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

17.4 Concomitant Drug Use

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

17.5 Common Adverse Reactions

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

17.6 Pregnancy

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

17.7 General Information on Use

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

Shake the inhaler well immediately before each use.

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

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

Manufactured for
Sunovion Pharmaceuticals Inc.
Marlborough, MA 01752 USA

For customer service, call 1-888-394-7377.
To report adverse events, call 1-877-737-7226.
For medical information, call 1-800-739-0565.

Month Year
901715R01

PHARMACIST — DETACH HERE AND GIVE LEAFLET TO PATIENT.

PATIENT INFORMATION

XOPENEX HFA® (pronounced zō-pen-eks hfa)
(levalbuterol tartrate)
Inhalation Aerosol

For Oral Inhalation Only

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

What is XOPENEX HFA?

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

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

Who should not use XOPENEX HFA?

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

What should I tell my doctor before using XOPENEX HFA?

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

- heart problems
- high blood pressure
- seizures
- diabetes
- thyroid problems
- any other medical conditions
- are pregnant or planning to become pregnant. It is not known if XOPENEX HFA will harm your unborn baby. Talk to your doctor if you are pregnant or plan to become pregnant.

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

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

Especially tell your doctor if you take:
- other asthma medicines
- heart medicines
- medicines that increase urination (diuretics)
- antidepressants
- medicine to treat chronic obstructive pulmonary disease (COPD) (methylxanthines)

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

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

How should I use XOPENEX HFA?

- Read the step-by-step Instructions for Using XOPENEX HFA at the end of this leaflet.

- Use XOPENEX HFA exactly as your doctor tells you to. **Do not** change your dose without talking to your doctor first.

- Your doctor will tell you how many times and when to use your XOPENEX HFA.
- An adult should help a child use XOPENEX HFA.
- **Do not use your XOPENEX HFA more often than your doctor tells you to.**
- **Get medical help right away if XOPENEX HFA:**
    - does not work as well for your asthma symptoms or
    - your asthma symptoms get worse or
    - you need to use your XOPENEX HFA more often than usual
- If you also use another medicine by inhalation, you should ask your doctor for instructions on when to use it while you are also using XOPENEX HFA.

What are the possible side effects of XOPENEX HFA?

XOPENEX HFA can cause serious side effects including:

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

- **heart problems.**
- **death.** If you use too much XOPENEX HFA you can have heart or lung problems that can lead to death.
- **serious allergic reactions.** Call your doctor and stop using XOPENEX HFA right away if you have any symptoms of an allergic reaction such as:
    - swelling of the face, throat or tongue
    - hives
    - rash
    - breathing problems
- **low potassium levels in your blood.**

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

The most common side effects of XOPENEX HFA include:

- accidental injury
- bronchitis
- dizziness
- pain
- sore throat
- runny nose
- vomiting
- palpitations
- chest pain
- fast heart rate
- tremors
- nervousness

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

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

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

How should I store XOPENEX HFA?

- Store XOPENEX HFA between 68°F to 77°F (20°C to 25°C).
- Keep XOPENEX HFA inhaler away from heat or open flame.
- Keep XOPENEX HFA inhaler away from freezing temperatures and direct sunlight.
- Do not puncture the XOPENEX HFA inhaler.
- Store XOPENEX HFA inhaler with the mouthpiece down.

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

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

General information about the safe and effective use of XOPENEX HFA

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

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

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

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

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

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

What are the ingredients in XOPENEX HFA?

Active ingredient: levalbuterol tartrate
Inactive ingredients: propellant HFA-134a, Dehydrated Alcohol USP, Oleic Acid NF

Instructions for Using XOPENEX HFA

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

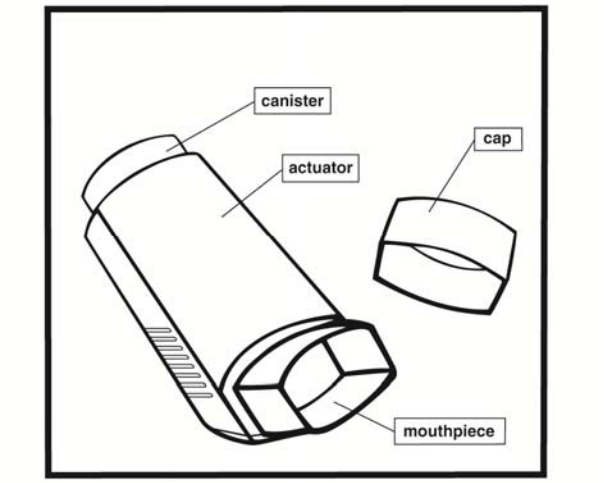


Figure 1

Using your XOPENEX HFA inhaler

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

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.

- 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.

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.

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.

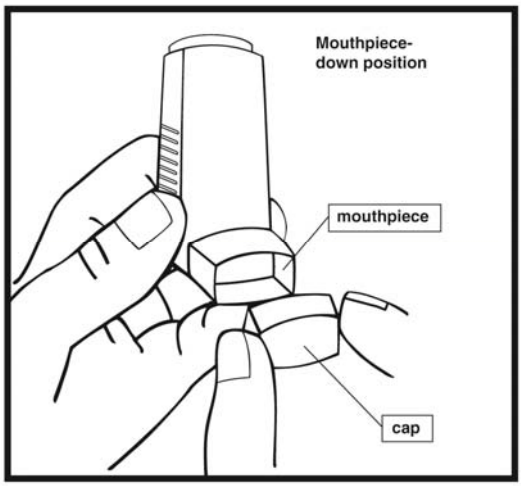


Figure 2

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.

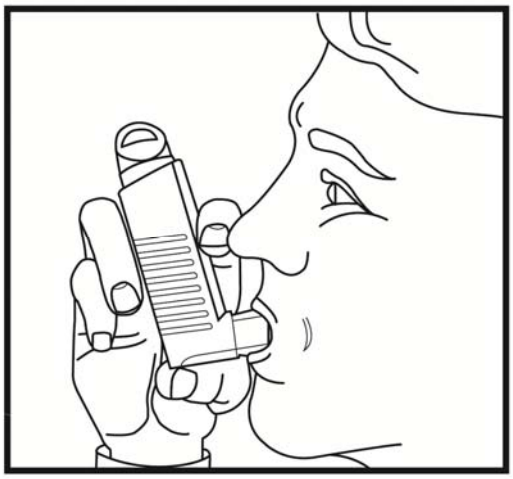


Figure 3

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.

5. Wait about 1 minute, then shake the inhaler well. Repeat steps 2 through 4.

6. Put the cap back on the mouthpiece after each time you use the XOPENEX HFA. Make sure the cap snaps firmly into place.

Cleaning your XOPENEX HFA inhaler:

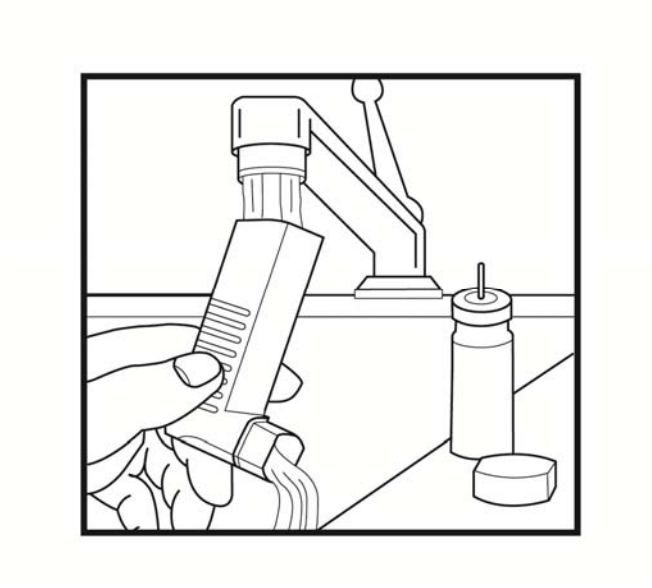


Figure 4

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

- Remove the canister and red mouthpiece cap. Do not clean the metal canister or allow the metal canister to become wet.
- Wash the actuator through the top and bottom with warm running water for at least 30 seconds.
- Shake the actuator to remove excess water.
- Air-dry the actuator completely. Blockage from medicine build-up is more likely to happen if the actuator is not allowed to air-dry thoroughly.

• When the actuator is dry, replace the canister and the mouthpiece cap.
• Make sure the canister is fully and firmly inserted into the actuator.
• If your actuator becomes blocked, it means that little or no medicine is coming out of the mouthpiece (see Figure 5). Wash your actuator and air-dry completely as described above.

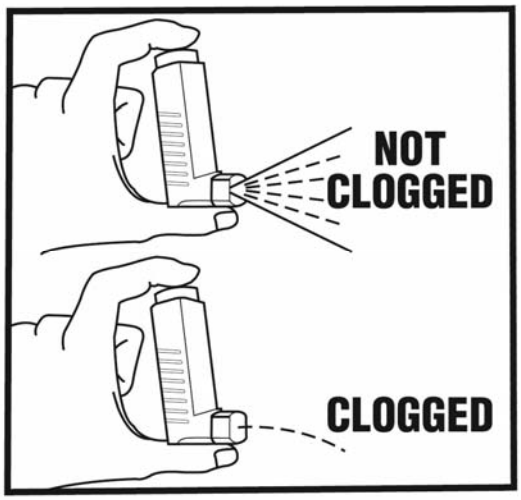


Figure 5

• If you need to use your inhaler before the plastic actuator is completely dry:

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

How should I store XOPENEX HFA?

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

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

SUNOVION

Manufactured for
Sunovion Pharmaceuticals Inc.
Marlborough, MA 01752 USA

For customer service, call 1-888-394-7377.
To report adverse events, call 1-877-737-7226.
For medical information, call 1-800-739-0565.

Revised Month Year
901715R01