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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
The recommended dosage of XOPENEX HFA for adults and children 4 years of age and older is 2 inhalations (90 mcg of levalbuterol free base) repeated every 4 to 6 hours; in some patients, 1 inhalation every 4 hours may be sufficient. (2.1)

- 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)
- 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)
- At least once a week, wash the actuator with warm water and let it air-dry completely. (2.2)

- For Oral Inhalation Only (2.2)
- Shake well before use.
- Prime the inhaler before using for the first time and when the inhaler has not been used for more than 3 days by releasing 4 test sprays into the air, away from the face.
- At least once a week, wash the actuator of XOPENEX HFA Inhalation Aerosol. (3)

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

- HIGHLIGHTS OF PRESCRIBING INFORMATION

- 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)

- DRUG INTERACTIONS
- May potentiate the effects of beta blockers. (7.1)
- May block bronchodilatory effects of beta-agonists and produce severe bronchospasm. Patients with asthma should not normally be treated with beta-blockers. (7.1)
- May worsen electrocardiographic changes or hypokalemia associated with diuretics. Consider monitoring potassium levels. (7.2)
- May decrease serum digoxin levels. Consider monitoring digoxin levels. (7.3)
- May potentiate the effects of albuterol on the cardiovascular system. Consider alternative therapy in patients taking MAO inhibitors or tricyclic antidepressants. (7.4)

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

* Sections or subsections omitted from the full prescribing information are not listed.
who experience immediate hypersensitivity reactions while receiving XOPENEX HFA. For hypersensitivity must be considered in the clinical evaluation of patients. 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 cardiovascular insufficiency, cardiac arrhythmias, and hypertension.

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 a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adults 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

<table>
<thead>
<tr>
<th>Body System</th>
<th>Preferred Term</th>
<th>XOPENEX HFA 90 mcg (n=403)</th>
<th>Racemic Albuterol HFA 180 mcg (n=179)</th>
<th>Placebo (n=166)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory System</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>9%</td>
<td>7%</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>8%</td>
<td>2%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Rhinitis</td>
<td>7%</td>
<td>2%</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Central Nervous System</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>4%</td>
<td>3%</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>3%</td>
<td>1%</td>
<td>2%</td>
<td></td>
</tr>
</tbody>
</table>

* 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, hemorrhia, 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

<table>
<thead>
<tr>
<th>Body System</th>
<th>Preferred Term</th>
<th>XOPENEX HFA 90 mcg (n=76)</th>
<th>Racemic Albuterol HFA 180 mcg (n=39)</th>
<th>Placebo (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digestive System</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>11%</td>
<td>8%</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>Body as a Whole</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accidental injury</td>
<td>9%</td>
<td>10%</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>Respiratory System</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>7%</td>
<td>13%</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>Bronchitis</td>
<td>3%</td>
<td>0%</td>
<td>0%</td>
<td></td>
</tr>
</tbody>
</table>

* 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 post-approval 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, angina, vertigo, angina, dysphonia, dyspnea, gastrointestinal reflex 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

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 MRHDID of levalbuterol tartrate for adults on a mg/m² 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/m² 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/m² 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/m² 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/m² 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/m² 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

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).
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 beta₂-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 beta₂-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 beta₂-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 633 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 (Cmax) and systemic exposure (AUC0,∞) 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 Cmax and AUC0,∞ 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/m² 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/m² 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/m² basis and approximately 240 times the MRHDID of levalbuterol tartrate for children on a mg/m² 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/m² 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 (tmax) 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 (FEV₁) measurements demonstrated that 90 mcg (2 inhalations) of XOPENEX HFA produced significantly greater improvement in FEV₁ over the pretreatment value than placebo. The results from one of the trials are shown in Figure 1 as the mean percent change in FEV₁ 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 on Day 1, the median time to onset of a 15% increase in FEV₁ 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 FEV₁ 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 FEV₁ measurements demonstrated that 90 mcg (2 inhalations) of XOPENEX HFA produced significantly greater improvement in FEV₁ 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 FEV₁ 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 FEV₁ 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 63402-510-01: 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

**Prim ing**: SHAK E 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.

### Parado xical Bronchospasm

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

### Concomi tant 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]).

### 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. 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:**
  - does not work as well for your asthma symptoms
  - your asthma symptoms get worse
  - 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.

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### PATIENT INFORMATION

**XOPENEX HFA® (z-o-pen-eks hfa)**

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.

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Manufactured for Sunovion Pharmaceuticals Inc.
Marlborough, MA 01752 USA

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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 February 2017 901715R03-MKT2
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  ○ rash
  ○ hives  ○ 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  • sore throat  • chest pain
• bronchitis  • runny nose  • fast heart rate
• dizziness  • vomiting  • tremors
• dizziness  • palpitations  • nervousness
• pain
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 Sunovion Pharmaceuticals Inc. at 1-877-737-7226.

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
XOPENEX HFA® (z-o-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):

• 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).

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.

- **Step 2**: Let it get wet. Medicine will not build up and block the spray of medicine if the inhaler is wet.

- **Step 7**: Shake the inhaler well for 5 seconds before use.

- **Step 8**: Inhale into your mouth and hold your breath for 10 seconds before use.

- **Step 5**: Take the cap off the mouthpiece of the actuator (See Figure 3). Check inside the mouthpiece for objects before use.

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

- **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 seconds before 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).

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

- **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 can back on the mouthpiece right away after use.

Make sure the cap snaps firmly into place.

Cleaning your XOPENEX HFA inhaler:

**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.

- **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).

**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.”

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.**
- **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.

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

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Revised February 2017

901715R03-MKT2
For Oral Inhalation Only

Xopenex HFA®
(levalbuterol tartrate) Inhalation Aerosol

For Oral Inhalation Only

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