Levalbuterol  
(Xopenex®, Xopenex HFA®)

Classification:  
Respiratory Agents; Bronchodilators

Description:  
Levalbuterol hydrochloride inhalation solution is a sterile, clear, colorless, preservative-free solution of the (R)-enantiomer of (racemic) albuterol. Levalbuterol tartrate aerosol for oral inhalation is a pressurized metered-dose aerosol inhaler (MDI) of the (R)-enantiomer of (racemic) albuterol. It contains a suspension of micronized levalbuterol tartrate, propellant HFA-134a (1,1,1,2-tetrafluoroethane), Dehydrated Alcohol USP, and Oleic Acid NF.

Vials of solution for inhalation must be stored in the protective foil pouch, protected from light and heat. Vials should be used within 2 weeks of opening pouch and 1 week if removed from pouch.

Inhalers should be protected from freezing temperatures and direct sunlight. Store inhaler with the actuator (or mouthpiece) down.

Pharmacology: Levalbuterol is an inhaled beta₂-adrenergic agonist. Activation of beta₂-adrenergic receptors on airway smooth muscle leads to the activation of adenylcyclase and to an increase in the intracellular concentration of cyclic AMP. This increase in cyclic AMP leads to the activation of protein kinase A, which inhibits the phosphorylation of myosin and lowers intracellular ionic calcium concentrations, resulting in relaxation. Levalbuterol relaxes the smooth muscles of all airways, from the trachea to the terminal bronchioles. Levalbuterol acts as a functional antagonist to relax the airway irrespective of the spasmogen involved, thus protecting against all bronchoconstrictor challenges. Increased cyclic AMP concentrations are also associated with the inhibition of release of mediators from mast cells in the airway.

While it is recognized that beta₂-adrenergic receptors are the predominant receptors on bronchial smooth muscle, data indicate that there is a population of beta₂-receptors in the human heart that comprise between 10% and 50% of cardiac beta-adrenergic receptors. The precise function of these receptors has not been established. 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.

Results from an in vitro study of binding to human beta-adrenergic receptors demonstrated that levalbuterol has approximately 2-fold greater binding affinity than racemic albuterol and approximately 100-fold greater binding affinity than (S)-albuterol.
Pharmacokinetics:
- Initial Response: 10 to 17 minutes with nebulization, 5.5 to 10.2 minutes with aerosol
- Duration: After 4 weeks of treatment, the duration of bronchodilatory effect (greater than a 15% increase in forced expiratory volume in 1 second (FEV-1) from baseline) is approximately 5 hours after a levalbuterol dose of 0.63 mg for nebulization and 6 hours after a 1.25-mg dose for nebulization. The duration of effect may be as long as 8 hours in some patients. After receiving a levalbuterol dose of 2 puffs per metered dose inhaler, the duration is 3 to 4 hours. The duration of effect with the inhaler may be as long as 6 hours in some patients.
- Absorption: A portion of inhaled dose is absorbed to systemic circulation
- Elimination: Half-life elimination: 3.3-4 hours. 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.

Indications: Xopenex 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.

Dosage:
For bronchospasm: The recommended starting dose of Levalbuterol solution for nebulization is 0.63 mg administered three times a day, every 6 to 8 hours. Patients with more severe asthma or patients who do not respond adequately with lower dose may benefit from a dosage of 1.25 mg three times a day. The recommended dose of Levalbuterol metered-dose inhaler is 2 puffs every 4-6 hours.

For exacerbation of asthma (acute, severe): The recommended dose of Levalbuterol metered-dose inhaler is 4-8 puffs every 20 minutes for up to 4 hours, then every 1-4 hours as needed. The recommended dose of Levalbuterol solution for nebulization is 1.25-2.5 mg every 20 minutes for 3 doses, then 1.25-5 mg every 1-4 hours as needed.

Contraindications and Precautions:
- Pregnancy category C
- Like other inhaled beta-adrenergic agonists, Levalbuterol can produce paradoxical bronchospasm, which may be life threatening
- Like all other beta-adrenergic agonists, can produce a clinically significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, ECG changes, and/or symptoms.
- Levalbuterol, 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.
- Large doses of intravenous racemic albuterol have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. As with other beta-adrenergic agonist
medications, levalbuterol may produce significant hypokalemia in some patients, which has the potential to produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation.

**Interactions:**

- Other short-acting sympathomimetic aerosol bronchodilators or epinephrine should be used with caution with Levalbuterol to avoid deleterious cardiovascular effects.
- **Beta-blockers:** Beta-adrenergic receptor blocking agents not only block the pulmonary effect of beta-agonists such as Levalbuterol, but may also produce severe bronchospasm in asthmatic patients. If there is no acceptable alternative to the use of beta-adrenergic blocking agents in patients with asthma, cardio-selective beta-blockers could be considered.
- **Monoamine Oxidase Inhibitors or Tricyclic Antidepressants:** Administer with extreme caution to patients being treated with MAOIs or TCAs, or within 2 weeks of discontinuation of such agents, because the action of Levalbuterol on the vascular system may be potentiated.
- **Diuretics:** The ECG changes and/or hypokalemia that may result from the administration of non-potassium sparing diuretics (such as loop or 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.

**Adverse Reactions:**

Immediate hypersensitivity reactions have occurred, including angioedema, oropharyngeal edema, urticaria, rash and anaphylaxis.

The most frequent (>10%) adverse reactions include: hyperglycemia, hypokalemia, rhinitis, and respiratory infections. Less frequent (2% to 10%) adverse reactions include nervousness, tremor, anxiety, dizziness, migraine, tachycardia, dyspepsia, pharyngitis, cough, and sinusitis.

**Costs and Monitoring:**

Monitoring should include pulmonary function tests, assessment of symptoms. Consider periodic bp, pulse, serum potassium and glucose monitoring during chronic therapy.

**Levalbuterol Costs:**

- Xopenex HFA Inhaler, 45 mcg/actuation, $0.20 actuation
- Levalbuterol Inhalation Solution, 0.63 mg/3mL: $1.66/nebule
- Levalbuterol Inhalation Solution, 1.25 mg/3mL: $1.66/nebule

**Albuterol Costs:**

- ProAir Respliclick, 117 mcg (90 mcg base)/actuation, $0.25 actuation
- Albuterol HFA, 90 mcg/actuation, $0.23 actuation
- Albuterol 2.5 mg/3 mL, $0.15/nebule
- Albuterol 5 mg/mL, $0.33/nebule
**Efficacy/Safety:**

**Solution for Inhalation**

- During chronic therapy, nebulized Levalbuterol 0.625 mg three times daily was as effective as nebulized racemic Albuterol 2.5 mg three times daily, and had a similar duration of action. Levalbuterol 1.25 mg three times daily was more effective.
- One small study in patients with chronic obstructive pulmonary disease (COPD) failed to show clear clinical advantages in using Levalbuterol over conventional nebulized bronchodilators.

**Adverse Effects**

- In a small sample of intensive care (ICU) patients with and without baseline tachycardia, no statistically or clinically significant differences were observed between maximum heart rate increases induced by equipotent doses of Albuterol and Levalbuterol.
- With single or multiple dosing, adverse effects of 0.625-mg doses of Levalbuterol were fewer than observed with 2.5-mg doses of racemic Albuterol, including tachycardia, nervousness, tremor, and changes in glucose and potassium levels. Adverse effects were similar with Levalbuterol 1.25 mg and racemic Albuterol 2.5 mg.

**Inhalation Aerosol**

- The efficacy and safety of XOPENEX HFA Inhalation Aerosol were established in two 8-week, multicenter, randomized, double-blind, active and placebo-controlled trials. In these two trials, XOPENEX HFA Inhalation Aerosol was compared to an HFA-134a placebo MDI, and the trials included a marketed albuterol HFA-134a MDI as an active control. Serial forced expiratory volume in 1 second (FEV1) measurements demonstrated that 90 mcg (2 inhalations) of XOPENEX HFA Inhalation Aerosol produced significantly greater improvement in FEV1 over the pretreatment value than placebo.
  - 90 mcg (2 inhalations) of XOPENEX HFA Inhalation Aerosol produced similar results in improvement in FEV1 as the control group (racemic albuterol HFA 180 mcg).
- **Adverse Effects**

**Adverse event information concerning XOPENEX HFA (levalbuterol tartrate) Inhalation Aerosol in adults and adolescents is derived from two 8-week, multicenter, randomized, double-blind, active- and placebo-controlled trials that compared XOPENEX HFA Inhalation Aerosol, a marketed albuterol HFA inhaler, and an HFA-134a placebo inhaler which found the incidence of systemic beta-adrenergic adverse effects (e.g., tremor, nervousness) to be low and comparable across all treatment groups, including placebo.

**Conclusions:**

Levalbuterol is the (R)-enantiomer of (racemic) albuterol. Levalbuterol has been proven to be effective in moderate-to-severe asthma in children and adults.

Clinical studies suggest no overwhelming or consistent superiority of levalbuterol over racemic albuterol with regard to effectiveness or safety. GOLD 2016 states that “for single-dose, as-needed use in COPD, there appears to be no advantage in using levalbuterol over conventional bronchodilators.” The NHLBI 2007 guidelines for the diagnosis and management
of asthma conclude that “levalbuterol administered in one-half the mg dose of albuterol provides comparable efficacy and safety.” Although there is no clear clinical advantage to using levalbuterol instead of albuterol, this is commonly done in our system and the two medications are now similarly priced.

**Recommendation:** Recommended for addition to the formulary at this time.

**References:**

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