

# Xopenex HFA™ (levalbuterol tartrate) Inhalation Aerosol

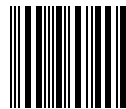
For Oral Inhalation Only

PHARMACIST-DETACH HERE  
AND GIVE INSTRUCTIONS  
TO PATIENT.

# Xopenex HFA™ (levalbuterol tartrate) Inhalation Aerosol

For Oral Inhalation Only

## PRESCRIBING INFORMATION



632700

## PATIENT'S INSTRUCTIONS FOR USE



632700

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

### ABOUT XOPENEX HFA INHALATION AEROSOL

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

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

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

### HOW TO USE YOUR XOPENEX HFA INHALATION AEROSOL

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

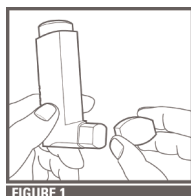


FIGURE 1

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

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

4. **WHILE BREATHING IN DEEPLY AND SLOWLY THROUGH YOUR MOUTH, FULLY DEPRESS THE TOP OF THE METAL CANISTER** with your middle finger as shown in Figure 2.



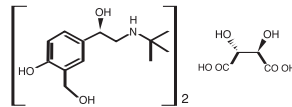
FIGURE 2

- Immediately after the puff is delivered, release your finger from the canister and remove the inhaler from your mouth.
5. **HOLD YOUR BREATH FOR 10 SECONDS, IF POSSIBLE.**
6. If your doctor has prescribed more than a single inhalation/puff, wait 1 minute between inhalations. Then, **SHAKE THE INHALER WELL** and repeat steps 3 through 5.
7. **REPLACE THE CAP ON THE MOUTHPIECE AFTER EACH USE.**

8. **CLEAN THE ACTUATOR OR MOUTHPIECE AT LEAST ONCE A WEEK.** See **CLEANING YOUR XOPENEX HFA INHALATION AEROSOL** for cleaning instructions.
9. **DISCARD THE CANISTER AFTER YOU HAVE USED 200 INHALATIONS.** The correct amount of medicine in each inhalation cannot be assured after 200 sprays, even though the canister is not completely empty. Never immerse the canister in water to determine how full the canister is ("float test"). Before you reach 200 sprays, you should consult your doctor to determine whether a refill is needed. Just as you should not take extra doses without consulting your doctor, you also should not stop using XOPENEX HFA Inhalation Aerosol without consulting your doctor.

### DESCRIPTION

The active component of XOPENEX HFA (levalbuterol tartrate) Inhalation Aerosol is levalbuterol tartrate, the (R)-enantiomer of albuterol. Levalbuterol tartrate is a relatively selective beta<sub>2</sub>-adrenergic receptor agonist (see **CLINICAL PHARMACOLOGY**). Levalbuterol tartrate has the chemical name (R)-α<sup>1</sup>-[[[1,1-dimethylethylamino)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<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 slightly soluble in ethanol.

NO PRINTING

Levalbuterol tartrate is the generic name for (R)-albuterol tartrate in the United States. XOPENEX HFA Inhalation Aerosol 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).

This product does not contain chlorofluorocarbons (CFCs).

### CLINICAL PHARMACOLOGY

**Mechanism of Action:** Activation of beta<sub>2</sub>-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<sub>2</sub>-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<sub>2</sub>-adrenergic receptors. The precise function of these receptors has not been established (see **WARNINGS**). 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.

### Preclinical

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

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

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

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

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<sub>max</sub>) and mean residence time are both extremely short, leading to a transient appearance of HFA-134a in the blood with no evidence of accumulation.

### Pharmacokinetics

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

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 Inhalation Aerosol 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.

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

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

### 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 Inhalation Aerosol 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 Inhalation Aerosol to patients with renal impairment.

### Clinical Trials

**Adults and Adolescents:** The efficacy and safety of XOPENEX HFA Inhalation Aerosol 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 Inhalation Aerosol (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<sub>1</sub>) measurements demonstrated that 90 mcg (2 inhalations) of XOPENEX HFA Inhalation Aerosol produced significantly greater improvement in FEV<sub>1</sub> 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<sub>1</sub> from test-day baseline at Day 1 (n=445) and Day 56 (n=387). The results from the second trial were similar.

For XOPENEX HFA Inhalation Aerosol on Day 1, the median time to onset of a 15% increase in FEV<sub>1</sub> 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<sub>1</sub> was 3 to 4 hours, with duration of effect in some patients of up to 6 hours.

**Pediatrics:** The efficacy and safety of XOPENEX HFA Inhalation Aerosol 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 Inhalation Aerosol (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<sub>1</sub> measurements demonstrated that 90 mcg (2 inhalations) of XOPENEX HFA Inhalation Aerosol produced significantly greater improvement in FEV<sub>1</sub> over the pretreatment value than placebo and were consistent with the efficacy findings in the adult studies.

For XOPENEX HFA Inhalation Aerosol, on Day 1 the median time to onset of a 15% increase in FEV<sub>1</sub> 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<sub>1</sub> was 3 hours, with a duration of effect in some pediatric patients of up to 6 hours.

### INDICATIONS AND USAGE

XOPENEX HFA (levalbuterol tartrate) Inhalation Aerosol 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.

### CONTRAINDICATIONS

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

### WARNINGS

1. **Paradoxical Bronchospasm:** Like other inhaled beta-adrenergic agonists, XOPENEX HFA Inhalation Aerosol can produce paradoxical bronchospasm, which may be life-threatening. If paradoxical bronchospasm occurs, XOPENEX HFA (levalbuterol tartrate) Inhalation Aerosol should be discontinued immediately and alternative therapy instituted. It should be recognized that paradoxical bronchospasm, when associated with inhaled formulations, frequently occurs with the first use of a new canister.
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 Inhalation Aerosol 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.
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.
4. **Cardiovascular Effects:** XOPENEX HFA Inhalation Aerosol, like other beta-adrenergic agonists, can produce clinically significant cardiovascular effects in some patients, as measured by heart rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of XOPENEX HFA Inhalation Aerosol at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce 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 Inhalation Aerosol, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.
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.
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 Inhalation Aerosol.

### PRECAUTIONS

#### General

XOPENEX HFA (levalbuterol tartrate) Inhalation Aerosol, 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. As with other beta-adrenergic agonist medications, XOPENEX HFA Inhalation Aerosol 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.

#### Information for Patients

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

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

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

NO PRINTING

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

