DISCLAIMER

All labeling reflected on this website is for informational and promotional purposes only. It is not intended to be used by healthcare professionals or patients for the purpose of prescribing or administering these products. Questions regarding the current content of product labeling should be directed to Akorn's Customer Service department at 800.932.5676.

XOPENEX®
Inhalation Solution
(levalbuterol hydrochloride)

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use XOPENEX® Inhalation Solution safely and effectively. See full prescribing information for XOPENEX® Inhalation Solution.

XOPENEX® (levalbuterol hydrochloride) Inhalation Solution, for inhalation use
Initial U.S. Approval: 1999

INDICATIONS AND USAGE

XOPENEX (levalbuterol hydrochloride) Inhalation Solution is a beta$_2$-adrenergic agonist indicated for:

- Treatment or prevention of bronchospasm in adults, adolescents, and children 6 years of age and older with reversible obstructive airway disease. (1)

DOSAGE AND ADMINISTRATION

- FOR ORAL INHALATION ONLY (2)
- *Children 6-11 years old:* 0.31 mg administered three times a day, by nebulization. Routine dosing should not exceed 0.63 mg three times a day. (2)
- *Adults and Adolescents ≥12 years old:* 0.63 mg administered three times a day, every 6 to 8 hours, by nebulization. The maximum recommended dose is 1.25 mg three times a day. (2)
- For use with a standard jet nebulizer (with a face mask or mouthpiece) connected to an air compressor. (2)

DOSAGE FORMS AND STRENGTHS

Inhalation Solution (unit-dose vial for nebulization): 0.31 mg/3 mL, 0.63 mg/3 mL and 1.25 mg/3 mL. (3)

CONTRAINDICATIONS

- Hypersensitivity to levalbuterol or racemic albuterol. (4)

WARNINGS AND PRECAUTIONS

- Life-threatening paradoxical bronchospasm may occur. Discontinue XOPENEX Inhalation Solution immediately and treat with alternative therapy. (5.1)
- Need for more doses of XOPENEX Inhalation Solution than usual may be a sign of deterioration of asthma and requires reevaluation of treatment. (5.2)
- XOPENEX Inhalation Solution is not a substitute for corticosteroids. (5.3)
- Cardiovascular effects may occur. Consider discontinuation of XOPENEX Inhalation Solution 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 Inhalation Solution immediately. (5.6)
- Hypokalemia and changes in blood glucose may occur. (5.7, 5.8)

ADVERSE REACTIONS

Most common adverse reactions are: palpitations, chest pain, tachycardia, headache, dizziness, tremor and nervousness. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Akorn, Inc. at 1-800-932-5676 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- Other short-acting sympathomimetic aerosol bronchodilators and adrenergic drugs: May potentiate effect. (7.1)
- Beta-blockers: May block bronchodilatory effects of beta-agonists and produce severe bronchospasm. Patients with asthma should not normally be treated with beta-blockers. (7.2)
- Diuretic: May worsen electrocardiographic changes or hypokalemia associated with diuretic may worsen. Consider monitoring potassium levels. (7.3)
- Digoxin: May decrease serum digoxin levels. Consider monitoring digoxin levels. (7.4)
- Monoamine oxidase inhibitors (MAOs) or tricyclic antidepressants: May potentiate effect of albuterol on the cardiovascular system. (7.5)

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

Revised: 06/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

XOPENEX (levalbuterol HCl) Inhalation Solution is indicated for the treatment or prevention of bronchospasm in adults, adolescents, and children 6 years of age and older with reversible obstructive airway disease.

2 DOSAGE AND ADMINISTRATION

XOPENEX Inhalation Solution is for oral inhalation only. Administer by nebulization using with a standard jet nebulizer (with a face mask or mouthpiece) connected to an air compressor. Do not exceed recommended dose.

Children 6-11 years old: The recommended dosage of XOPENEX Inhalation Solution for patients 6-11 years old is 0.31 mg administered three times a day, by nebulization. Routine dosing should not exceed 0.63 mg three times a day.

Adults and Adolescents ≥12 years old: The recommended starting dosage of XOPENEX Inhalation Solution for patients 12 years of age and older is 0.63 mg administered three times a day, every 6 to 8 hours, by nebulization.

Patients 12 years of age and older with more severe asthma or patients who do not respond adequately to a dose of 0.63 mg of XOPENEX Inhalation Solution may benefit from a dosage of 1.25 mg three times a day.

Patients receiving the highest dose of XOPENEX Inhalation Solution should be monitored closely for adverse systemic effects, and the risks of such effects should be balanced against the potential for improved efficacy.

The use of XOPENEX Inhalation Solution can be continued as medically indicated to help control recurring bouts of bronchospasm. During this time, most patients gain optimal benefit from regular use of the inhalation solution.

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

The drug compatibility (physical and chemical), efficacy, and safety of XOPENEX Inhalation Solution when mixed with other drugs in a nebulizer have not been established.

The safety and efficacy of XOPENEX Inhalation Solution have been established in clinical trials when administered using the PARI LC Jet™ and PARI LC Plus™ nebulizers, and the PARI Master® Dura-Neb® 2000 and Dura-Neb® 3000 compressors. The safety and efficacy of XOPENEX Inhalation Solution when administered using other nebulizer systems have not been established.

3 DOSAGE FORMS AND STRENGTHS

Inhalation Solution 3 mL unit-dose, vials in three dosage strengths of levalbuterol; 0.31 mg, 0.63 mg, 1.25 mg. Each strength of XOPENEX Inhalation Solution is available in a shelf carton containing one or more foil pouches, each containing 12 unit-dose vials.

4 CONTRAINDICATIONS

XOPENEX Inhalation Solution is contraindicated in patients with a history of hypersensitivity to levalbuterol or racemic albuterol. Reactions have included urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal edema *[see Warnings and Precautions (5.6)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Paradoxical Bronchospasm

XOPENEX Inhalation Solution can produce paradoxical bronchospasm, which may be life-threatening. If paradoxical bronchospasm occurs, XOPENEX Inhalation Solution 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 vial.

5.2 Deterioration of Asthma

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

5.3 Use of Anti-Inflammatory Agents

XOPENEX Inhalation Solution is not a substitute for corticosteroids. The use of beta-adrenergic

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

5.4 Cardiovascular Effects

XOPENEX Inhalation Solution, like other beta-adrenergic agonists, can produce clinically significant cardiovascular effects in some patients, as measured by heart rate, blood pressure, and symptoms. Although such effects are uncommon after administration of XOPENEX Inhalation Solution 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 Inhalation Solution, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

5.5 Do Not Exceed Recommended Dose

Do not exceed the recommended dose. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma. The exact cause of death is unknown, but cardiac arrest following an unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected.

5.6 Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions may occur after administration of levalbuterol or racemic albuterol. Reactions have included 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 Inhalation Solution.

5.7 Coexisting Conditions

XOPENEX Inhalation Solution, 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.

Changes in blood glucose may occur. 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 Inhalation Solution 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

The following serious adverse reactions are described below and elsewhere in the labeling:

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

6.1 Clinical Trials Experience

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

Adults and Adolescents 12 Years of Age and Older:

Adverse reaction information concerning XOPENEX Inhalation Solution in adults and adolescents is derived from one 4-week, multicenter, randomized, double-blind, active-, and placebo-controlled trial in 362 patients with asthma 12 years of age and older. Adverse reactions reported in ≥2% of patients receiving XOPENEX Inhalation Solution or racemic albuterol and more frequently than in patients receiving placebo are listed in Table 1.

Table 1: Adverse Reactions Reported in a 4-Week, Controlled Clinical Trial in Adults and Adolescents ≥12 Years Old

	Percent of Patients[a]			
Body System Preferred Term	Placebo (n=75)	XOPENEX 1.25 mg (n=73)	XOPENEX 0.63 mg (n=72)	Racemic albuterol 2.5 mg (n=74)
Body as a Whole				
Allergic reaction	1.3	0	0	2.7
Flu syndrome	0	1.4	4.2	2.7
Accidental injury	0	2.7	0	0
Pain	1.3	1.4	2.8	2.7
Back pain	0	0	0	2.7
Cardiovascular System				
Tachycardia	0	2.7	2.8	2.7
Migraine	0	2.7	0	0
Digestive System				
Dyspepsia	1.3	2.7	1.4	1.4
Musculoskeletal System				
Leg cramps	1.3	2.7	0	1.4
Central Nervous System				
Dizziness	1.3	2.7	1.4	0
Hypertonia	0	0	0	2.7
Nervousness	0	9.6	2.8	8.1
Tremor	0	6.8	0	2.7
Anxiety	0	2.7	0	0
Respiratory System				
Cough increased	2.7	4.1	1.4	2.7
Infection viral	9.3	12.3	6.9	12.2
Rhinitis	2.7	2.7	11.1	6.8
Sinusitis	2.7	1.4	4.2	2.7
Turbinate edema	0	1.4	2.8	0

[a] One treatment group, racemic albuterol 1.25 mg, with 68 subjects is omitted.

The incidence of certain systemic beta-adrenergic adverse reactions (e.g., tremor, nervousness) was slightly less in the XOPENEX Inhalation Solution 0.63 mg group compared with the other active treatment groups. The clinical significance of these small differences is unknown.

Changes in heart rate 15 minutes after drug administration and in plasma glucose and potassium 1 hour after drug administration on day 1 and day 29 were clinically comparable in the XOPENEX Inhalation Solution 1.25 mg and racemic albuterol 2.5 mg groups (see Table 2). Changes in heart rate and plasma glucose were slightly less in the XOPENEX Inhalation Solution 0.63 mg group compared with the other active treatment groups (see Table 2). The clinical significance of these small differences is unknown. After 4 weeks, effects on heart rate, plasma glucose, and plasma potassium were generally diminished compared with day 1 in all active treatment groups.

Table 2: Mean Changes from Baseline Heart Rate at 15 Minutes and Glucose and Potassium at 1 Hour after First Dose (Day 1) in Adults and Adolescents ≥12 Years Old

	Mean Changes (day 1)		
Treatment	Heart Rate (bpm)	Glucose (mg/dL)	Potassium (mEq/L)
XOPENEX 0.63 mg, n=72	2.4	4.6	-0.2
XOPENEX 1.25 mg, n=73	6.9	10.3	-0.3
Racemic albuterol 2.5 mg, n=74	5.7	8.2	-0.3
Placebo, n=75	-2.8	-0.2	-0.2

No other clinically relevant laboratory abnormalities related to administration of XOPENEX Inhalation Solution were observed in this study.

In the clinical trials, a slightly greater number of serious adverse events, discontinuations due to adverse events, and clinically significant ECG changes were reported in patients who received XOPENEX 1.25 mg compared with the other active treatment groups.

The following adverse reactions, considered potentially related to XOPENEX, occurred in less than 2% of the 292 subjects who received XOPENEX and more frequently than in patients who received placebo in any clinical trial:

Body as a Whole:	chills, pain, chest pain
Cardiovascular System:	ECG abnormal, ECG change, hypertension, hypotension, syncope
Digestive System:	diarrhea, dry mouth, dry throat, dyspepsia, gastroenteritis, nausea
Hemic and Lymphatic System:	lymphadenopathy
Musculoskeletal System:	leg cramps, myalgia
Nervous System:	anxiety, hyperesthesia of the hand, insomnia, paresthesia, tremor
Special Senses:	eye itch

The following reactions, considered potentially related to XOPENEX, occurred in less than 2% of the treated subjects but at a frequency less than in patients who received placebo: asthma exacerbation, cough increased, wheezing, sweating, and vomiting.

Pediatric Patients 6 to 11 Years of Age:

Adverse reaction information concerning XOPENEX Inhalation Solution in pediatric patients is derived from one 3-week, multicenter, randomized, double-blind, active-, and placebo-controlled trial in 316 pediatric patients 6 to 11 years of age. Adverse reactions reported in ≥2% of patients in any treatment group and more frequently than in patients receiving placebo are listed in Table 3.

Table 3: Most Frequently Reported Adverse Reactions (≥2% in Any Treatment Group) and Those Reported More Frequently Than in Placebo during the Double-Blind Period (ITT Population, 6-11 Years Old)

	Percent of Patients				
Body System Preferred Term	Placebo (n=59)	XOPENEX 0.31 mg (n=66)	XOPENEX 0.63 mg (n=67)	Racemic albuterol 1.25 mg (n=64)	Racemic albuterol 2.5 mg (n=60)
Body as a Whole					
Abdominal pain	3.4	0	1.5	3.1	6.7
Accidental injury	3.4	6.1	4.5	3.1	5.0
Asthenia	0	3.0	3.0	1.6	1.7
Fever	5.1	9.1	3.0	1.6	6.7
Headache	8.5	7.6	11.9	9.4	3.3
Pain	3.4	3.0	1.5	4.7	6.7
Viral infection	5.1	7.6	9.0	4.7	8.3

Body System Preferred Term	Percent of Patients				
	Placebo (n=59)	XOPENEX 0.31 mg (n=66)	XOPENEX 0.63 mg (n=67)	Racemic albuterol 1.25 mg (n=64)	Racemic albuterol 2.5 mg (n=60)
Digestive System					
Diarrhea	0	1.5	6.0	1.6	0
Hemic and Lymphatic					
Lymphadenopathy	0	3.0	0	1.6	0
Musculoskeletal System					
Myalgia	0	0	1.5	1.6	3.3
Respiratory System					
Asthma	5.1	9.1	9.0	6.3	10.0
Pharyngitis	6.8	3.0	10.4	0	6.7
Rhinitis	1.7	6.1	10.4	3.1	5.0
Skin and Appendages					
Eczema	0	0	0	0	3.3
Rash	0	0	7.5	1.6	0
Urticaria	0	0	3.0	0	0
Special Senses					
Otitis media	1.7	0	0	0	3.3

Note: Subjects may have more than one adverse event per body system and preferred term.

Changes in heart rate, plasma glucose, and serum potassium are shown in Table 4. The clinical significance of these small differences is unknown.

Table 4: Mean Changes from Baseline Heart Rate at 30 Minutes and Glucose and Potassium at 1 Hour after First Dose (Day 1) and Last Dose (Day 21) in Children 6-11 Years Old

Treatment	Mean Changes (Day 1)		
	Heart Rate (bpm)	Glucose (mg/dL)	Potassium (mEq/L)
XOPENEX 0.31 mg, n=66	0.8	4.9	-0.31
XOPENEX 0.63 mg, n=67	6.7	5.2	-0.36
Racemic albuterol 1.25 mg, n=64	6.4	8.0	-0.27
Racemic albuterol 2.5 mg, n=60	10.9	10.8	-0.56
Placebo, n=59	-1.8	0.6	-0.05
XOPENEX 0.31 mg, n=60	0	2.6	-0.32
XOPENEX 0.63 mg, n=66	3.8	5.8	-0.34
Racemic albuterol 1.25 mg, n=62	5.8	1.7	-0.18
Racemic albuterol 2.5 mg, n=54	5.7	11.8	-0.26
Placebo, n=55	-1.7	1.1	-0.04

6.2 Post-marketing Experience

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

In addition, XOPENEX Inhalation Solution, 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

7.1 Short-Acting Bronchodilators

Avoid concomitant use of other short-acting sympathomimetic bronchodilators or epinephrine in patients being treated with XOPENEX Inhalation Solution. If additional adrenergic drugs are to be administered by any route, they should be used with caution to avoid deleterious cardiovascular effects.

7.2 Beta-blockers

Beta-adrenergic receptor blocking agents not only block the pulmonary effect of beta-adrenergic agonists such as XOPENEX Inhalation Solution, 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., 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.

7.3 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.

7.4 Digoxin

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

7.5 Monoamine Oxidase Inhibitors or Tricyclic Antidepressants

XOPENEX Inhalation Solution 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 levalbuterol 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

Teratogenic Effects: Pregnancy Category C.

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

During worldwide marketing experience, various congenital anomalies, including cleft palate and limb defects, have been reported in newborns of women treated with racemic albuterol, which contains the levalbuterol isomer (active drug substance of XOPENEX Inhalation Solution). However, since multiple medications were taken during some of the pregnancies and there was no consistent pattern of anomalies, it was not possible to establish a relationship between racemic albuterol use and the occurrence of these congenital anomalies.

In animal studies, oral administration of levalbuterol HCl to pregnant New Zealand White rabbits found no evidence of teratogenicity at doses up to 25 mg/kg/day (approximately 108 times the maximum recommended daily inhalation [MRDI] dose of levalbuterol HCl for adults on a mg/m^2 basis).

However, other studies demonstrated that racemic albuterol sulfate was teratogenic in mice and rabbits at doses comparable to the human therapeutic range. Pregnant mice administered racemic albuterol sulfate subcutaneously had a dose-related increased incidence of cleft palate in their fetuses (4.5% of fetuses at 0.25 mg/kg/day or greater, corresponding to approximately 0.3 times the MRDI dose, 9.3% of fetuses at 2.5 mg/kg/day, approximately 3 times the MRDI dose of levalbuterol HCl for adults on a mg/m^2 basis). The drug did not induce cleft palate formation when administered subcutaneously at a dose of 0.025 mg/kg/day (approximately 0.03 times the MRDI dose of levalbuterol HCl for adults on a mg/m^2 basis). In addition, oral administration of racemic albuterol sulfate to pregnant rabbits resulted in an increased incidence of cranioschisis in fetuses (approximately 215 times the MRDI dose of levalbuterol HCl for adults on a mg/m^2 basis).

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

8.2 Labor and Delivery

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

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

8.3 Nursing Mothers

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

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

8.4 Pediatric Use

Pediatric Patients 6 Years of Age and Older

The safety and efficacy of XOPENEX Inhalation Solution have been established in pediatric patients 6 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 6 Years of Age

XOPENEX Inhalation Solution is not indicated for pediatric patients less than 6 years of age.

Clinical trials with XOPENEX Inhalation Solution in this age group failed to meet the primary efficacy endpoint and demonstrated an increased number of asthma-related adverse reactions following chronic XOPENEX treatment.

XOPENEX Inhalation Solution was studied in 379 pediatric patients less than 6 years of age with asthma or reactive airway disease - (291 patients 2 to 5 years of age, and 88 patients from birth to less than 2 years of age). Efficacy and safety data for XOPENEX Inhalation Solution in this age group are primarily available from one 3-week, multicenter, randomized, double-blind, active and placebo-controlled study (Study 1) in 211 pediatric patients between the ages of 2 and 5 years, of whom 119 received XOPENEX Inhalation Solution. Over the 3 week treatment period, there were no significant treatment differences in the Pediatric Asthma Questionnaire (PAQ) total score between groups receiving XOPENEX Inhalation Solution 0.31 mg, XOPENEX Inhalation Solution 0.63 mg, racemic albuterol, and placebo. Additional safety data following chronic dosing is available from a 4-week, multicenter, randomized, modified-blind, placebo-controlled study (Study 2) of 196 patients between the ages of birth and 3 years, of whom 63 received open-label XOPENEX Inhalation Solution. In these two studies, treatment-emergent asthma exacerbations or asthma-related adverse reactions and treatment discontinuations due to asthma occurred at a higher frequency in XOPENEX Inhalation-treated subjects compared to control (Table 5). Other adverse reactions were consistent with those observed in the clinical trial population of patients 6 years of age and older [see *Adverse Reactions (6.1)*].

Table 5: Asthma-related Adverse Reactions in 3- and 4-Week Clinical Trials in Children Birth to <6 Years of Age

	Asthma Exacerbations* n (%)	Treatment Discontinuations due to Asthma n (%)	Asthma-related Adverse Reactions** n (%)
Study 1			
XOPENEX 0.31 mg, n=58	6 (10)	4 (7)	–
XOPENEX 0.63 mg, n=51	7 (14)	6 (12)	–
Racemic albuterol, n=52	3 (6)	2 (4)	–
Placebo, n=50	2 (4)	2 (4)	–
Study 2			
XOPENEX 0.31 mg, n=63	–	2 (3)	6 (10)
Levalbuterol HFA inhalation aerosol, n=65	–	1 (2)	8 (12)
Placebo, n=68	–	0	3 (4)

*Asthma exacerbation defined as worsening of asthma symptoms or pulmonary function that required any of the following: emergency department visit, hospitalization, therapeutic intervention with oral or parenteral steroids, unscheduled clinic visit to treat acute asthma symptoms

**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 Inhalation Solution did not include sufficient numbers of subjects aged 65 years and older to determine whether they respond differently from younger subjects. Only 5 patients 65 years of age and older were treated with XOPENEX Inhalation Solution in a 4-week clinical study [see *Clinical Pharmacology (12)* and *Clinical Studies (14)*] (n=2 for 0.63 mg and n=3 for 1.25 mg). In these patients, bronchodilation was observed after the first dose on day 1 and after 4 weeks of treatment. In general, patients 65 years of age and older should be started at a dose of 0.63 mg of XOPENEX Inhalation Solution. If clinically warranted due to insufficient bronchodilator response, the dose of XOPENEX Inhalation Solution may be increased in elderly patients as tolerated, in conjunction with frequent clinical and laboratory monitoring, to the maximum recommended daily dose [see *Dosage and Administration (2)*].

8.6 Renal Impairment

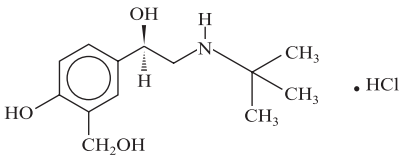
Albuterol is known to be substantially excreted by the kidney, and the risk of toxic reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal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

11 DESCRIPTION

XOPENEX Inhalation Solution is a sterile, clear, colorless, preservative-free solution of the hydrochloride salt of levalbuterol, the (R)-enantiomer of the drug substance racemic albuterol. Levalbuterol HCl is a relatively selective $beta_2$-adrenergic receptor agonist [see *Clinical Pharmacology (12)*]. The chemical name for levalbuterol HCl is (R)-α^1-[[(1,1- dimethylethyl) amino]methyl]-4-hydroxy-1,3-benzenedimethanol hydrochloride, and its established chemical structure is as follows:



The molecular weight of levalbuterol HCl is 275.8, and its empirical formula is $C_{13}H_{21}NO_3$•HCl. It is a white to off-white, crystalline solid, with a melting point of approximately 187°C and solubility of approximately 180 mg/mL in water.

Levalbuterol HCl is the USAN modified name for (R)-albuterol HCl in the United States.

XOPENEX Inhalation Solution is supplied in unit-dose vials and requires no dilution before administration by nebulization. Each 3 mL unit-dose vial contains 0.31 mg of levalbuterol (as 0.36 mg of levalbuterol HCl) or 0.63 mg of levalbuterol (as 0.73 mg of levalbuterol HCl) or 1.25 mg of levalbuterol (as 1.44 mg of levalbuterol HCl), sodium chloride to adjust tonicity, and sulfuric acid to adjust the pH to 4.0 (3.3 to 4.5).

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 release of mediators from mast cells in the airway. 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 (5.4)*]. 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 Pharmacodynamics

Adults and Adolescents ≥12 Years Old

In a randomized, double-blind, placebo-controlled, cross-over study, 20 adults with mild-to-moderate asthma received single doses of XOPENEX Inhalation Solution (0.31 mg, 0.63 mg, and 1.25 mg) and racemic albuterol sulfate inhalation solution (2.5 mg). All doses of active treatment produced a significantly greater degree of bronchodilation (as measured by percent change from pre-dose mean FEV_1) than placebo, and there were no significant differences between any of the active treatment arms. The bronchodilator responses to 1.25 mg of XOPENEX Inhalation Solution and 2.5 mg of racemic albuterol sulfate inhalation solution were clinically comparable over the 6-hour evaluation period, except for a slightly longer duration of action (>15% increase in FEV_1 from baseline) after administration of 1.25 mg of XOPENEX Inhalation Solution. Systemic beta-adrenergic adverse effects were observed with all active doses and were generally dose-related for (R)-albuterol. XOPENEX Inhalation Solution at a dose of 1.25 mg produced a slightly higher rate of systemic beta-adrenergic adverse effects than the 2.5 mg dose of racemic albuterol sulfate inhalation solution.

In a randomized, double-blind, placebo-controlled, cross-over study, 12 adults with mild-to-moderate asthma were challenged with inhaled methacholine chloride 20 and 180 minutes following administration of a single dose of 2.5 mg of racemic albuterol sulfate, 1.25 mg of XOPENEX, 1.25 mg of (S)-albuterol, or placebo using a Pari LC Jet™ nebulizer. Racemic albuterol sulfate, XOPENEX, and (S)-albuterol had a protective effect against methacholine-induced bronchoconstriction 20 minutes after administration, although the effect of (S)-albuterol was minimal. At 180 minutes after administration, the bronchoprotective effect of 1.25 mg of XOPENEX was comparable to that of 2.5 mg of racemic albuterol sulfate. At 180 minutes after administration, 1.25 mg of (S)-albuterol had no bronchoprotective effect.

In a clinical study in adults with mild-to-moderate asthma, comparable efficacy (as measured by change from baseline FEV_1) and safety (as measured by heart rate, blood pressure, ECG, serum potassium, and tremor) were demonstrated after a cumulative dose of 5 mg of XOPENEX Inhalation Solution (four consecutive doses of 1.25 mg administered every 30 minutes) and 10 mg of racemic albuterol sulfate inhalation solution (four consecutive doses of 2.5 mg administered every 30 minutes).

12.3 Pharmacokinetics

Adults and Adolescents ≥12 Years Old

The inhalation pharmacokinetics of XOPENEX Inhalation Solution were investigated in a randomized cross-over study in 30 healthy adults following administration of a single dose of 1.25 mg and a cumulative dose of 5 mg of XOPENEX Inhalation Solution and a single dose of 2.5 mg and a cumulative dose of 10 mg of racemic albuterol sulfate inhalation solution by nebulization using a PARI LC Jet™ nebulizer with a Dura-Neb® 2000 compressor.

Following administration of a single 1.25 mg dose of XOPENEX Inhalation Solution, exposure to (R)-albuterol (AUC of 3.3 ng•hr/mL) was approximately 2-fold higher than following administration of a single 2.5 mg dose of racemic albuterol inhalation solution (AUC of 1.7 ng•hr/mL) (see Table 5). Following administration of a cumulative 5 mg dose of XOPENEX Inhalation Solution (1.25 mg given every 30 minutes for a total of four doses) or a cumulative 10 mg dose of racemic albuterol inhalation solution (2.5 mg given every 30 minutes for a total of four doses), C_{max} and AUC of (R)-albuterol were comparable (see Table 6).

Table 6: Mean (SD) Values for Pharmacokinetic Parameters in Healthy Adults

	Single Dose		Cumulative Dose	
	XOPENEX 1.25 mg	Racemic albuterol sulfate 2.5 mg	XOPENEX 5 mg	Racemic albuterol sulfate 10 mg
C_{max} (ng/mL) (R)-albuterol	1.1 (0.45)	0.8 (0.41)**	4.5 (2.20)	4.2 (1.51)**
T_{max} (h)$^\gamma$ (R)-albuterol	0.2 (0.17, 0.37)	0.2 (0.17, 1.50)	0.2 (-0.18*, 1.25)	0.2 (-0.28*, 1.00)
AUC (ng•hr/mL) (R)-albuterol	3.3 (1.58)	1.7 (0.99)**	17.4 (8.56)	16.0 (7.12)**
$T_{½}$ (h) (R)-albuterol	3.3 (2.48)	1.5 (0.61)	4.0 (1.05)	4.1 (0.97)

$^\gamma$ Median (Min, Max) reported for T_{max}.

* A negative T_{max} indicates C_{max} occurred between first and last nebulizations.

** Values reflect only (R)-albuterol and do not include (S)-albuterol.

Children 6-11 Years Old

The pharmacokinetic parameters of (R)- and (S)-albuterol in children with asthma were obtained using population pharmacokinetic analysis. These data are presented in Table 7. For comparison, adult data obtained by conventional pharmacokinetic analysis from a different study also are presented in Table 7.

In children, AUC and C_{max} of (R)-albuterol following administration of 0.63 mg XOPENEX Inhalation Solution were comparable to those following administration of 1.25 mg racemic albuterol sulfate inhalation solution.

When the same dose of 0.63 mg of XOPENEX Inhalation Solution was given to children and adults, the predicted C_{max} of (R)-albuterol in children was similar to that in adults (0.52 vs.

0.56 ng/mL), while predicted AUC in children (2.55 ng•hr/mL) was about 1.5-fold higher than that in adults (1.65 ng•hr/mL). These data support lower doses for children 6-11 years old compared with the adult doses [see *Dosage and Administration (2)*].

Table 7: (R)-Albuterol Exposure in Adults and Pediatric Subjects (6-11 years)

	Children 6-11 years				Adults ≥12 years	
Treatment	XOPENEX 0.31 mg	XOPENEX 0.63 mg	Racemic albuterol 1.25 mg	Racemic albuterol 2.5 mg	XOPENEX 0.63 mg	XOPENEX 1.25 mg
$AUC_{0-\infty}$ (ng•hr/mL)[c]	1.36	2.55	2.65	5.02	1.65[a]	3.3[b]
C_{max} (ng/mL)[d]	0.303	0.521	0.553	1.08	0.56[a]	1.1[b]

a The values are predicted by assuming linear pharmacokinetics
b The data obtained from Table 6
c Area under the plasma concentration curve from time 0 to infinity
d Maximum plasma concentration

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 Inhalation Solution 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 Inhalation Solution 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 HCl, 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 4 times the MRDI dose of levalbuterol HCl for adults and approximately 5 times the MRDI dose of levalbuterol HCl 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 540 times the MRDI dose of levalbuterol HCl for adults and approximately 630 times the MRDI dose of levalbuterol HCl for children on a mg/m^2 basis) and doses in the golden hamster study were up to 50 mg/kg/day (approximately 90 times the MRDI dose of levalbuterol HCl for adults on a mg/m^2 basis and approximately 105 times the MRDI dose of levalbuterol HCl 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 hydrochloride. Reproduction studies in rats using racemic albuterol sulfate demonstrated no evidence of impaired fertility at oral doses up to 50 mg/kg/day (approximately 108 times the maximum recommended daily inhalation dose of levalbuterol HCl for adults on a mg/m^2 basis).

14 CLINICAL STUDIES

Adults and Adolescents ≥12 Years Old

The safety and efficacy of XOPENEX Inhalation Solution were evaluated in a 4-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study in 362 adult and adolescent patients 12 years of age and older, with mild-to-moderate asthma (mean baseline FEV_1 60% of predicted). Approximately half of the patients were also receiving inhaled corticosteroids. Patients were randomized to receive XOPENEX 0.63 mg, XOPENEX 1.25 mg, racemic albuterol sulfate 1.25 mg, racemic albuterol sulfate 2.5 mg, or placebo three times a day administered via a PARI LC Plus™ nebulizer and a Dura-Neb® portable compressor. Racemic albuterol delivered by a chlorofluorocarbon (CFC) metered-dose inhaler (MDI) was used on an as-needed basis as the rescue medication.

Efficacy, as measured by the mean percent change from baseline FEV_1, was demonstrated for all active treatment regimens compared with placebo on day 1 and day 29. On both day 1 (see Figure 1) and day 29 (see Figure 2), 1.25 mg of XOPENEX demonstrated the largest mean percent change from baseline FEV_1 compared with the other active treatments. A dose of 0.63 mg of XOPENEX and 2.5 mg of racemic albuterol sulfate produced a clinically comparable mean percent change from baseline FEV_1 on both day 1 and day 29.

Figure 1: Mean Percent Change from Baseline FEV_1 on Day 1, Adults and Adolescents ≥12 years old

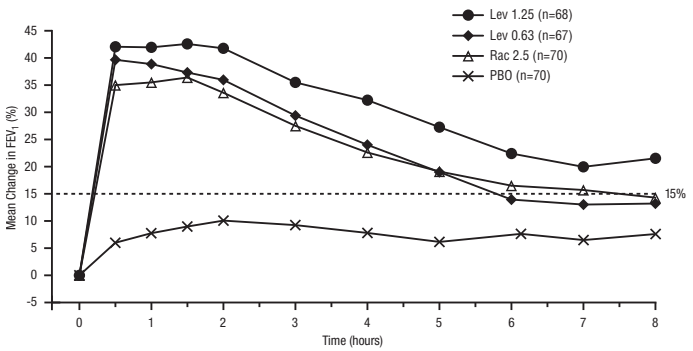
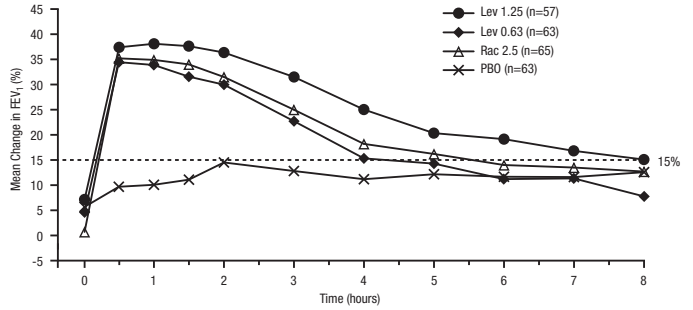


Figure 2: Mean Percent Change from Baseline FEV_1 on Day 29, Adults and Adolescents ≥12 years old



The mean time to onset of a 15% increase in FEV_1 over baseline for levalbuterol at doses of 0.63 mg and 1.25 mg was approximately 17 minutes and 10 minutes, respectively, and the mean time to peak effect for both doses was approximately 1.5 hours after 4 weeks of treatment. The mean duration of effect, as measured by a >15% increase from baseline FEV_1, was approximately 5 hours after administration of 0.63 mg of levalbuterol and approximately 6 hours after administration of 1.25 mg of levalbuterol after 4 weeks of treatment. In some patients, the duration of effect was as long as 8 hours.

Children 6-11 Years Old

A multicenter, randomized, double-blind, placebo- and active-controlled study was conducted in children with mild-to-moderate asthma (mean baseline FEV_1 73% of predicted) (n=316). Following a 1-week placebo run-in, subjects were randomized to XOPENEX (0.31 or 0.63 mg), racemic albuterol (1.25 or 2.5 mg), or placebo, which were delivered three times a day for 3 weeks using a PARI LC Plus™ nebulizer and a Dura-Neb® 3000 compressor.

Efficacy, as measured by mean peak percent change from baseline FEV_1, was demonstrated for all active treatment regimens compared with placebo on day 1 and day 21. Time profile FEV_1 curves for day 1 and day 21 are shown in Figure 3 and Figure 4, respectively. The onset of effect (time to a 15% increase in FEV_1 over test-day baseline) and duration of effect (maintenance of a >15% increase in FEV_1 over test-day baseline) of levalbuterol were clinically comparable to those of racemic albuterol.

Figure 3: Mean Percent Change from Baseline FEV_1 on Day 1, Children 6-11 Years of Age

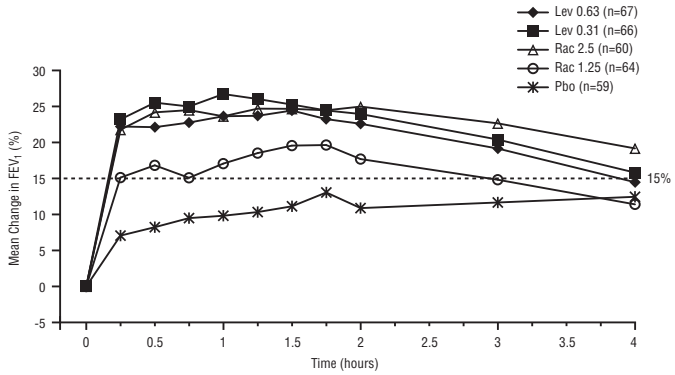
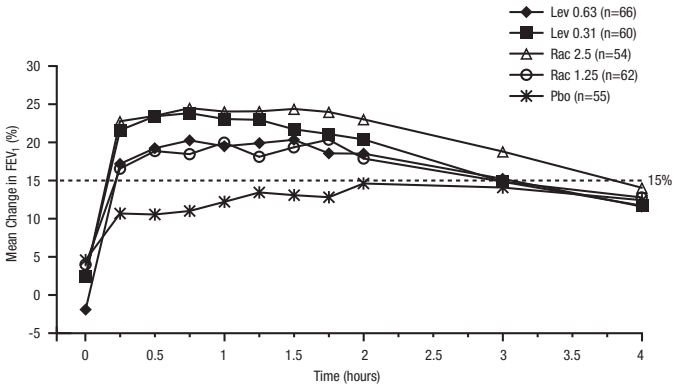


Figure 4: Mean Percent Change from Baseline FEV_1 on Day 21, Children 6-11 Years of Age



16 HOW SUPPLIED/STORAGE AND HANDLING

XOPENEX Inhalation Solution is supplied in 3 mL unit-dose, low-density polyethylene (LDPE) vials as a clear, colorless, sterile, preservative-free, aqueous solution, in three different strengths of levalbuterol (0.31 mg, 0.63 mg, 1.25 mg). Each strength of XOPENEX Inhalation Solution is available in a shelf-carton containing one or more foil pouches, each containing 12 unit-dose LDPE vials.

XOPENEX (levalbuterol HCl) Inhalation Solution, 0.31 mg *(foil pouch label color green)* contains 0.31 mg of levalbuterol (as 0.36 mg of levalbuterol HCl) and is available in cartons of 24 unit-dose LDPE vials (NDC 17478-172-24).

XOPENEX (levalbuterol HCl) Inhalation Solution, 0.63 mg *(foil pouch label color yellow)* contains 0.63 mg of levalbuterol (as 0.73 mg of levalbuterol HCl) and is available in cartons of 24 unit-dose LDPE vials (NDC 17478-173-24).

XOPENEX (levalbuterol HCl) Inhalation Solution, 1.25 mg *(foil pouch label color red)* contains 1.25 mg of levalbuterol (as 1.44 mg of levalbuterol HCl) and is available in cartons of 24 unit-dose LDPE vials (NDC 17478-174-24).

XOPENEX Inhalation Solution is also available as a concentrate in individually pouched 0.5 mL unit-dose vials containing 1.25 mg of levalbuterol (NDC 17478-171-30).

Store XOPENEX Inhalation Solution in the protective foil pouch at 20 to 25°C (68 to 77°F) [see USP Controlled Room Temperature]. Protect from light and excessive heat. Keep unopened vials in the foil pouch. Once the foil pouch is opened, the vials should be used within 2 weeks. Vials removed from the pouch, if not used immediately, should be protected from light and used within 1 week. Discard any vial if the solution is not colorless.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information and Instructions for Using XOPENEX Inhalation Solution).

Patients should be given the following information:

Hypersensitivity

Query patients about previously experienced hypersensitivity to levalbuterol or racemic albuterol and counsel patients to report any hypersensitivity reactions to their physician.

Frequency of Use

Inform patients not to increase the dose or use XOPENEX Inhalation Solution more frequently than recommended without consulting their physician. If patients find that treatment with XOPENEX Inhalation Solution 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.

Paradoxical Bronchospasm

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

Concomitant Drug Use

Inform patients using XOPENEX Inhalation Solution, that other inhaled drugs and asthma medications should be taken only as directed by their physician.

Common Adverse Reactions

Advise patients of the common adverse reactions of treatment with XOPENEX Inhalation Solution including palpitations, chest pain, fast heart rate, headache, dizziness, tremor and nervousness.

Pregnancy

Advise patients who are pregnant or nursing to contact their physician about the use of XOPENEX Inhalation Solution.

General Information on Storage and Use

Advise patients to store XOPENEX Inhalation Solution in the foil pouch between 20°C to 25°C (68°F to 77°F) protected from light and excessive heat. Do not use after the expiration date stamped on the container. Store unused vials in the protective foil pouch. Once the foil pouch is opened, use the vials within 2 weeks. Use vials removed from the pouch, immediately, or protect from light and use within 1 week. Discard any vial if the solution is not colorless.

Advise patients not to mix XOPENEX Inhalation Solution with other drugs in a nebulizer.

AKORN

Distributed by: **Akorn, Inc.**
Lake Forest, IL 60045

Manufactured for: **Oak Pharmaceuticals, Inc.**

For customer service, call 1-800-932-5676.
To report adverse events, call 1-800-932-5676.
For medical information, call 1-800-932-5676.

XP00N June 2017

AKNX024-642R01

PI002 Rev. 06/18