XOPENEX HFA- levalbuterol tartrate aerosol, metered
Praxis, LLC

XOPENEX HFA ®(levalbuterol tartrate) inhalation aerosol, for oral inhalation use

8 USE IN SPECIFIC POPULATIONS

8.1 PREGNANCY

Risk Summary

There are no adequate and well-controlled studies of XOPENEX HFA in pregnant women. There are clinical considerations with the use of XOPENEX HFA in pregnant women *[see Clinical Considerations]*

Following oral administration of levalbuterol HCl to pregnant rabbits, there was no evidence of teratogenicity at doses up to 25 mg/kg/day [approximately 750 times the maximum recommended human daily inhalation dose (MRHDID) of levalbuterol tartrate for adults on a mg/m ^{2}basis]; however, racemic albuterol sulfate was teratogenic in mice (cleft palate) and rabbits (cranioschisis) at doses slightly higher than the human therapeutic range (*see Data*)

The estimated background risk of major birth defects and miscarriage for the indicated population(s) are unknown. In the U.S. general population, the estimated risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

In women with poorly or moderately controlled asthma, there is an increased risk of preeclampsia in the mother and prematurity, low birth weight, and small for gestational age in the neonate. Pregnant women should be closely monitored and medication adjusted as necessary to maintain optimal control

Labor or 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

Data

Animal Data

The oral administration of levalbuterol HCl to pregnant New Zealand White rabbits during

the period of organogenesis found no evidence of teratogenicity at doses up to 25 mg/kg/day (approximately 750 times the MRHDID of levalbuterol tartrate for adults on a mg/m ^{2}basis). In a rat developmental study, a racemic albuterol sulfate (comprising approximately 50% levalbuterol)/HFA-134a formulation administered by inhalation did not produce any teratogenic effects at exposures approximately 160 times the MRHDID (on a mg/m ^{2}basis at a maternal dose of 10.5 mg/kg)

However, other developmental studies with the racemic albuterol sulfate, did result in teratogenic effects in mice and rabbits at doses slightly higher than the human therapeutic range. In a rabbit development study, orally administered albuterol sulfate induced cranioschisis in 7 of 19 fetuses (37%) at approximately 1500 times the MRHDID (on a mg/m ^{2}basis at a maternal dose of 50 mg/kg). In a mouse developmental study, subcutaneously administered albuterol sulfate produced cleft palate formation in 5 of 111 (4.5%) fetuses at an exposure approximately 2 times MRHDID for adults (on a mg/m ^{2}basis at a maternal dose of 0.25 mg/kg/day) and in 10 of 108 (9.3%) fetuses at approximately 20 times MRHDID (on a mg/m ^{2}basis at a maternal dose of 2.5 mg/kg/day). Similar effects were not observed at approximately 0.2 times MRHDID of levalbuterol tartrate for adults on a mg/m ^{2}basis (i.e., less than the therapeutic dose). Cleft palate also occurred in 22 of 72 (30.5%) fetuses from females treated subcutaneously with isoproterenol (positive control)

8.2 Lactation

Risk Summary

There are no available data on the presence of levalbuterol in human milk, the effects on the breastfed child, or the effects on milk production

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for XOPENEX HFA and any potential adverse effects on the breastfed child from XOPENEX HFA or from the underlying maternal condition

8.4 PEDIATRIC USE

Pediatric Patients 4 Years of Age and Older

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 *Adverse Reactions (6)*and *Clinical Studies (14)*]

Pediatric Patients less than 4 Years of Age

XOPENEX HFA is not indicated for pediatric patients less than 4 years of age. A clinical trial in pediatric patients below the age of 4 years showed no statistical significant difference between treatment groups in the primary efficacy endpoint. There was an increased incidence of asthma-related adverse reactions reported in pediatric patients below the age of 4 years treated with XOPENEX HFA compared to placebo

XOPENEX HFA was evaluated in one 4-week, multicenter, randomized, modified-blind, placebo-controlled, parallel group trial of 196 pediatric patients ages birth to <4 years of age with asthma or reactive airway disease (68 patients birth to <2 years of age and 128 patients 2 to <4 years of age). XOPENEX HFA 45 mcg (N=23), XOPENEX HFA 90 mcg (N=42), levalbuterol inhalation solution 0.31 mg (N=63), and placebo HFA (N=68) were administered three times daily. XOPENEX HFA or placebo HFA was delivered with

the Monaghan AeroChamber MAX™ Valved Holding Chamber with mask. The primary efficacy endpoint was the mean change in Pediatric Asthma Caregiver Assessment (PACA) total score from baseline over the 4 week treatment period. There was no statistical difference in the change in PACA total score between XOPENEX HFA and placebo. Regarding safety, an increased number of treatment-emergent asthma-related adverse reactions were reported in XOPENEX HFA-treated patients. Eight subjects reported asthma-related adverse reactions for XOPENEX HFA compared to 3 subjects for placebo. There was one subject that discontinued treatment due to asthma in the XOPENEX HFA group compared to zero subjects in the placebo group (Table 3). Other adverse reactions were consistent with those observed in the clinical trial population of patients 4 years of age and older *[see Adverse Reactions (6.1)]*

Table 3: Asthma-related Adverse Reactions in a 4-Week Clinical Trial in Children Birth to <4 Years of Age *

	XOPENEX HFA 45-90 mcg (n=65)	Levalbuterol inhalation solution 0.31 mg (n=63)	Placebo (n=68)
Asthma-related adverse reactions*, n (%)	8 (12%)	6 (10%)	3 (4%)
Treatment discontinuations due to asthma, n (%)	1 (2%)	2 (3%)	0

*This table includes the following Preferred Terms (whether considered by the investigator to be related or unrelated to drug): asthma, cough, hypoxia, status asthmaticus, tachypnea

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

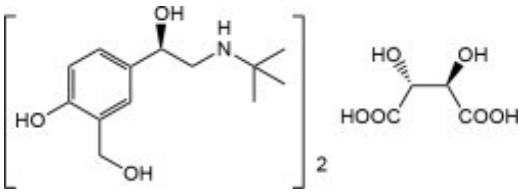
10 OVERDOSAGE

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 (6)*, 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 inhalation aerosol 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 inhalation aerosol is a pressurized metered-dose aerosol inhaler (MDI) fitted with a dose indicator, 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

After priming with 4 actuations, each actuation of the inhaler delivers 67.8 mcg of levalbuterol tartrate (equivalent to 51.6 mcg of levalbuterol free base) from the valve and 59 mcg of levalbuterol tartrate (equivalent to 45 mcg of levalbuterol free base) from the actuator mouthpiece. Each 15 g canister provides 200 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

12.3 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*(8.6)]

13 NONCLINICAL TOXICOLOGY

13.1 CARCINOGENESIS & MUTAGENESIS & IMPAIRMENT OF FERTILITY

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 MRHDID) of levalbuterol tartrate for adults and approximately 15 times the MRHDID 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 MRHDID of levalbuterol tartrate for adults and approximately 1800 times the MRHDID 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 MRHDID of levalbuterol tartrate for adults on a mg/m ^{2}basis and approximately 240 times the MRHDID of levalbuterol tartrate for children on a mg/m ^{2}basis)

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

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 MRHDID of levalbuterol tartrate for adults on a mg/m ^{2}basis)

13.2 ANIMAL PHARMACOLOGY & OR TOXICOLOGY

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

14 CLINICAL STUDIES

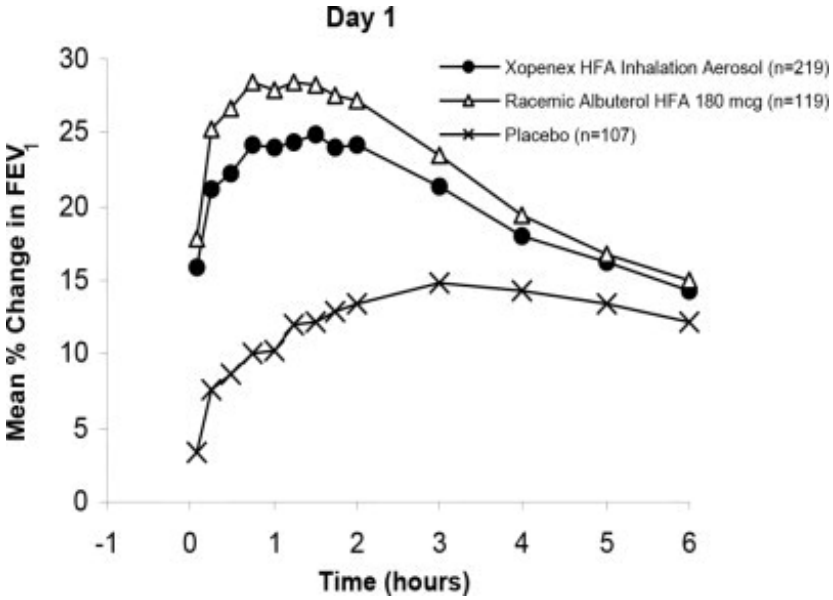
14.1 Bronchospasm Associated with Asthma

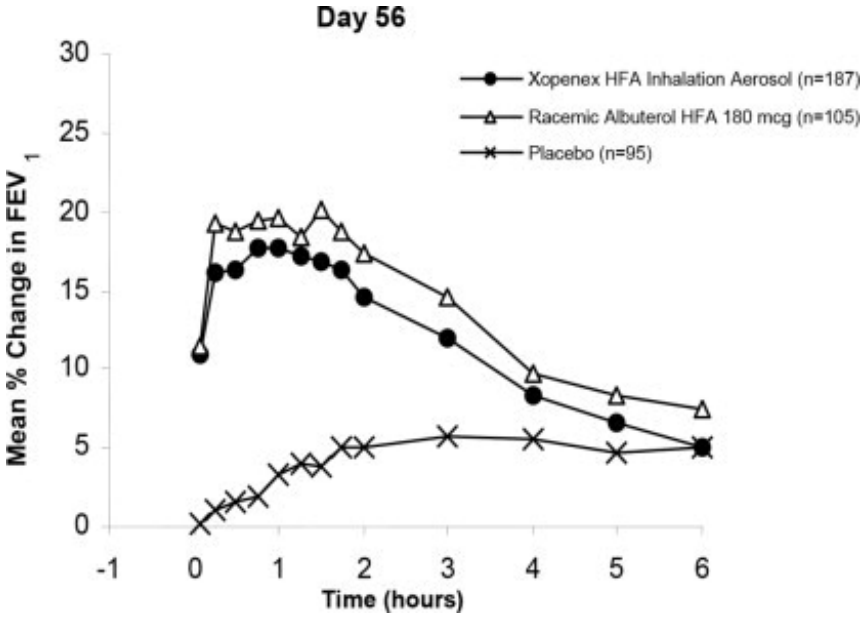
Adults and Adolescent Patients 12 Years of Age and Older

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_1over 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 inhalation aerosol is supplied as a pressurized aluminum canister in a box:

- NDC 27437-056-01: Canister labeled with a net weight of 15 grams containing 200 metered actuations (or inhalations)

Each canister is fitted with a dose indicator and is supplied with a blue plastic actuator 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 mouthpiece down

Contents under pressure

Do not puncture or incinerate. Do not store near heat or open flame. Exposure to temperatures above 120°F may cause bursting. Never throw container into fire or incinerator. 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, even though the canister is not completely empty. When the dose indicator display window shows a red zone, approximately 20 inhalations are left, and a refill is required. The canister should be discarded when the dose indicator display window shows zero, indicating that 200 actuations have been used

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the **FDA-approved patient labeling**(Patient Information and Instructions for Use)

Patients should be given the following information:

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

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

Paradoxical Bronchospasm

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

Concomitant Drug Use

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

Common Adverse Reactions

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

Pregnancy

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

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. When the dose indicator display window shows a red zone, approximately 20 inhalations are left, and a refill is required. Discard the inhaler when the dose indicator display window shows zero, indicating that 200 sprays have been used. 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 [advise the patient to read the **FDA-approved patient labeling**–(Patient Information and Instructions for Use)]

LUPIN ®

Manufactured for and Distributed by:

Lupin Pharmaceuticals, Inc.

Baltimore, MD 21202

To report adverse events, call 1-800-399-2561.

For patent information: https://www.lupin.com/US/specialty/patent-information/

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SPL PATIENT PACKAGE INSERT

PATIENT INFORMATION
XOPENEX HFA ®
(zō-pen-eks hfa)

(levalbuterol tartrate)
inhalation aerosol, for oral inhalation use

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.
- XOPENEX HFA has not been shown to be safe and effective in children younger than 4 years of age.

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 Patient Information leaflet for a complete list of ingredients in XOPENEX HFA.

Before you use XOPENEX HFA, tell your doctor about all of your medical conditions, including if you:

- have heart problems.
- have high blood pressure.
- have seizures.
- have diabetes.
- have thyroid problems.
- are pregnant or plan 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. Talk to your doctor about the best way to feed your baby if you use XOPENEX HFA..

Tell your doctor about all the medicines you take, including prescription and over-the-counter 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 inhaled medicines or asthma medicines
- heart medicines
- medicines that increase urination (diuretics)
- antidepressants
- medicine to treat chronic obstructive pulmonary disease (COPD). Ask your doctor or pharmacist for a list of these medicines if you are not sure..

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

How should I use XOPENEX HFA?

- **Read the step-by-step Instructions for Use for XOPENEX HFA at the end of this Patient Information leaflet.**
- **XOPENEX HFA is for oral inhalation use only.**
- **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. Your doctor should show you how your child should 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:**

o **does not work as well for your asthma symptoms**
o **your asthma symptoms get worse**
o **you need to use XOPENEX HFA more often than usual**

- **While you are using XOPENEX HFA, do not use other inhaled medicines and asthma medicines unless your doctor tells you to.**

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:**

o swelling of the face, throat or tongue
o hives
o rash
o 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

These are not all the possible side effects of XOPENEX HFA.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.
You may also report side effects to Lupin Pharmaceuticals, Inc. at 1-800-399-2561.

How should I store XOPENEX HFA?

- Store XOPENEX HFA at room temperature between 68°F to 77°F (20°C to 25°C).
- Do not use or store XOPENEX HFA inhaler near heat or open flame. Temperatures above 120°F may cause the canister to burst.
- Do not freeze XOPENEX HFA.
- Keep XOPENEX HFA out of direct sunlight.
- Do not put a hole in the XOPENEX HFA canister.

- Store XOPENEX HFA with the mouthpiece down.
- Throw away XOPENEX HFA when the dose indicator display window reaches zero "0", showing that all 200 sprays (actuations) have been used.
- Do not throw XOPENEX HFA 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

You can ask your pharmacist or doctor for information about XOPENEX HFA that is written for health professionals

What are the ingredients in XOPENEX HFA?

Active ingredient: levalbuterol tartrate

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

INSTRUCTIONS FOR USE SECTION

XOPENEX HFA ®

(zō-pen-eks hfa)

(levalbuterol tartrate)

inhalation aerosol, for oral inhalation use

Important Information:

- **For oral inhalation use only**
- **Use XOPENEX HFA exactly as your doctor tells you to.**
- If you have any questions about the use of your inhaler, ask your doctor or pharmacist

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

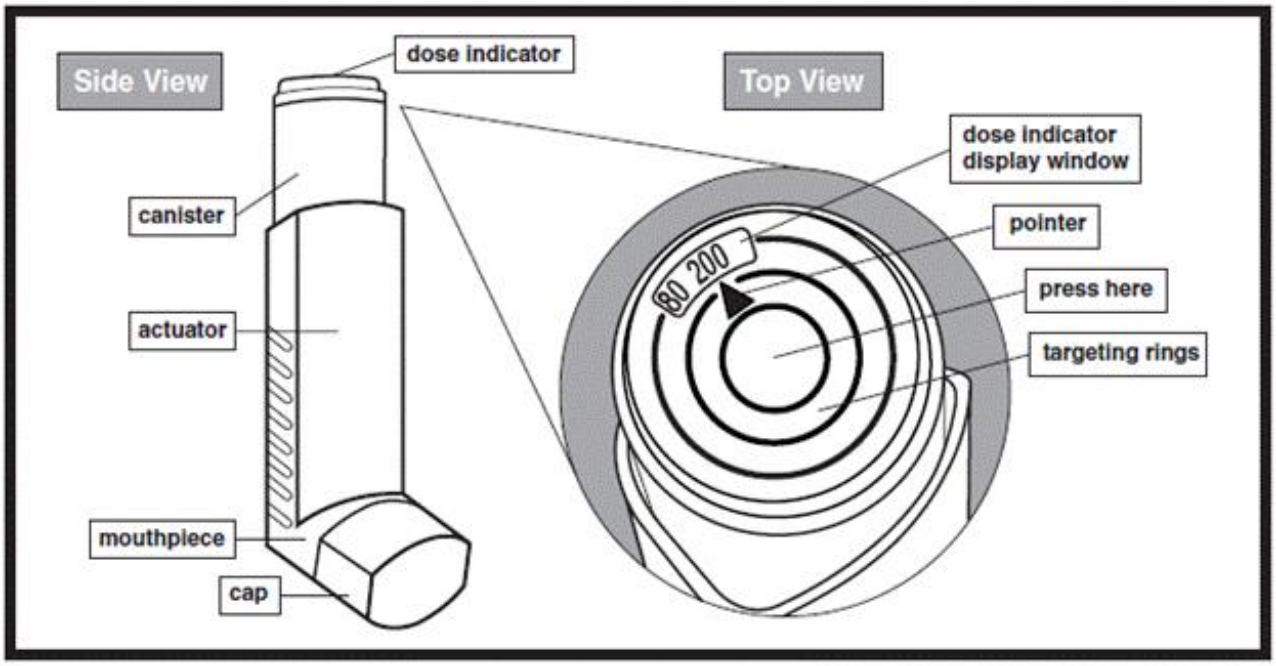

Figure 1

- XOPENEX HFA comes as a canister that fits into an actuator with a dose indicator.
  - **Do not**use the XOPENEX HFA actuator with a canister of medicine from any other inhaler
  - **Do not**use the XOPENEX HFA canister with an actuator from any other inhaler
- The dose indicator display window will show you how many sprays of medicine you have left in your inhaler. A spray of medicine is released each time you press down on the center of the dose indicator
- It is important that you pay attention to the number of sprays left in your XOPENEX HFA inhaler by reading the dose indicator. You should also keep track of the number of sprays used from your inhaler

Each canister of XOPENEX HFA contains enough medicine for you to spray your medicine 200 times (See Figure 2a)

- The pointer will be pointing between 180 and 200 after you take 10 sprays. This means that there are 190 sprays of medicine left in the canister (**See Figure 2b**)
- The pointer will be pointing to 180 after you take 10 more sprays. This means that there are 180 sprays of medicine left in the canister (**See Figure 2c**)

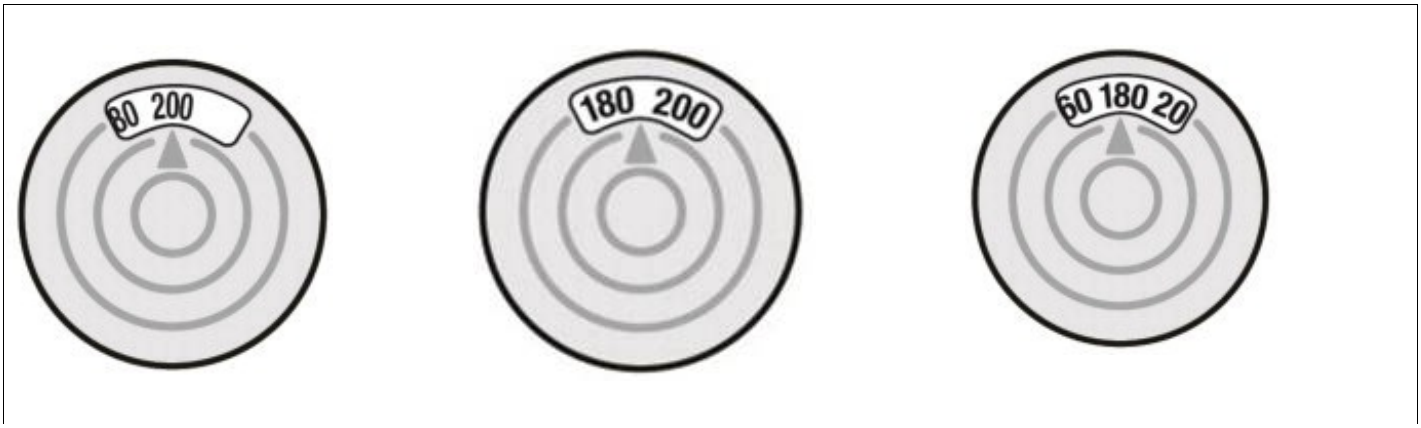

Figure 2a	**Figure 2b**	**Figure 2c**
200 sprays	190 sprays	180 sprays

- The dose indicator display window will continue to move after every 10 sprays. The number on the dose indicator display window will continue to change after every 20 sprays

Figure 2d

- The dose indicator display window will change to red, as shown in the shaded area, when there are only 20 sprays of medicine left in your inhaler (See **Figure 2d**). You should refill your prescription or ask your doctor if you need another prescription for XOPENEX HFA
- When the number in the dose indicator display window reaches zero "0", this means that 200 sprays of medicine have been used. Throw away your XOPENEX HFA inhaler

Note: Do notplace the canister under water to find out the amount of medicine left in the canister

Preparing your XOPENEX HFA inhaler for use:

- Your XOPENEX HFA inhaler should be at room temperature before you use it
- **Shake the inhaler well before each use.**

Priming your XOPENEX HFA inhaler:

Before you use XOPENEX HFA for the first time or if you have not taken your medicine for 3 days in a row, you must prime the inhaler.

- Look at the dose indicator on top of the inhaler. Make sure that the pointer on the dose indicator is pointing to the "200" inhalation mark before you use your XOPENEX HFA inhaler for the first time
- Take the cap off the mouthpiece of the actuator (**See Figure 3**). Check inside the mouthpiece for objects before use

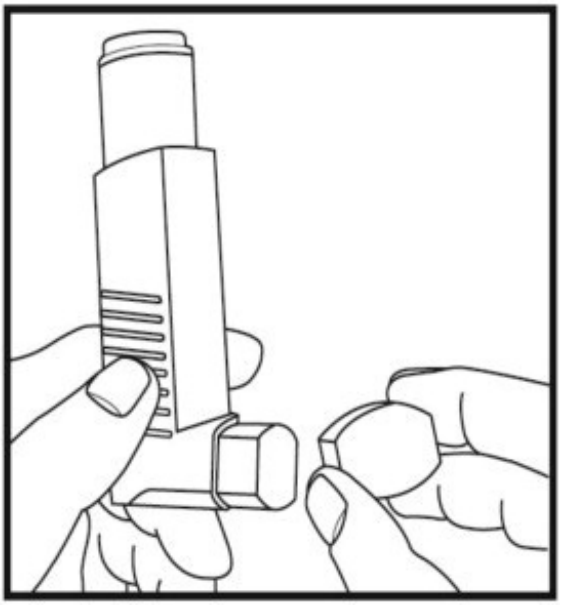

Figure 3

- Hold the inhaler in the upright position away from the face and shake the inhaler well (**See Figure 4**)

Figure 4

- Press down fully on the center of the dose indicator to release a spray of medicine from the mouthpiece (**See Figure 5**). You may hear a soft click from the dose indicator as it counts down during use

Figure 5

- **Avoid spraying in your eyes**
- Repeat the priming **steps 3 more times**(**See Figure 4 and Figure 5**) to finish priming the inhaler
- After priming 4 times the first time you use your XOPENEX HFA inhaler, the dose indicator should be pointing to "200" and your inhaler is now ready to use

If you do not use your XOPENEX HFA inhaler for more than 3 days, you will need to prime the inhaler again before use

Using your XOPENEX HFA inhaler:

Step 1: Take the cap off the mouthpiece of the actuator(**See Figure 3**). Check inside the mouthpiece for objects. Make sure the canister fits firmly in the actuator

Step 2: Shake the inhaler well for 5 secondsbefore use

Step 3: Hold the inhaler upright with the mouthpiece pointing towards you. **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 (**See Figure 6**)

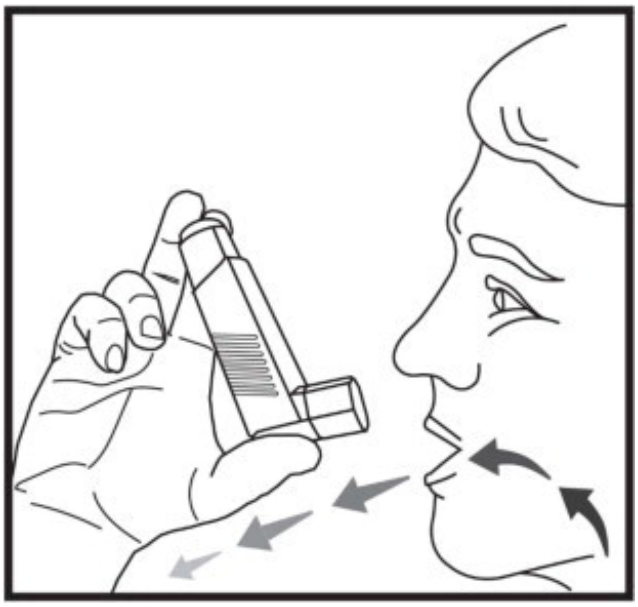

Figure 6

Step 4: Put the mouthpiece in your mouth and close your lips around it

Figure 7

Step 5: While breathing in deeply and slowly, press down on the center of the targeting rings (**See Figure 7**) until a spray of medicine has been released. Then stop pressing the dose indicator

Step 6: When you have finished breathing in, remove the mouthpiece from your mouth. Close your mouth and hold your breath for 10 seconds if possible. Then breathe out gently

Step 7: Wait about 1 minute, then shake the inhaler well. **Repeat steps 3 through 6**to take your second spray of XOPENEX HFA

Step 8: Put the cap back on the mouthpiece right away after use

Make sure the cap snaps firmly into place

Cleaning your XOPENEX HFA inhaler:

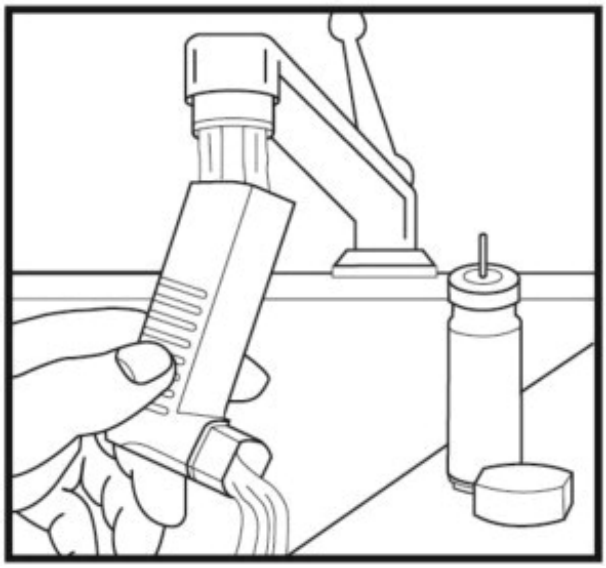

Figure 8

Clean the inhaler 1 time each week. It is very important to keep the actuator clean so that medicine will not build up and block the spray from the mouthpiece (**See Figure 8**)

To clean the actuator:

Step 1: Take the canister out of the actuator (**See Figure 9**). **Do not**clean the canister or let it get wet

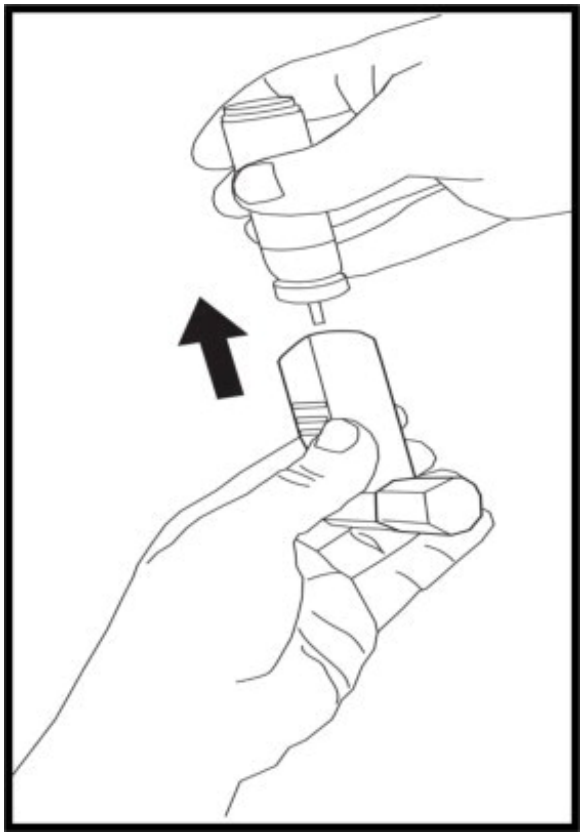

Figure 9

Step 2: Take the cap off the mouthpiece

Step 3: Hold the actuator under the faucet and run warm water through it for at least 30 seconds. Turn the actuator upside down and rinse the actuator again through the mouthpiece for at least 30 seconds (**See Figure 10**)

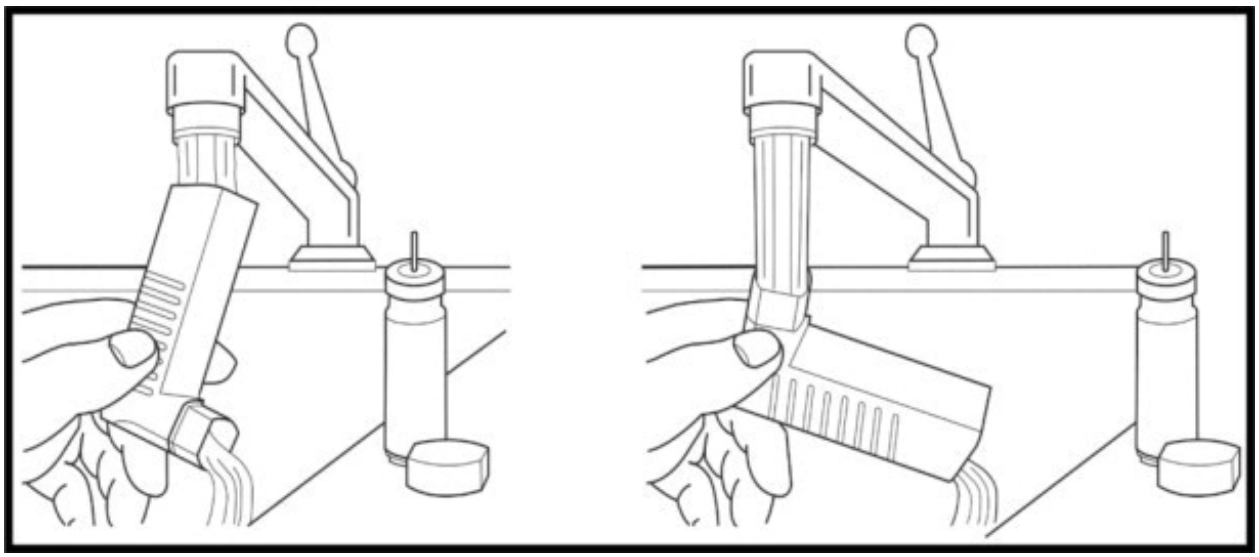

Figure 10

Step 4: Shake off as much water from the actuator as you can

Step 5: Look inside the actuator and mouthpiece to make sure any medicine build-up has been completely washed away. Medicine build-up is more likely to happen if the actuator is not allowed to air-dry completely

Step 6: Let the actuator air-dry overnight. **Do not**put the canister back into the actuator if it is still wet

Step 7: When the actuator is dry, put the canister back in the actuator and put the cap back on the mouthpiece. Make sure to firmly press the canister down in the actuator

Note: If your actuator becomes blocked, it means that little or no medicine is coming out of the mouthpiece (**See Figure 11**). **Repeat Steps 1 through 7**above in the section "**To clean the actuator**"

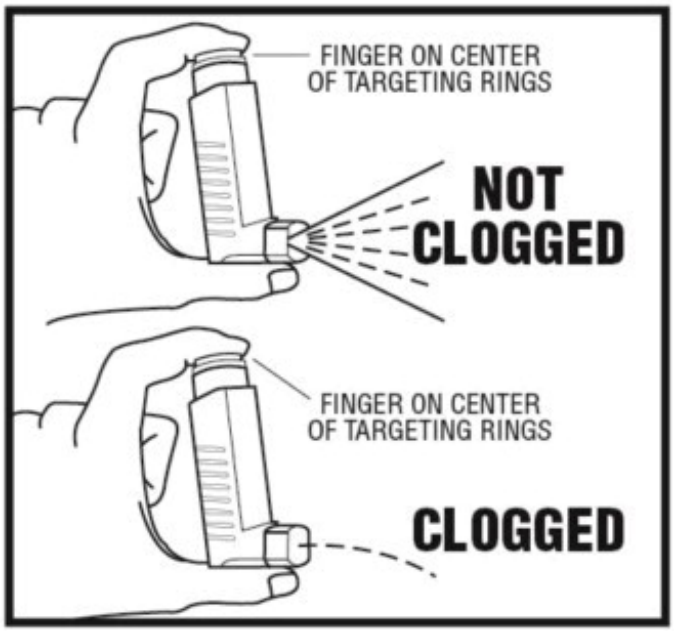

Figure 11

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

- Shake off as much water from the actuator as you can
- Put the canister back into the actuator and shake the inhaler well
- To remove most of the water from your inhaler, press down on the center of the targeting rings 2 times to release a total of 2 sprays into the air away from your face
- Take your prescribed dose of medicine
- **Repeat Steps 1 through 7**above in the section "**To clean the actuator"**

How should I store XOPENEX HFA?

- Store XOPENEX HFA at room temperature between 68°F to 77°F (20°C to 25°C)
- Do not use or store XOPENEX HFA inhaler near heat or open flame. Temperatures above 120°F may cause the canister to burst
- Do not freeze XOPENEX HFA
- Keep XOPENEX HFA out of direct sunlight
- Do not put a hole in the XOPENEX HFA canister
- Store XOPENEX HFA with the mouthpiece down

- Throw away XOPENEX HFA when the dose indicator display window reaches zero "0", showing that all 200 sprays (actuations) have been used
- Do not throw XOPENEX HFA into a fire or incinerator

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

This Patient Information and Instructions for Use has been approved by the U.S. Food and Drug Administration.

LUPIN ®

Manufactured for and Distributed by:

Lupin Pharmaceuticals, Inc.

Baltimore, MD 21202

To report adverse events, call 1-800-399-2561.

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Revised July 2023

901715R03

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

PRINCIPAL DISPLAY PANEL – TRADE CARTON - 45 MCG 200 ACTUATIONS

NDC 27437-056-01 Net Contents: 15g

Xopenex HFA ®

(levalbuterol tartrate)

Inhalation Aerosol

45 mcg/actuation

200 Metered Inhalations

FOR ORAL INHALATION WITH Xopenex HFA ®ACTUATOR ONLY

Shake well before using.

Rx only

LUPIN ®

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

PRINCIPAL DISPLAY PANEL – TRADE CARTON - 45 MCG 200 ACTUATIONS

NDC 27437-056-01 Net Contents: 15g

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(levalbuterol tartrate)

Inhalation Aerosol

45 mcg/actuation

200 Metered Inhalations

FOR ORAL INHALATION WITH Xopenex HFA ®ACTUATOR ONLY

Shake well before using.

Rx only

LUPIN ®

XOPENEX HFA

levalbuterol tartrate aerosol, metered

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:59368-411
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
LEVALBUTEROL TARTRATE (UNII: ADS4I3E22M) (LEVALBUTEROL -	LEVALBUTEROL	45 ug

UNII:EDN2NBH5SS)	LEVALBUTEROL	45 ug

Inactive Ingredients

Ingredient Name	Strength
ALCOHOL (UNII: 3K9958V90M)	
NORFLURANE (UNII: DH9E53K1Y8)	
OLEIC ACID (UNII: 2UMI9U37CP)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:59368-411-01	1 in 1 CARTON	11/10/2023	
1		200 in 1 INHALER; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA021730	11/10/2023	

Labeler - Praxis, LLC (016329513)

Establishment

Name	Address	ID/FEI	Business Operations
Praxis, LLC		016329513	manufacture(59368-411) , label(59368-411) , pack(59368-411)

Revised: 1/2023 Praxis, LLC